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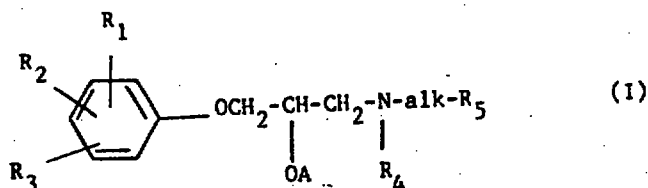
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(54) PROPANOLAMINE DERIVATIVES

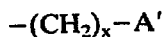
(71) We, BOEHRINGER INGELHEIM GmbH, a Body Corporate-organised under the laws of the Federal Republic of Germany of Ingelheim am Rhein, Federal Republic of Germany, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:-

This invention relates to novel 1-aryloxy-2-hydroxy-3-alkyleneaminopropanes having interesting pharmacological properties.

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



[wherein R₁ represents a hydrogen or halogen atom, a trifluoromethyl or nitro group, a straight-chained or branched alkyl group having from 1 to 8 carbon atoms, a straight-chained or branched alkoxy group having from 1 to 4 carbon atoms, an alkoxyalkyl group having from 2 to 8 carbon atoms, an alkenyl or alkynyl group having from 2 to 5 carbon atoms, an alkenyloxy or alkynyloxy group having from 3 to 6 carbon atoms, an optionally bridged and/or unsaturated cycloalkyl or cycloalkoxy group having from 3 to 12 carbon atoms, a group of formula



(in which x is zero or an integer from 1 to 3 and A' represents a cyano, amino, carboxamido

or hydroxy group), a group of formula



- 5 (in which R_6 represent a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms),
a C_1 to C_6 aliphatic, araliphatic or aromatic acyl, acyloxy or acylamino group, a group of
formula

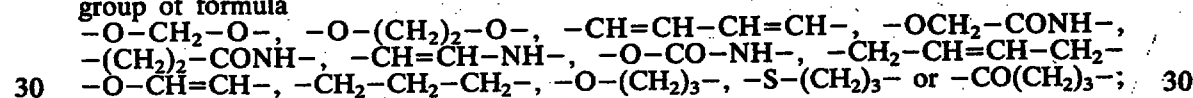


- 10 (in which R_7 and R_8 , which may be the same or different, each represents a hydrogen atom
or an alkyl group or, together with the nitrogen atom to which they are attached, represent
a heterocyclic group), an aryl, aryloxy or aralkoxy group (optionally substituted by one or
more halogen atoms, alkyl, nitro, cyano and/or carboxyl groups), a group of formula



- 15 (in which R_9 represents a C_1 to C_6 alkyl group or acyl group such as a group CH_3SO_2- ,
 $(\text{CH}_3)_2\text{N}-\text{SO}_2$ or $\text{alkyl}-\text{O}-\text{CO}-$), or a group of formula $-\text{CONH-alkyl}$, $-\text{CO-N}$
20 $(\text{alkyl})_2$, $-\text{CONH-NH}_2$, $-\text{CH}_2\text{SO}_2\text{CH}_3$ or $-\text{CO}-\text{NH}-\text{OH}$;

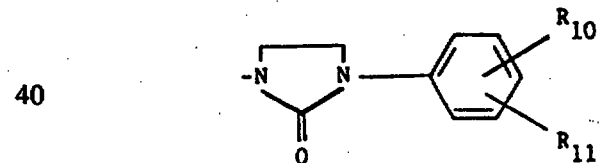
- R_2 represents a hydrogen or halogen atom, a straight-chained or branched alkyl or alkoxy
group having from 1 to 4 carbon atoms, an aralkoxy group having from 7 to 14 carbon
atoms, an alkenyl group having from 2 to 4 carbon atoms, or a cyano, nitro, hydroxy or
amino group; and R_3 represents a hydrogen or halogen atom, a straight-chained or
25 branched alkyl or alkoxy group having from 1 to 4 carbon atoms, an aralkoxy group having
from 7 to 14 carbon atoms, or a hydroxy group; or R_2 and R_3 together represent a divalent
group of formula



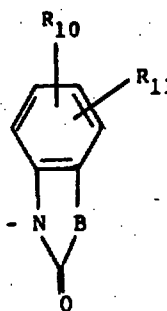
R_4 represents a hydrogen atom, an alkyl group having from 1 to 5 carbon atoms or an
optionally substituted aralkyl group having from 7 to 14 carbon atoms;

R_5 represents a heterocyclic group of the formula

- 35



or



- 50 [in which R_{10} and R_{11} , which may be the same or different, each represents a hydrogen or
halogen atom, a straight-chained or branched alkyl or alkoxy group having from 1 to 4
carbon atoms, a trifluoromethyl or carboxamido group or a divalent group having the
formula

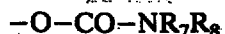
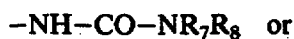


- 55 (wherein y is 1 or 2) bonded with the two free bonds in the *ortho*-position relative to each
other; and B represents a divalent group of the formula $>\text{NR}_{12}$ (in which R_{12} represents a
hydrogen atom or a C_1 to C_6 alkyl, alkenyl, alkynyl, cycloalkyl or optionally substituted aryl
group), a group $-\text{OCH}_2-$ (wherein the oxygen atom is attached to the phenyl nucleus), or
60 a group $-(\text{CH}_2)_2-$;

alk represents a straight-chained or branched alkylene group having from 1 to 12 carbon
atoms; and

- 65 A represents a hydrogen atom or an acyl group or a group of the formula
 $-\text{CONH-alkyl}$, $-\text{CO-N}(\text{alkyl})_2$, $-\text{CONH-NH}_2$, $-\text{CH}_2\text{SO}_2\text{CH}_3$ or $-\text{CONHOH}$] and
acid addition salts thereof.

In compounds of general formula I (as herein described), R_1 may, for example, represent a group of the formula



(in which R_7 and R_8 , together with the nitrogen atom to which they are attached, form a pyrrolidino, piperidino or morpholino group), or a phenyl, phenoxy or benzyloxy group;

R_2 may, for example, represent a benzyloxy group, or, together with the group R_3 , form a divalent group in which the two free bonds are bonded to the phenyl nucleus in an ortho-position relative to each other;

R_3 may, for example, represent a benzyloxy or hydroxy group; and

A may, for example, represent an acyl group or a group of the formula $-\text{CONH}-\text{alkyl}$, $-\text{CON}(\text{alkyl})_2$, $-\text{CONH}-\text{NH}_2$, $-\text{CH}_2\text{SO}_2\text{CH}_3$ or $-\text{CO}-\text{NH}-\text{OH}$.

When R_1 , R_2 and/or R_3 in the compounds according to the invention represent alkyl or alkoxy groups, these groups may, for example, be methyl, methoxy, ethyl, ethoxy, isopropyl or isopropoxy groups. When R_1 represents an alkenyl, alkynyl, alkenyloxy or alkynyloxy group these may be, for example, a vinyl, allyl, ethynyl, allyloxy or propargyloxy group. Cycloalkyl or cycloalkoxy groups suitable for R_1 are, for example, cyclopropyl, cyclopentyl, cyclopentyloxy or adamantyl groups. Suitable halogen atoms for R_1 , R_2 and/or R_3 are, for example, fluorine, chlorine, bromine, or iodine atoms.

Suitable acyl groups for R_1 are, for example, acetyl, propionyl, butyryl or isobutyryl groups, or phenacetyl, benzoyl or naphthoyl groups optionally substituted in the aromatic nucleus by one or more halogen atoms, or C_1 to C_6 alkyl, nitro, cyano or carboxyl groups. The same groups may, if desired, be used for the group A.

Similarly when R_1 represents an acyloxy or acylamino group, the acyl group therein may be one of the acyl groups above mentioned.

When R_2 together with the group R_3 represents the group $-\text{OCH}_2-\text{O}-$, this group is preferably the 3,4- $\text{OCH}_2-\text{O}-$ group.

The group alk may, for example, be an ethylene, trimethylene, tetramethylene, hexamethylene, dodecamethylene, 1-methylethylene, 2-methylethylene, 1,1-dimethylethylene, 1,1-dimethylpropylene, 1,1-dimethylbutylene or 1,1,4,4-tetramethylbutylene group.

It will be appreciated that acid addition salts of compounds of general formula I for use in medicine should be physiologically acceptable acid addition salts. Other acid addition salts, however, may be useful in the preparation of compounds of general formula I or the physiologically acceptable acid addition salts thereof.

Compounds of general formula I and the salts thereof possess at least one chiral carbon atom and thus it will be appreciated that the compounds according to the invention may exist in the form of optical isomers and racemic mixtures thereof. All such forms of compounds of general formula I are intended to be within the scope of the present invention.

Acid addition salts of the compounds according to the invention may be conveniently formed from acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulphuric acid, or from organic acids such as, for example, methanesulfonic acid, maleic acid, acetic acid, oxalic acid, lactic acid, tartaric acid, 8-chloro-theophylline, salicylic acid, citric acid, β -naphthoic acid, adipic acid, 1,1-methylene-bis-(2-hydroxy-3-naphthoic) acid or from an acidic synthetic resin, such as, for example, from a sulfonated polystyrol resin.

As stated above the compounds according to the present invention and acid addition salts thereof possess interesting pharmacological properties. In particular, they exhibit a combination of α - and β -adrenolytic properties and may thus be useful in the treatment and/or prophylaxis of coronary disease and for the treatment of cardiac arrhythmia, particularly of tachycardia. Compounds which we have tested have exhibited a stronger action than commercial products such as Propranolol and Toliprolol. The compounds of general formula I may also be useful in the treatment of various forms of hypertonic disease and compared with known α -blockers, such as, for example, phentolamine, compounds which we have tested have exhibited the advantage of a low or even no tachycardiac effect.

Compounds of general formula I may also be useful as antidepressant compounds and thus may be administered in the treatment of diseases resulting from depression.

A preferred compound according to the present invention which our tests have shown to be effective as an α - and β -adrenolytically active blood-pressure decreasing agent, is 1-(α -naphthoxy)-3-[1,1-dimethyl-3-(benzimidazolidinon-2-yl)-propylamino]-propan-2-ol and the acid addition salts thereof, for example, the hydrochloride. Our tests in genetically

hypertonic rats have shown that this substance, when administered as a single i.p. or oral dose as well as when administered several times orally, produces a decrease in blood pressure and bradycardia lasting for up to 24 hours (doses of 10 and 30 mg/kg). In narcotized rabbits and cats, blood pressure decrease and bradycardia have been produced when this compound is administered intravenously in a dose of 3 mg/kg. We have found that the α -adrenolytic action of this compound is weaker than that of phentolamine (isolated seminal vesicle of the rat) by several orders of magnitude, and the β -adrenolytic action is 3 to 4 times greater than that of Propranolol.

A preferred compound according to the invention by virtue of a favorable β -adrenolytic activity and an advantageous bradycardiac action (p.o.) is 1-(2-bromo-phenoxy)-3-(N-benzimidazolonyl-3-propylamino)-propan-2-ol, and the acid addition salts thereof, for example, the hydrochloride. We have found that this compound exhibits a β -adrenolytic activity approximately 10 to 12 times stronger than the known compound Propranolol when administered p.o. to guinea-pigs in urethane narcosis.

Preferred compounds according to the invention by reason of their favorable pharmacological properties are the following:-

a) *Compounds with favorable β -adrenolytic properties*

1-[3,3-dimethyl-3-(3-o-chlorophenoxy-2-hydroxypropyl)-propylamino]-3-phenylimidazolidin-2-one;

1-(2-chlorophenoxy)-3-[1,1-dimethyl-3-(benzimidazolidinon-2-ol)-propylamino]-propan-2-ol;

1-[1,1-dimethyl-3-(3-phenylimidazolidinon-2-yl)propylamino]-3-(2-methylphenoxy)-propan-2-ol;

1-(2-allylphenoxy)-3-(N-benzimidazolonyl-3-propylamino)-propan-2-ol;

1-(3-methylphenoxy)-3-(N-benzimidazolonyl-3-propylamino)-propan-2-ol;

1-(3-methoxyphenoxy)-3-[1,1-dimethyl-3-(3-phenylimidazolidinonyl)propylamino-1]-propan-2-ol;

1-(2-propargyloxyphenoxy)-3-[1,1-dimethyl-3-(3-phenylimidazolidinonyl)propylamino-1]propan-2-ol;

1-(2-acetyl-4-aminobutylphenoxy)-3-(3-N-benzimidazolonyl-1,1-dimethyl-1-propylamino)propan-2-ol;

1-(2-chloro-5-methylphenoxy)-3-(3-N-benzimidazolonyl-1,1-dimethyl-1-propylamino)-propan-2-ol; and acid addition salts thereof;

b) *Compounds with favorable blood pressure decreasing and/or bradycardiac properties*
1-(2-chlorophenoxy)-3-[1,1-dimethyl-3-(benzimidazolidinon-2-yl)-propylamino]-propan-2-ol;

1-[1,1-dimethyl-3-(3,4-dihydro-1,4-2H-benzoxaz-3-onyl)-propylamino]-propan-2-ol;

1-[1,1-dimethyl-3-(3-phenylimidazolidinon-2-yl)propylamino]-3-(3-methylphenoxy)-propan-2-ol;

1-(3-methylphenoxy)-3-[N-(1,2,3,4-tetrahydroquinol-2-one)-1,1-dimethyl-propylamino]-propan-2-ol;

1-(2-n-propylphenoxy)-3-[1,1-dimethyl-3-(3-phenylimidazolidinonyl)-propylamino]propan-2-ol;

1-(4-methoxyphenoxy)-3-[1,1-dimethyl-3-(3-phenylimidazolidinonyl)-propylamino-1]-propan-2-ol;

1-(2-allylphenoxy)-3-[1,1-dimethyl-2-(3-phenylimidazolidinonyl)ethylamino-1]-propan-2-ol;

1-(3-trifluoromethylphenoxy)-3-[1,1-dimethyl-2-(3-phenyl-imidazolidinonyl)ethylamino-1]-propan-2-ol-(2);

1-(indanyloxy)-3-[1,1-dimethyl-3-(3-phenylimidazolidinonyl)-propylamino-1]propan-2-ol;

1-(3,5-dimethylphenoxy)-3-[1,1-dimethyl-3-(3-phenylimidazolidinonyl)-propylamino-1]-propan-2-ol;

1-(2-propargyloxyphenoxy)-3-[1,1-dimethyl-3-(3-phenyl-imidazolidinonyl)propylamino-1]propan-2-ol;

1-(3-methoxyphenoxy)-3-[1,1-dimethyl-3-(3-phenylimidazolidinonyl)propylamino-1]propan-2-ol;

1-(3,5-dimethylphenoxy)-3-[2-(3-phenylimidazolidinonyl)-ethylamino-1]propan-2-ol;

1-(3-methylphenoxy)-3-[2-(3-phenylimidazolidinonyl)-ethylamino-1]-propan-2-ol;

1-(3,5-dimethylphenoxy)-3-[3-(3-phenylimidazolidinonyl)-propylamino-1]-propan-2-ol;

1-(2,6-dimethylphenoxy)-3-[1,1-dimethyl-3-(N-benzimidazolonyl)-propylamino-1]propan-2-ol;

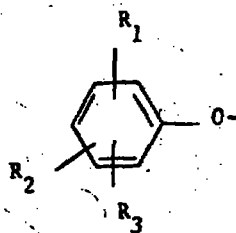
1-(3,5-dimethylphenoxy)-3-[1,1-dimethyl-3-(N-benzimidazolonyl)-propylamino-1]-propan-2-ol;

1-(2-bromophenoxy)-3-[1-methyl-2-(N-benzimidazolonyl)-ethylamino-1]propan-2-ol;
 1-(3-methylphenoxy)-3-[1-methyl-2-(N-benzimidazolonyl)-ethylamino-1]propan-2-ol;
 1-(2,4-dichlorophenoxy)-3-[1-methyl-2-(N-benzimidazolonyl)-ethylamino-1]propan-2-ol;
 1-(4-chlorophenoxy)-3-[1,1-dimethyl-N-(1,2,3,4-tetra-hydroquinolonyl)-propylamino]-
 propan-2-ol; and acid additional salts thereof.

A preferred compound by virtue of having favorable antidepressive properties is, for example, 1-(2,6-dichlorophenoxy)-3-(N-benzimidazolonyl-3-propylamino-1)propan-2-ol.

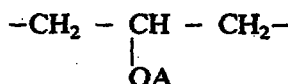
Compounds of general formula I may in general be prepared by processes which essentially link the following 4 radicals together:-

1. An aryloxy radical of formula



(wherein R_1 , R_2 and R_3 are as hereinbefore defined),

2. an (optionally esterified) 2-hydroxypropylene side chain of formula



(wherein A is as hereinbefore defined),

3. an imino group of formula



(wherein R_4 is as hereinbefore defined), and

4. a heterocyclic group of formula

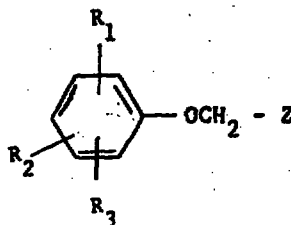


(wherein alk and R_5 are as hereinbefore defined).

In principle, these individual groups may be combined in any desired sequence.

Thus, the compounds of formula I according to the invention may be prepared by any of the following processes, which processes form further features of the present invention:-

a) reacting a compound of formula

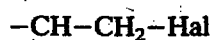


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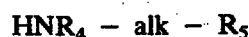
(wherein R_1 , R_2 and R_3 are as hereinbefore defined and Z represents a group of the formula $-\text{CH}-\text{CH}_2$



or



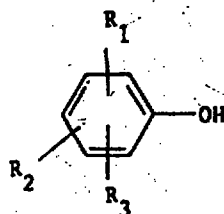
(wherein Hal represents a halogen atom, and A is as hereinbefore defined)] with a compound of formula



(III)

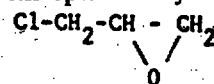
(wherein R_4 , R_5 and alk are as hereinbefore defined).

Compounds of general formula II as defined above may be prepared from phenols of general formula

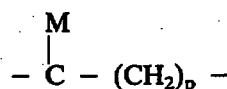


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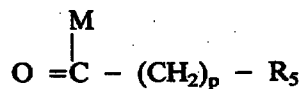
(wherein R_1 , R_2 and R_3 are as hereinbefore defined) by reacting with epichlorohydrin



b) [for the preparation of compounds of general formula I wherein R_4 is a hydrogen atom and alk represents a group of the formula

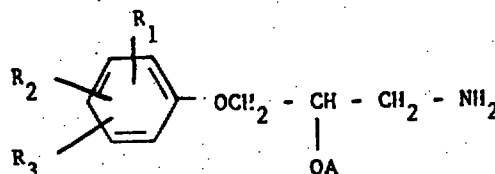


(in which M represents a hydrogen atom or a methyl group and p is an integer from 1 to 4)] which comprises reductively aminating a compound of formula



(V)

(in which R_5 , M and p are as hereinbefore defined) with a compound of formula

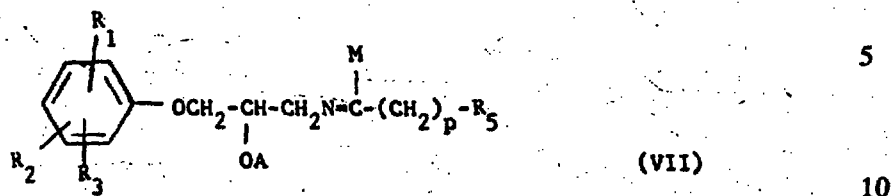


(VI)

(wherein R_1 , R_2 , R_3 and A are as hereinbefore defined)

The reductive amination is conveniently effected in the presence of conventional hydrogenation agents, such as, for example, LiAlH_4 , SDMA or under the conditions of catalytic hydrogenation.

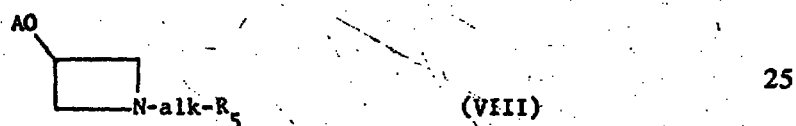
If desired, compounds of general formula I may be produced by reduction of the Schiff's base of formula



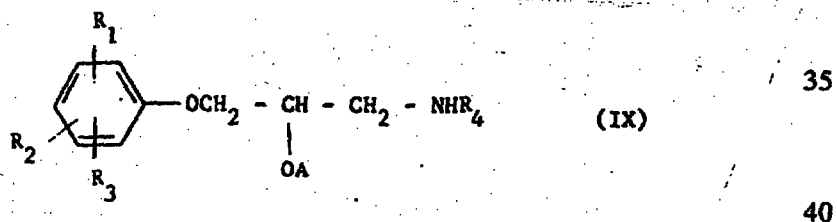
(wherein R_1 , R_2 , R_3 , R_5 , A, M and p are as hereinbefore defined) which is formed in an intermediate step of the above reaction.

The above processes are preferably avoided for the production of such compounds of general formula I where the substituents R_1 , R_2 and/or R_3 are unstable in reductive conditions, for example when these groups contain an unsaturated $\text{C}=\text{C}$, $-\text{C}=\text{N}$ or $\text{C}=\text{O}$ bond.

c) (to prepare a compound of general formula I [as hereinbefore defined wherein R_4 represents a hydrogen atom]), reacting a phenol of formula IV (as hereinbefore defined) with a compound of formula



(wherein R_5 , alk and A are as herein defined);
d) reacting an amine of formula

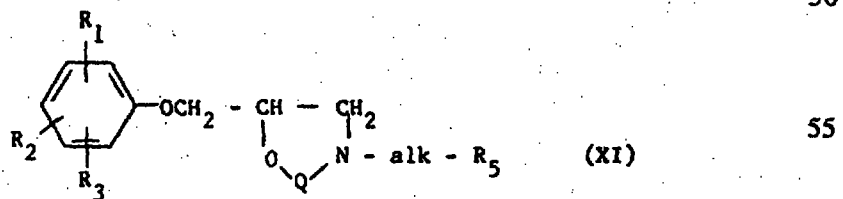


(wherein R_1 , R_2 , R_3 , R_4 and A are as herein defined) with a compound of formula



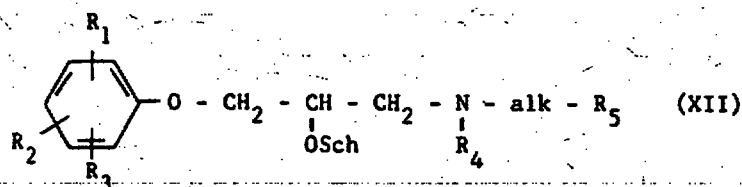
(wherein R_5 and alk are as herein defined and X represents a leaving group, preferably a halogen atom, or a mesyl or tosyl group).

e) (for the preparation of compounds of general formula I in which R_4 and A represent hydrogen atoms) hydrolytically splitting the oxazolidine ring of a compound of formula



(wherein R_1 , R_2 , R_3 , alk and R_5 are as herein defined and Q represents a $-\text{CH}_2-$ or $-\text{CO}-$ group).

f) (for the preparation of compounds of general formula I in which A represents a hydrogen atom) removing the protecting group from a compound of formula



(wherein R_1, R_2, R_3, R_4, R_5 and alk are as herein defined and Sch represents a conventional protecting group, for example, an acyl, benzyl group or acetal group)

Removal of the protecting group may, if desired, be effected hydrolytically (for example, in an aqueous alkaline or acid medium) or hydrogenolytically (for example, by catalytic hydrogenation). In the latter case, the production of compounds of formula I with groups unstable to reduction is generally not possible.

Further processes for producing substances according to the invention comprise converting one or several of the substituents R_1, R_2, R_3 or R_4, R_{10} or R_{11} into other substituents according to the invention. The following processes exemplify this:

g) (for the preparation of compounds of general formula I wherein R_1, R_2, R_3 and R_5 represent groups which are not affected by catalytic hydrogenation, and R_4 represents a hydrogen atom) catalytically hydrogenating a compound of formula I (in which R_4 represents an arylmethyl group);

h) (for the preparation of compounds of general formula I wherein at least one of R_1, R_2 and R_3 represents a hydroxy group) which comprises splitting the benzyloxy group from a compound of formula I (in which at least one of R_1, R_2 and R_3 represents a benzyloxy group).

Splitting of the benzyloxy group is preferably effected by ether splitting using a hydrohalic acid or borotrihalide or by catalytic hydrogenation.

i) (for the preparation of compounds of general formula I wherein R_1 represents a group of the formula $-\text{CONH}_2, -\text{CONH-alkyl}, -\text{CON(alkyl)}_2, -\text{CO-NHNH}_2$ or $-\text{CONHOH}$) aminolysing a compound of formula I (wherein R_1 represents a group of the formula $-\text{COO-alkyl}$);

k) (for the preparation of compounds of general formula I wherein at least one of the groups R_1, R_2, R_3, R_{10} and R_{11} represents a halogen atom) halogenating a compound of formula I (wherein at least one of R_1, R_2, R_3, R_{10} and R_{11} represents a hydrogen atom).

The halogenation is preferably effected using a hydrohalic acid in the presence of hydrogen peroxide. By using only one equivalent of hydrohalic acid $/\text{H}_2\text{O}_2$, halogen substitution on only one aryl group may be effected.

l) (for the preparation of compounds of general formula I wherein R_4 represents an alkyl group) alkylating a compound of formula I (wherein R_4 represents a hydrogen atom).

Alkylation may be conveniently effected using an alkyl halide, alkyl mesylate or alkyl tosylate, or (for the preparation of compounds wherein R_4 represents a methyl group) using formaldehyde/formic acid;

m) (for the preparation of compounds of general formula I in which R_1 represents a halogen atom or a cyano group) subjecting a compound of formula I (wherein R_1 represents a primary amino group) to the Sandmeyer reaction, i.e. diazotization followed by reaction with a copper I halide (for the preparation of compounds in which R_1 represents a halogen atom) or copper I cyanide (for the preparation of compounds wherein R_1 represents a cyano group);

n) (for the preparation of compounds of general formula I wherein R_1 represents a group which may be prepared by reduction, and R_2 and R_3 are groups which are not affected by reduction) reducing a compound of formula I (wherein R_1 represents a reducible group). Thus, for example, R_1 in the starting compound may represent an $-\text{NO}_2$ or COO-Alkyl group, whereby compounds in which R_1 represents an amino or $-\text{CH}_2\text{OH}$ group respectively are produced.

o) (for the preparation of compounds of general formula I wherein at least one of the groups R_1, R_2 and R_3 represents a hydroxy group) subjecting a compound of formula I (wherein at least one of the groups R_1, R_2 and R_3 represents a C_1 to C_6 alkoxy group) to ether splitting.

Ether splitting may conveniently be effected using a concentrated hydrohalic acid. The alkoxy group(s) present in the compound of formula I used as starting material is/are preferably methoxy groups.

When in any of the above processes, a free base of a compound of formula I is produced, this free base may if desired be converted to an acid addition salt thereof in known manner. Similarly acid addition salts of compounds of general formula I produced by these processes may be converted in known manner to the corresponding free bases.

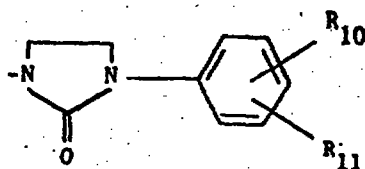
Compounds of general formula I and the acid additional salts thereof may exist in the form of optical isomers. Thus, when any of the above processes produce a racemate of the compound of formula I or acid addition salt thereof, this racemate may, if desired, be resolved into its individual optical isomers by known techniques. This may be conveniently achieved by converting the racemate into the corresponding diastereomeric salts thereof using optically active acids such as, for example, dibenzoyl or di-*p*-toluyl-D-tartaric acid, D-3-bromo-camphorsulphonic acid and (-)-2,3,4,5-di-*O*-isopropylidene-2-keto-L-gulonic acid. Separation of the diastereomeric salts is effected by fractional crystallization and a solubilizer, for example, allylamine in petroleum ether, may if desired be added following the first crystallization.

Alternatively, optical isomers of compounds of general formula I may be prepared by using a corresponding optically active starting material in any of the above processes.

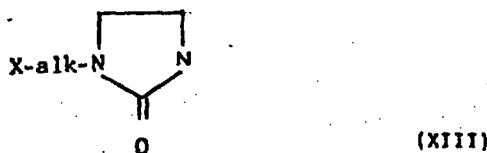
We have found that the pharmacological activity (especially the β -adrenolytic activity) of compounds of general formula I is stronger in those optical isomers having an S- absolute configuration.

Starting compounds of general formulae II, V to VII and IX, and intermediates of formulae XI and XII are known compounds. They may, if desired, be obtained by processes known *per se* from compounds of general formulae III and IV. Phenols of general formula IV are generally already known or else they may be formed by known methods. However certain compounds of general formulae III and VIII and acid addition salts thereof are novel and are described and claimed, together with processes for their preparation, in our copending patent applications nos. 7941737 (Serial No. 1592976) and 7941738 (Serial No. 1592977) (Patent Specifications Nos. and) respectively.

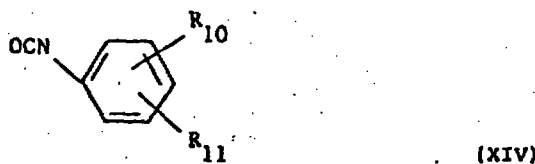
Intermediates of formula X may be prepared by, for example, the following processes:
a₁) (Wherein R₅ represents a group of formula



- wherein R₁₀ and R₁₁ are as hereinbefore defined) by the reaction of an oxazolidinone of formula XIII

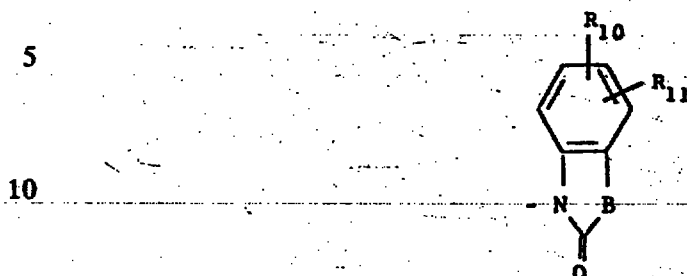


(wherein X and alk are as hereinbefore defined) with an isocyanate of formula XIV

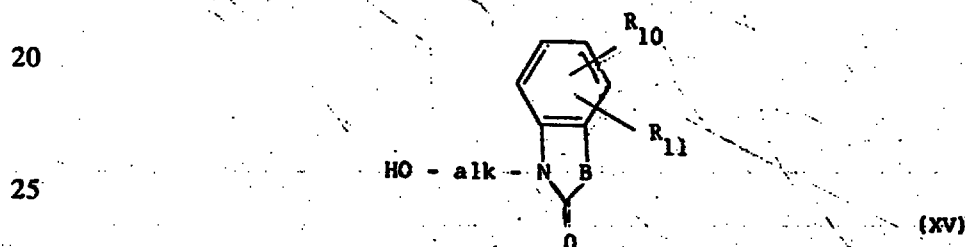


(wherein R₁₀ and R₁₁ are as hereinbefore defined).

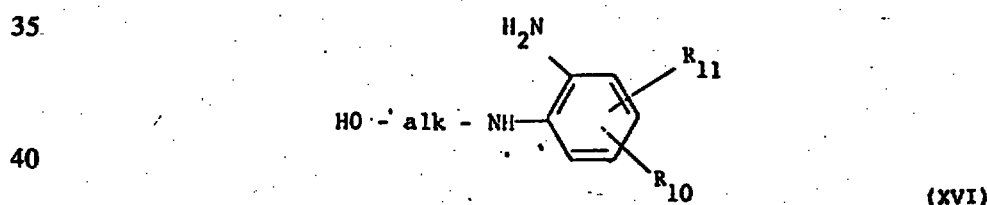
b₁) (Wherein R₅ represents a group of formula



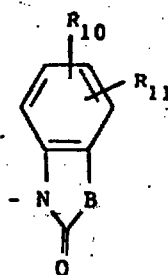
15 - wherein R₁₀, R₁₁ and B are as hereinbefore defined) by the halogenation of a compound of formula XV



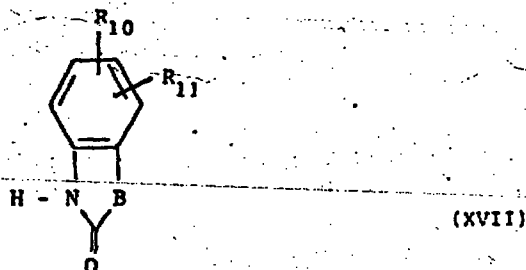
30 (wherein alk, R₁₀, R₁₁ and B are as hereinbefore defined).
The compound of formula XV may be produced by the cyclization of a compound of formula XVI



45 (wherein alk, R₁₀ and R₁₁ are as hereinbefore defined).
Halogenation may be achieved by using conventional halogenation agents (for example SOCl₂ or POCl₃).
c₁) (Wherein R₅ represents a group of formula



- wherein R_{10} , R_{11} and B are as hereinbefore defined) by the reaction of a compound of formula XVII



(wherein R_{10} , R_{11} and B are as hereinbefore defined) with a dihalogen alkylene of formula XVIII



(wherein alk is as hereinbefore defined and X_1 and X_2 represent different halogen atoms), for example, an α - bromo - ω - chloro - alkylene.

The production of intermediates of formula X is exemplified hereinafter in Examples α and β .

According to a 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 acceptable acid addition salt thereof in association with a pharmaceutical carrier or excipient.

Compositions according to the invention are conveniently in a form suitable for oral, rectal or parenteral administration. Suitable forms being, for example, tablets, coated tablets, solutions, emulsions, powders, capsules, syrups, suppositories or forms adapted to provide sustained release of the active ingredient.

Compositions according to the invention are preferably in the form of dosage units, each dosage unit advantageously comprising from 1 to 500 mg of the active ingredient. For oral administration each dosage unit preferably comprises from 2 to 200 mg of active ingredient and for parenteral administration each dosage unit preferably comprises from 1 to 20 mg of active ingredient.

If desired, the compositions according to the invention may additionally comprise at least one further active ingredient, such as, for example, a coronary dilator, such as dipyridamol; a cardiac glycoside or tranquillizer, such as chlorodiazepoxide, diazepam or oxazepam; a vasodilator, such as glyceryl trinitrate or isosorbide dinitrate; a diuretic such as chlorothiazide; a sympathicomimetic, such as isoprenaline or orciprenaline; a hypotensive, such as clonidine, reserpine or guanethidine; an anti-Parkinson agent, such as benzohehexol; and an α -blocker such as phentolamine.

Tablets containing the active ingredient(s) according to the invention may be produced for example, by admixing the active substance(s) with known excipients, for instance, inert diluants, such as calcium carbonate, calcium phosphate or lactose, disintegrants, such as corn starch or alginic acid, binders such as starch or gelatin, lubricants such as magnesium stearate or talcum and/or agents for obtaining sustained release, such as carboxypoly-methylene, carboxymethyl cellulose, cellulose acetatephthalate, or polyvinyl acetate.

If desired, the tablets may consist of several layers. Coated tablets may be produced by covering tablet cores produced analogously to the tablets described above with a coat, the coat consisting of agents conventionally applied for tablet-coats, such as polyvinylpyrrolidone, shellac, gum arabic, talcum, titanium dioxide or sugar. To obtain sustained release or to avoiding incompatibilities, the core may also consist of several layers. The tablet-coat may also consist of several layers for obtaining sustained release, whereby the excipients mentioned above for the tablets may be used.

Syrups of the active substance(s) and/or combination of active substances according to the invention may comprise in addition to the active ingredient(s), a sweetener, such as saccharin, cyclamate, glycerin or sugar, as well as an agent improving the taste, for example flavouring such as vanillin or orange extract. These syrups may also comprise suspension auxiliaries or thickeners, such as sodium carboxymethyl cellulose, wetting agents, such as condensation products of fatty alcohols with ethylene oxide, or preservatives, such as *p*-hydroxybenzoates.

Injection solutions may be produced in conventional manner, for example with the addition of preservatives, such as *p*-hydroxybenzoates or stabilizers, such as complexons, and may be filled into injection vials or ampoules.

- 5 Capsules containing the active substance(s) and/or combinations thereof may be produced, for example, by admixing the active ingredient(s) with inert carriers, such as lactose or sorbitol and filling the mixture into gelatin capsules.

Suppositories may be produced, for example, by admixing the active substance(s) and/or combination of active substance(s) with conventional carriers, such as neutral fats or polyethylene glycol and/or derivatives thereof.

- 10 The following Examples serve to illustrate the preparation of compounds according to the invention and pharmaceutical compositions containing them:-

EXAMPLE 1

- 15 1-(α -Naphthoxy)-3-[1,1-dimethyl-3-(*N*-benzimidazol-2-yl)-propylamino-1-propan-2-ol-hydrochloride monohydrate (according to process a))

- 3 g of 1-(3-amino-3,3-dimethylpropyl)-benzimidazol-idin-2-one are refluxed with 3.3 g of 1-(naphthyl-(1-oxy)-propylene-(2,3)-oxide in 12 ml of 98% alcohol for 3 hours. After distilling off the alcohol, the residue is dissolved in a little methanol, acidified with 1 N hydrochloric acid and shaken with ethyl acetate. After distillation of the ethyl acetate, the hydrochloride crystallizes after addition of ether and a little water as the monohydrate. The yield amounts to 60% of theory, the melting point after recrystallization from alcohol is 161°C.

- 20 Analogously to the process of Example 1, the following substances of general formula Ia were prepared by reacting the corresponding epoxide of formula II with the corresponding aminoalkyl compound of formula III in 98% ethanol at reflux temperature
- 25

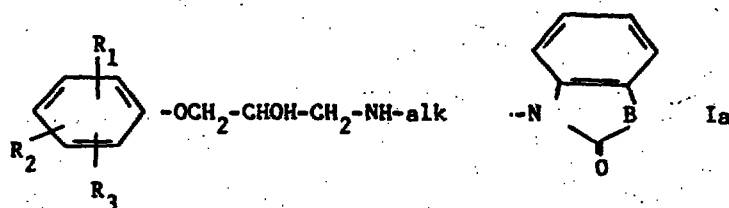


TABLE 1

R_1	R_2	R_3	Alk	B	m.p. (°C)
H	2,3=CH=CH-CH=CH-		$(CH_3)_2\overset{ }{C}-CH_2-$	-NH-	217 hydrochloride
2-Cl	H	H	-ditto-	-ditto-	214 hydrochloride
2-Cl	H	H	$-(CH_2)_2-$	-ditto-	169 maleate
2-Cl	H	H	$(CH_3)_2\overset{ }{C}(CH_2)_2-$	-OCH ₂ -	153 <i>p</i> -aminobenzoate
2-Cl	H	H	-ditto-	-NH-	166 maleate
H	2,3-CH=CH-CH=CH-		-ditto-	-OCH ₂ -	125 hydrochloride monohydrate
H	-ditto-		-ditto-	$-(CH_2)_2-$	95 hydrochloride monohydrate
3-CH ₃	H	H	-ditto-	-NH-	164 hydrochloride monohydrate
3-CH ₃	H	H	-ditto-	-OCH ₂ -	104 hydrochloride monohydrate
3-CH ₃	H	H	-ditto-	$-(CH_2)_2-$	107 formate
2-Cl	H	H	-ditto-	-ditto-	85 formate
2-allyloxy	H	H	-ditto-	-NH-	154 maleate

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TABLE 1 (continued)

R ₁	R ₂	R ₃	Alk	B	m.p. (°C)
2-allyloxy	H	H	(CH ₃) ₂ C(CH ₂) ₂ -	-OCH ₂	183 sulfate
ditto	H	H	-ditto-	(CH ₂) ₂	108 <i>p</i> -aminobenzoate
H	2,3-CH=CH-CH=CH-		(CH ₃) ₂ C-(CH ₂) ₃ -	-NH-	134 succinate
2-allyl	H	H	(CH ₃) ₂ C-(CH ₂) ₂ -	-ditto-	162 maleate
ditto	H	H	(CH ₃) ₂ C-(CH ₂) ₃ -	-OCH ₂ -	181 <i>p</i> -aminobenzoate
2-CH ₃	H	H	(CH ₃) ₂ C-(CH ₂) ₂ -	-NH-	187 maleate
2-CH ₃	H	H	(CH ₃) ₂ C-(CH ₂) ₃ -	-ditto-	134 <i>p</i> -aminobenzoate
2-CH ₃	H	H	(CH ₃) ₂ C-(CH ₂) ₂ -	-OCH ₂ -	157 <i>p</i> -aminobenzoate
2-CH ₃	H	H	(CH ₃) ₂ C-(CH ₂) ₂ -	-(CH ₂) ₂ -	143 <i>p</i> -aminobenzoate
2- <i>n</i> -propyl	H	H	-ditto-	-NH-	165 maleate
2- <i>n</i> -propoxy	H	H	-ditto-	-OCH ₂ -	186 sulfate
4-OCH ₃	H	H	-ditto-	-NH-	193 maleate
ditto	H	H	-ditto-	-OCH ₂ -	159 <i>p</i> -aminobenzoate
2-CN	H	H	-ditto-	-NH-	167 maleate

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Analogously to Example 1 the following compounds of general formula Ib were obtained by reacting the corresponding (optionally substituted) aminoalkyl-N-phenylimidazolidin-2-one of general formula III in 98% ethanol at reflux temperature.

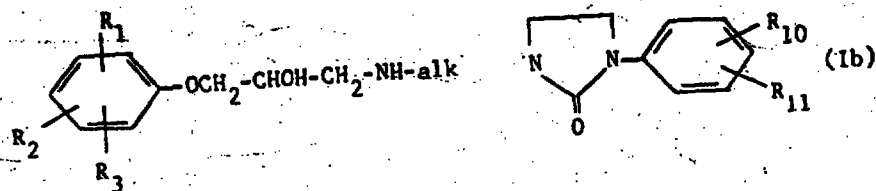


TABLE 2

R ₁	R ₂	R ₃	Alkylene	R ₁₀	R ₁₁	m.p. °C
2-Cl	H	H	(CH ₃) ₂ C-(CH ₂) ₂ -	H	H	185 hydrochloride
H	2,3-CH=CH-CH=CH-		-ditto-	H	H	228 hydrochloride
3-CH ₃	H	H	-ditto-	H	H	150 hydrochloride
2-allyloxy	H	H	-ditto-	H	H	222 sulfate
2-Cl	H	H	-ditto-	2-OCH ₃ , 4-OCH ₃		183 sulfate
2-Cl	H	H	-(CH ₂) ₃ -	H	H	78 base, 152 hydrochloride
2-allyl	H	H	(CH ₃) ₂ C(CH ₂) ₂ -	H	H	118 formate
2-CH ₃	H	H	-ditto-	H	H	181 hydrochloride
2-Cl	H	H	-ditto-	H	3-CF ₃	133 formate
2-n-propyl	H	H	-ditto-	H	H	110 formate
2-n-propoxy	H	H	-ditto-	H	H	226 sulfate
2-CN	H	H	-ditto-	H	H	186 hydrochloride

EXAMPLE 2

1-(o-Tolyloxy)-3-[1-methyl-2-(benzimidazol-2-yl-ethyl-amino)-propan-2-ol (according to process b)]

A solution of 5.8 g of 3-acetyl-benzimidazol-2-one and 5.06 g of 1-(2-methylphenoxy)-3-aminopropan-2-ol in 120 ml of methanol is hydrogenated after addition of 750 ml of platinum oxide until an uptake of 1 equivalent of hydrogen is effected. The title compound has a melting point of 160°C.

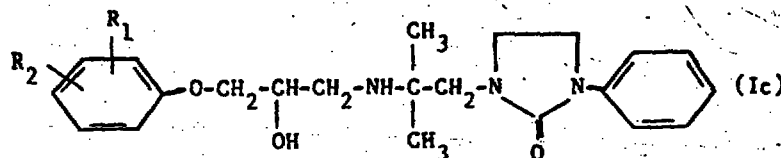
EXAMPLE 3

1-(2,4-dichlorophenoxy)-3-[1,1-dimethyl-2-(3-phenylimidazolidinonyl)-ethylamino-1]-propan-2-ol. HCl (according to process a)]

4.25 g (0.015 mol) of 1,1-dimethyl-2-(3-phenylimidazolidinonyl)-ethylamine are dissolved in 30 ml of ethanol and combined with a solution of 3.3 g (0.015 mol) of 1-(2,5-dichlorophenoxy)-2,3-epoxypropane. After the mixture has been refluxed for one hour, the solvent is distilled off *in vacuo*. The residue is purified by column-chromatography over silica gel. Evaporation of similar fractions gives an oily residue, which is dissolved in ethyl acetate, washed twice with water and dried over $MgSO_4$. After distilling off the ethyl acetate, 3.2 g of base are obtained. The base is dissolved in ether, the solution filtered and crystallization effected by cooling. The colourless crystals are removed by suction filtration and dried. Yield: 1.7 g, m.p. 106-109°C.

Processing of the remaining chromatography fractions, gives a further 1.9 g of pure substance.

Analogously to the process described in Example 3, the following compounds of formula Ic were produced by reacting the corresponding phenoxy-2,3-epoxypropane of formula II with 1,1-dimethyl-2-(3-phenylimidazolidinonyl)-ethylamine in ethanol at reflux temperature:



R_1	R_2	m.p. °C (Base)
2-CN	H	117 - 118
2-Br	H	106 - 109
3-CH ₃	H	112 - 115
2-CH ₂ -CH=CH ₃	H	85 - 87
2-Cl	6-Cl	98 - 100
2-Cl	5-CH ₃	Oil
2-Cl	H	96 - 101
2-O-CH ₂ -CH=CH ₂	H	134 - 136 oxalate
2-CH ₃	6-CH ₃	73 - 76
3-OCH ₃	H	184 - 186 oxalate
4-COC ₂ H ₅	H	138 - 139
3-CH ₃	5-CH ₃	177 - 180 oxalate

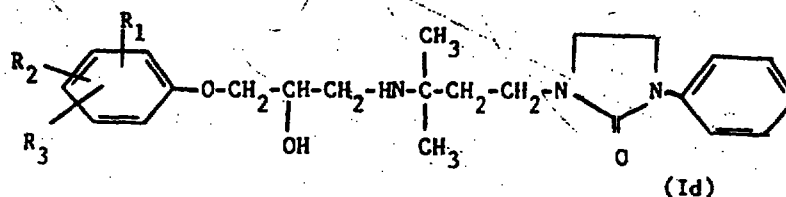
EXAMPLE 4

1-(2-Propargyloxyphenoxy)-3-[1,1-dimethyl-3-(3-phenylimidazolidinonyl)-propylamino-1]-propan-2-ol oxalate (according to process a))

- 4.8 g (0.017 mol) of 1-dimethyl-3-(3-phenylimidazolidinonyl)-propylamine hydrochloride are dissolved in 20 ml of methanol, 8.5 g (0.017 mol) of 2N NaOH are then added and combined with a solution of 3.46 g (0.017 mol) of 1-(2-propargyloxyphenoxy)-2,3-epoxypropane in 20 ml of methanol. The mixture is refluxed for one hour, and the solvent then distilled off. The residue is taken up in ether, and the solution is washed with water, separated and dried over Na₂SO₄. After distilling off the ether, the residue is purified over a silica gel column. The uniform fractions are combined and evaporated. The residue dissolved in ethyl acetate, is washed with water and dried, and, then the ethyl acetate distilled off. The remaining basic residue is dissolved in acetone and a solution of 3 g of oxalic acid in acetone is added. After addition of ether, colourless crystals of the oxalate are produced. The product is recrystallized from a mixture of acetonitrile, ethanol and methanol by addition of ether. The colourless crystals produced (1.6 g) have a melting point of 207-209°C. Evaporation of the mother-liquor gives further solid substance, which melts after recrystallization from methanol/ether at 205 - 207°C.

Yield: 1.5 g. Thin-layer chromatography of both fractions shows them to be uniform.

- Analogously to Example 4, the following compounds of formula Id were obtained from the corresponding 1-phenoxy-2,3-epoxypropane of general formula II and 1,1-dimethyl-3-(3-phenylimidazolidinonyl)-propylamine HCl in alkaline methanol:



R ₁	R ₃	R ₂	m.p.°C (Base)
2-NO ₂	H	H	84 - 86
2-Cl	H	6-Cl	84 - 86
2-Br	H	H	104 - 107
2-Cl	H	5-CH ₃	76 - 78
3-CH ₃	H	4-CH ₃	102 - 104
H	3,4-(CH ₂) ₃ -		97 - 99
4-CO-C ₂ H ₅	H	H	147 - 150
3-CH ₃	H	5-CH ₃	84 - 86
2-O-CH ₂ -C≡CH	H	H	207 - 208 (oxalate)
2-Cl	H	4-Cl	150 - 163 (hydrochloride)
4-OCH ₃	H	H	97 - 99
3-OCH ₃	H	H	83 - 85
3-CF ₃	H	H	119 - 121

EXAMPLE 5

1-(4-hydroxyphenoxy)-3-[1,1-dimethyl-3-(3-phenylimidazolidinonyl)-propylamino-1]-propan-2-ol oxalate (according to process o))

2.5 g of 1-(4-methoxyphenoxy)-3-[1,1-dimethyl-3-(3-phenylimidazolidinonyl)-propylamino-1]-propan-2-ol are heated in 15 ml HBr for 100 hours to 100°C. HBr is then distilled off *in vacuo* and the residue treated with water. After distilling off the water, the residue is made alkaline with NH_4OH , extracted with ethyl acetate, and the organic phase is dried and the solvent evaporated *in vacuo*. The residue is dissolved in acetone and added to a solution of 3 g oxalic acid in acetone. After addition of ether the oxalate crystallizes out. It is isolated, dried and recrystallized from ethanol.

M.p. 198 - 200°C, yield: 200 mg.

EXAMPLE 6

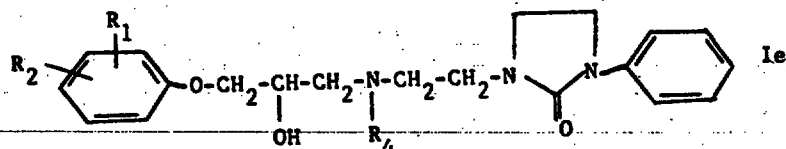
1-(4-Methoxyphenoxy)-3-[2-(3-phenylimidazolidinonyl)ethyl-amino-1]-propan-2-ol (according to process d))

A mixture of 2.8 g (0.0122 mol) of 1-(2-chloroethyl)-3-phenyl-imidazolidin-2-one, 2.4 g (0.0122 mol) of 1-(4-methoxyphenoxy)-3-amino-2-propanol, 15 ml of diglyme (i.e. diethyleneglycol-dimethylether) and 1.3 g (0.0122 mol) of sodium hydroxide solution are heated for two hours to 150 - 160°C while stirring. After distilling off the solvent, the residue is treated with ethyl acetate, washed with NaOH and H_2O and allowed to stand overnight. The crystalline substance which separates is recrystallized from ethyl acetate. The colourless, crystalline compound melts at 108 to 110°C.

Yield: 500 mg.

Processing of the mother liquor, gives another 200 mg of pure substance of m.p. 107 to 110°C. Thin-layer chromatography of both fractions shows them to be uniform.

Analogously to the method of Example 6, the following compounds of formula Ie were produced by reacting the corresponding 1-phenoxy-3-aminopropan-2-ol of general formula IX with 1-(2-chloroethyl)-3-phenylimidazolidin-2-one in an alkaline diglyme solution:



R ₁	R ₂	R ₄	m.p. °C(hydrochloride)
3-OCH ₃	H	CH ₃	130 - 134
4-CN	H	CH ₃	102 - 104
4-Cl	H	CH ₃	137 - 140
3-CH ₃	5-CH ₃	H	199 - 201
3-CH ₃	H	H	92 - 95 (Base)

Analogously to Example 5, the following substances of formula Ie were produced by saponifying the corresponding 4-(and/or 3-)methoxy compound by means of HBr at 100°C:

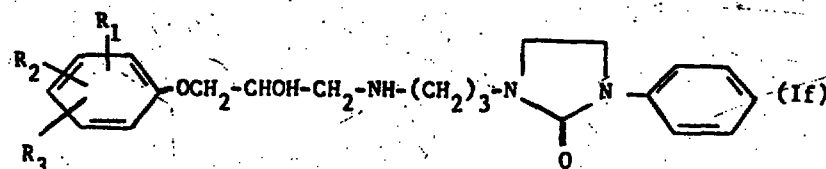
R ₁	R ₂	m.p. °C
4-OH	H	150 - 155
3-OH	H	viscous

EXAMPLE 7

1-(2-Cyanophenoxy)-[3-(3-phenylimidazolidinonyl)-propylamino-1]-propan-2-ol (according to process a))

- 0.875 g (0.005 mol) of 1-(2-cyanophenoxy)-2,3-epoxy-propane and 1.3 g (0.005 mol) of N-1-aminopropyl-(3)-3-phenylimidazolidin-2-one are dissolved in 10 ml of ethanol and refluxed for 1 hour after addition of 0.75 ml of triethylamine. 2.5 ml of 1N NaOH are then added. The solvent is distilled off *in vacuo*, the residue admixed with water and shaken with ethyl acetate. The organic phase is washed, dried and evaporated. The residue is dissolved in ethyl acetate and cooled to effect crystallization. The colourless crystals melt at 105 to 108°C. Yield: 800mg, thin-layer chromatography uniform.

Analogously to Example 7, the following compounds of formula If were produced by reacting the corresponding epoxide of general formula II with the corresponding aminoalkyl-N-phenylimidazolidin-2-one of general formula III in ethanol at reflux temperature:



R ₁	R ₂	R ₃	m.p. °C (Base)
2-Cl	5-CH ₃	H	112 - 114
2-Cl	4-Cl	H	119 - 121
2-Cl	6-Cl	H	93 - 95
2-Br	H	H	107 - 110
2-CH ₂ -CH=CH ₂	H	H	114 - 116
3-OCH ₃	H	H	86 - 88
4-CO-CH ₃	H	H	129 - 131
H	2,3-(-CH=CH-) ₂		84 - 87
2-CH ₃	6-CH ₃	H	102 - 104
3-CH ₃	H	H	94 - 97
2-O-CH ₂ -CH=CH ₂	H	H	108 - 110
3-CH ₃	4-CH ₃	H	78 - 79
H	3,4-(CH ₂) ₃ -		101 - 103
4-Cl	H	H	128 - 131
2-CO-CH ₃	H	H	85 - 88
3-CH ₃	5-CH ₃	H	103 - 104
2-NO ₂	H	H	102 - 104
3-CF ₃	H	H	105 - 107

EXAMPLE 8

1-(2-Cyanophenoxy)-3-(1,1-dimethyl-4-(N-benzimidazolonyl-butylamino-1)-propan-2-ol (according to process a))

1.75 g (0.01 mol) of 1-(2-cyanophenoxy)-2,3-epoxy-propane and 2.16 g (0.008 mol) of N-(1,1-dimethyl-1-aminobutyl)-benzimidazol-2-one are dissolved in 80 ml of ethanol, 8 ml of 1N NaOH are added and the mixture is heated to boiling point for 1 hour while stirring. The ethanol is subsequently distilled off, the residue stirred with water and shaken with ethyl acetate. After drying the organic phase, the ethyl acetate is distilled off. The remaining basic residue is purified over a silica gel column, whereby 2.5 g of pure substance is obtained. The thin-layer chromatogram is uniform. The oily substance does not crystallize, neither as base nor as salt.

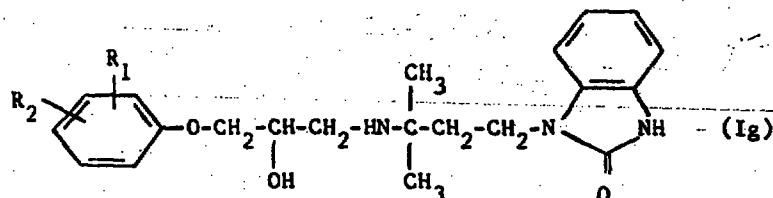
The substance 1-(2-bromophenoxy)-3-(1,1-dimethyl-4-(N-benzimidazolonyl)-butylamino-1)-propan-2-ol was prepared analogously, from 1-(2-bromophenoxy)-2,3-epoxypropane and N-(1,1-dimethyl-1-aminobutyl)-benzimidazol-2-one in ethanol-NaOH at reflux temperature.

EXAMPLE 9

1-(3-Methoxyphenoxy)-3-(1,1-dimethyl-3-(N-benzimidazolonyl)-propylamino-1)-propan-2-ol-maleate (according to process a))

4 g (0.022 mol) of 1-(3-methoxyphenoxy)-2,3-epoxy-propane are dissolved in 50 ml of methanol and a solution of 4.4 g (0.02 mol) of N-(1,1-dimethyl-1-aminopropyl)-benzimidazolone in 50 ml of methanol is added. After refluxing the mixture for 1.5 hrs., the solvent is distilled off and the residue purified over a silica gel column. The uniform fractions yield 7 g of residue after distillation of the solvent mixture. The residue is dissolved in acetone and added with stirring to a solution of maleic acid in acetone. After addition of ether, the maleate crystallizes. It is removed and recrystallized from methanol by addition of ether. Yield: 6 g, m.p. 167 - 169°C. Thin-layer chromatographically uniform.

Analogously to Example 9, the following compounds of general formula Ig were produced by refluxing the corresponding 1-phenoxy-2,3-epoxypropane with N-(1,1-dimethyl-1-aminopropyl)-benzimidazol-2-one in methanol:



R ₁	R ₂	m.p. °C maleate
2-Cl	6-Cl	168 - 170
2-Br	H	160 - 162
2-Cl	5-CH ₃	174 - 175
2-CH ₃	6-CH ₃	183 - 184
3-CF ₃	H	185 - 187
4-CO-C ₂ H ₅	H	195 - 197
2-CO-CH ₃	4-NHCOC ₃ H ₇	145 - 147
4-NO ₂	H	213 - 215
3-CH ₃	5-CH ₃	136 - 139 (Base)
2-O-CH ₂ -C≡CH	H	154 - 157
2-Cl	4-Cl	191 - 193

Analogously to Example 5, the following compounds of formula Ig were produced by saponification of the corresponding 4-(and/or 3-)methoxy compounds, in particular with HBr, at 100°C.

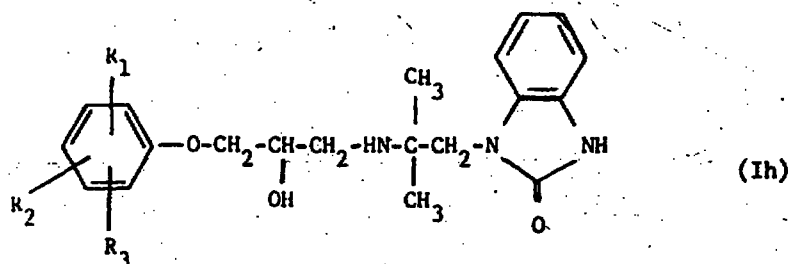
5	R ₁	R ₂	m.p. °C maleate	5
	4-OH	H	121 - 125	
10	3-OH	H	156 - 159	10

EXAMPLE 10

15 *1-(2-Propargyloxyphenoxy)-3-(1,1-dimethyl-2(N-benzimidazolonyl)-ethylamino-1)-propan-2-ol hydrochloride (according to process a)*

2.25 g (0.011 mole) of 1-(2-propargyloxyphenoxy)-2,3-epoxypropane are dissolved in 50 ml of methanol and a methanolic solution of 2 g (0.01 mol) of N-(1,1-dimethyl-1-aminoethyl)-benzimidazolone is added. After refluxing for one hour, the solvent is distilled off, the residue dissolved in ethanol and ether is added. The hydrochloride separates as colourless crystals. The salt is removed and recrystallized by addition of ether. Yield: 2.3 g, m.p. 203-205°C, thin-layer chromatographically uniform.

Analogously to Example 10, the following compounds of general formula Ih are produced by refluxing the corresponding 1-phenoxy-2,3-epoxypropane of general formula II and N-(1,1-dimethyl-1-aminoethyl)benzimidazol-2-one in methanol.



R ₁	R ₂	R ₃	m.p. °C hydrochloride
2-CN	H	H	195 - 197
2-Cl	6-Cl	H	242 - 244
2-Br	H	H	201 - 203
2-CH ₂ -CH=CH ₂	H	H	243 - 245
2-Cl	5-CH ₃	H	210 - 212
4-OCH ₃	H	H	214 - 216
3-OCH ₃	H	H	191 - 194
2-O-CH ₂ -CH=CH ₂	H	H	179 - 181
2-Cl	4-Cl	H	239 - 241

37

Analogously to Example 5, the following compounds of formula Ih were produced by saponifying the corresponding 4-(and/or 3-)methoxy compound with HBr at 100°C.

5

R ₁	R ₂	R ₃	m.p. °C (hydrobromide)
4-OH	H	H	248 - 251
3-OH	H	H	230 - 232

5

10

10

Analogously to Example 10, the compounds of formula Ih listed in the following table were produced at reflux temperature from the corresponding 1-phenoxy-2,3-epoxypropane of general formula II and N-(1,1-dimethyl-1-aminoethyl)-benzimidazol-2-one in methanol:

15

15

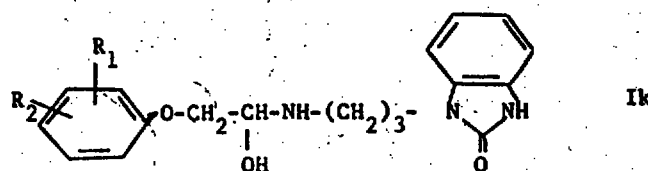
R ₁	R ₂	R ₃	m.p. °C (Base)
2-Cl	6-Cl	H	132 - 136
2-CN	H	H	90 - 94
2-Br	H	H	128 - 130
2-O-CH ₂ -CH=CH ₂	H	H	78 - 81
3-CH ₃	H	H	104 - 105
3-CF ₃	H	H	139 - 140
2-CO-CH ₃	4-NHCOC ₃ H ₇	H	166 - 169
4-OCH ₃	H	H	117 - 120
4-COC ₂ H ₅	H	H	143 - 146
H	2,3-(-CH=CH-) ₂		150 - 154
3-OCH ₃	H	H	viscous
2-Cl	4-Cl	H	140 - 143
2-O-CH ₂ -C≡CH	H	H	101 - 103

EXAMPLE 11

1-3-(*m*-tolylloxy)-3-(*N*-benzimidazolonyl-3-propylamino-1-)-propan-2-ol (according to process a))

3.28 g of (0.02 mol) of 1-(*m*-tolylloxy)-2,3-epoxy-propane and 3.8 g (0.02 mol) of 3-benzimidazolonylpropylamine-(1) and dissolved in 100 ml of ethanol and refluxed for 30 minutes. After distilling off the solvent, the residue is fractionated over a silica gel column. When the mixture of solvents has been distilled off, the uniform fractions yield a residue which is recrystallized from ethyl acetate with addition of petroleum-ether. After isolating and drying 2.8 g of base are obtained. M.p. 133 - 135°C, thin-layer chromatographically uniform.

Analogously to Example 11, the following compounds of formula Ik are produced by refluxing the corresponding 1-phenoxy-2,3-epoxypropane of general formula II and 3-benzimidazolonylpropylamine-(1) in ethanol:



R ₁	R ₂	m.p. °C
2-CN	H	158 - 159 (oxalate)
2-Br	H	137 - 140 (hydrochloride)
2-Cl	5-CH ₃	178 - 180 (hydrochloride)
2-Cl	H	140 - 143 (hydrochloride)
4-OCH ₃	H	131 - 132 (Base)
2-O-CH ₂ -CH=CH ₂	H	101 - 104 (Base)
2-Cl	6-Cl	154 - 158 (Base)
4-NH-CO-C ₃ H ₇	6-CO-CH ₃	140 - 143 (Base)
4-CO-CH ₃	H	122 - 125 (Base)
2-CH ₂ -CH=CH ₂	H	97 - 99 (Base)

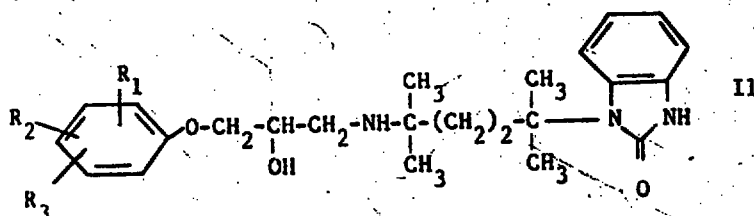
EXAMPLE 12
 1-(2-Cyanophenoxy)-3-(1,1,4,4-tetramethyl-4-(N-benzimidazolonyl)-butylamino-1)-propan-2-ol oxalate (according to process a)

2.61 g (0.01 mol) of N-1-amino-1,1,4,4-tetramethylbutyl-benzimidazolone and 3.5 g (0.02 mol) of 1-(2-cyanophenoxy)-2,3-epoxypropane are dissolved in 100 ml of ethanol and refluxed for one hour.

After distilling off the ethanol, the residue remaining is mixed with water, NaOH added, and the solution shaken with ethyl acetate. The organic phase is washed with water and dried over sodium sulfate. The ethyl acetate is distilled off and the base is purified over silica gel. The combined uniform fractions are evaporated, and the residue is dissolved in acetonitrile followed by addition of a solution of 1.5 g of oxalic acid in acetonitrile. Addition of ether causes the colourless oxalate to crystallize. The salt is recrystallized from acetonitrile by addition of ether.

Yield: 1.7 g; melting point 107 - 109°C, thin-layer chromatographically uniform.

Analogously to Example 12, the following compounds of formula I were produced by refluxing the corresponding 1-phenoxy-2,3-epoxypropane of general formula II and N-1-amino-1,1,4,4-(tetramethylbutyl)-benzimidazol-2-one in ethanol:



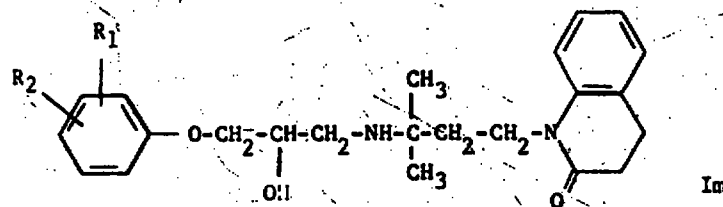
R ₁	R ₂	R ₃	m.p. °C (Base)
2-Cl	4-Cl	H	99 - 103
2-Cl	5-CH ₃	H	100 - 103
2-O-CH ₂ -CH=CH ₂	H	H	120 - 125
2-CH ₂ -CH=CH ₂	H	H	147 - 148
2-Cl	6-Cl	H	113 - 115
3-OCH ₃	H	H	128 - 131
4-CO-CH ₃	H	H	131 - 133
2-Br	H	H	100 - 102
2-CH ₃	6-CH ₃	H	118 - 122
4-CH ₃	H	H	135 - 137
2-OCH ₃	H	H	91 - 93
2-CH ₃	4-CH ₃	H	109 - 111
4-OCH ₃	H	H	108 - 111
2-O-CH ₂ -C≡CH	H	H	109 - 110
3-CH ₃	H	H	118 - 119
H	2,3-(CH=CH-) ₂		90 - 92

EXAMPLE 13

1-(2,4-Dichlorophenoxy)-3-[1,1-dimethyl-3-N-(1,2,3,4-tetrahydroquinolonyl-propylamino)-propan-2-ol oxalate (according to process a))

4.6 g of N-1-amino-1,1-dimethylpropyl-1,2,3,4-tetrahydroquinol-2-one and 6 g of 1-(2,4-dichlorophenoxy)-2,3-epoxypropane are dissolved in 100 ml of ethanol and, after refluxing the mixture for one hour, evaporated. The residue is mixed with water, acidified with HCl and shaken with ether. The aqueous phase is made alkaline with dilute NaOH and the base precipitating is dissolved in ether. After washing with water, the solution is dried over Na₂SO₄, separated and evaporated. The residue is purified over a silica gel column. The combined fractions are evaporated. The basic residue is dissolved in acetonitrile, mixed with a solution of oxalic acid in acetonitrile and ether is added, whereby the oxalate precipitates in fine crystals. After recrystallization from ethanol/ether, 3.1 g of a colourless crystalline substance are obtained, the melting point of which is 144-145°C, the thin-layer chromatogram is uniform.

Analogously to Example 13, further compounds of formula Im were produced by refluxing the corresponding 1-phenoxy-2,3-epoxypropane of general formula II with N-1-amino-1,1-dimethylpropyl-1,2,3,4-tetrahydroquinol-2-one in ethanol

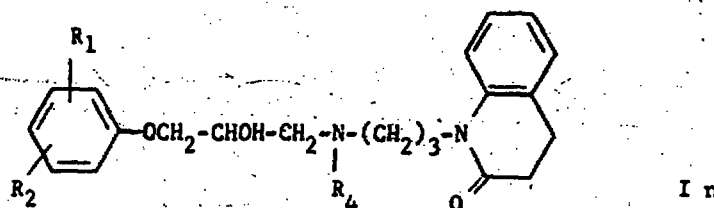


R ₁	R ₂	m.p. °C (salt)	
2-Cl	6-Cl	viscous oil	Hydrochloride
2-Cl	5-CH ₃	151-153	oxalate
4-Cl	H	116-117	base
2-CH ₂ -CH=CH ₂	H	118-120	maleate
2-CN	H	93-97	hydrochloride
2-OCH ₃	H	128-129	oxalate
4-OCH ₃	H	85-86	base
2-O-CH ₂ -C≡CH	H	82-84	oxalate
2-CH ₃	6-CH ₃	113-115	oxalate

Analogously to Example 5, the following compounds of formula Im were produced by saponifying the corresponding 4-(and/or 2-) methoxy compounds with HBr at 100°C:

R ₁	R ₂	m.p. °C (salt)	
2-OH	H	199-200	
4-OH	H	123-124	(base)

Analogously to Example 13, the following compounds of formula



were produced by refluxing the corresponding 1-phenoxy-2,3-epoxypropane of general formula II with N-1-amino-propyl-1,2,3,4-tetrahydroquinol-2-one or N-1-benzylaminopropyl-1,2,3,4-tetrahydroquinol-2-one in ethanol:

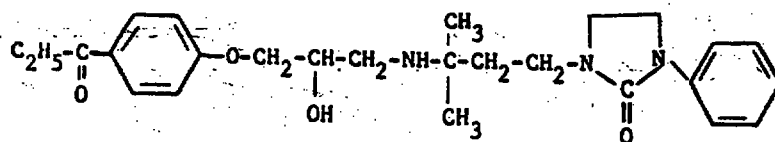
R ₁	R ₂	R ₄	Mp, °C HCl-salt
2-Br	H	H	164-167
2-OCH ₃	H	H	126-128
3-CH ₃	H	H	125-126
4-OCH ₃	H	H	116-117
2-CH ₃	H	H	148-149
R ₁	R ₂	R ₄	m.p. °C
2-OCH ₃	H	-CH ₂ -C ₆ H ₅	oil
3-CH ₃	H	-CH ₂ -C ₆ H ₅	oil
4-OCH ₃	H	-CH ₂ -C ₆ H ₅	oil
3-OCH ₃	H	-CH ₂ -C ₆ H ₅	oil
2-CH ₃	H	-CH ₂ C ₆ H ₅	oil

EXAMPLE 14

1-(3-Methoxyphenoxy)-3-[N-(1,2,3,4-tetrahydroquinol-2-yl)-propylamino]-propan-2-ol-hydrochloride (according to process a))

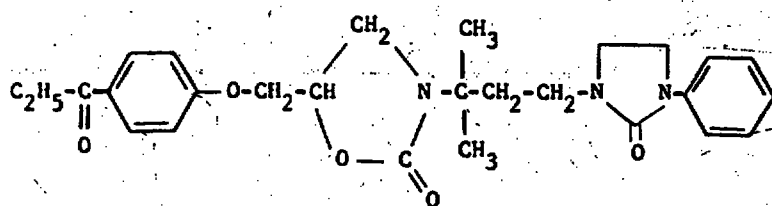
6.1 g of 1-(3-methoxyphenoxy)-3-[N-(1,2,3,4-tetrahydroquinol-2-yl)-benzylpropylamino]-propan-2-ol- are dissolved in 50 ml of methanol and hydrogenated over palladium charcoal at 60°C under 6 atmospheres. When uptake of hydrogen has finished, the catalyst is removed by suction filtration, the solvent distilled off and the residue purified over silica gel. After distilling off the solvent mixture, the uniform fractions yield a residue which is dissolved in alcoholic HCl. After addition of ether it is recrystallized from methanol. Yield: 2.7 g melting point: 122-123°C. The thin-layer chromatogram is uniform.

EXAMPLE 15



(according to process e))

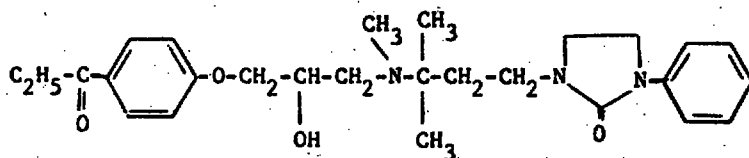
A solution of 0.5 g (0.00105 mol)



and 1.5g KOH in 20ml ethanol and 5ml water is prepared. The solution is refluxed for one hour and evaporated. The residue is mixed with 40 ml of water, acidified with 10% HCl, shaken twice with methylene chloride (40 ml). The aqueous phase is made alkaline with 10% NaOH while cooling with ice, shaken twice with 50 ml of methylene chloride, and then the methylene chloride phase is washed once with 50 ml of water, dried over Na₂SO₄, and evaporated. The residue is recrystallized from isopropanol.

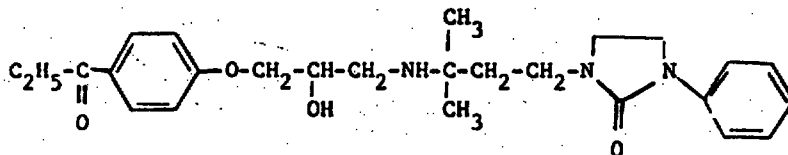
M.p. 147-149°C.

EXAMPLE 16



(according to process l))

A solution of 1.1 g (0.0024 mol)

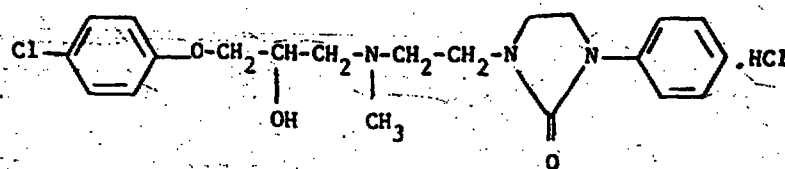


in 3 ml of formic acid and 6 ml of 30% formalin solution is prepared. This solution is refluxed for one hour on a water-bath. CO₂ evolution is observed. The reaction mixture is cooled, diluted with 30 ml of water and shaken twice with 50 ml portions of ether. The aqueous phase is made alkaline with 10% NaOH, and then extracted 3 times with 30 ml portions of ethyl acetate. The ethyl acetate phase is washed once with 20 ml of water, dried over Na₂SO₄ and evaporated.

The residue is purified over a silica gel column with a solution of 70 ml of ethyl acetate, 30 ml of isopropanol and 2.5 ml of 25% ammonia. The pure compound is dissolved in acetonitrile, acidified with alcoholic HCl, precipitated with ether, removed by suction filtration and recrystallized from acetonitrile and ether. M.p. 191-195°C.

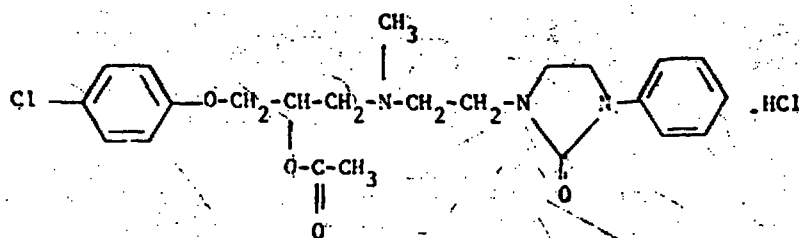
Thin-layer chromatogram: pure.

EXAMPLE 17



(according to process f))

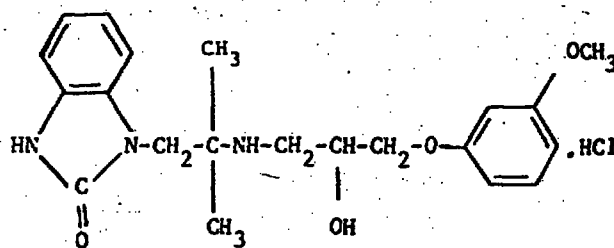
880 mg (~0.002 mol)



are dissolved in 15 cm³ of ethanol. 1 g of KOH dissolved in 3 ml of water is added and the mixture is refluxed for 1 hour. The solvent is distilled off *in vacuo*. The residue is mixed with water and shaken twice with ethyl acetate. The ethyl acetate phase is washed with water, dried over Na₂SO₄ and evaporated after filtering. The hydrochloride is recrystallized from acetonitrile by addition of ether.

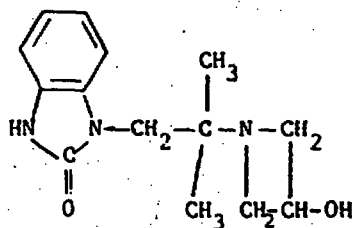
M.p. 135-137°C.

EXAMPLE 18



(according to process c))

0.7 g (~0.0025 mol)



are dissolved in 20 cm³ benzyl alcohol, then 0.4 g (~0.003 mol) of 3-methoxyphenol and 0.1 g KOH are added. The solution is then allowed to react for 5 hours at an oil-bath temperature of 140°C. The solvent is distilled off *in vacuo*. The residue is acidified in 1 N HCl and shaken twice with ethyl acetate. The water-phase is made alkaline with 1 N NaOH

and shaken twice with a little ethyl acetate. The ethyl acetate phase is dried over Na_2SO_4 and evaporated. The residue is purified over a silica gel column.

EXAMPLE 19

5 **1-(2-Aminophenoxy)-3-[3-(3-phenylimidazolidinonyl)-propyl-amino-1]-propan-2-ol** 5
(according to process n))

3 g of 1-(2-nitrophenoxy)-3-[3-(3-phenylimidazolinonyl)-propylamino-1]-propan-2-ol are dissolved in 100 ml of methanol and hydrogenated over Raney-nickel at room temperature and at normal pressure. After uptake of the theoretical quantity of hydrogen, the catalyst is removed by suction filtration and the solvent distilled off *in vacuo*. The residue is dissolved in acetonitrile and acidified with methanolic HCl. The colourless crystals separating are filtered off and dried. Yield: 1.9 g m.p. 190-192°C, t.l.c. uniform. 10

EXAMPLE 20

15 **1-(2-Cyanophenoxy)-3-[3-(3-phenylimidazolidinonyl)-propylamino-1]-propan-2-ol** (accord- 15
ing to process l))

876 mg (0.0015 mol) of 1-(2-aminophenoxy)-3-[3-(3-phenylimidazolidinonyl)-propylamino-1]-propan-2-ol dihydrochloride are dissolved in 5 ml of water. After addition of 1 ml of conc. HCl, a solution of 207 mg of NaNO_2 in 25 ml of water at 3 to 5°C is added dropwise. The homogeneous solution is stirred for 60 minutes at 20°C. Then the solution is slowly added dropwise to a hot mixture of 800 mg $\text{CuSO}_4 \cdot \text{H}_2\text{O}$, 850 mg of KCN and 5 ml of water while stirring at 80 to 90°C. When the addition is complete, the solution is made alkaline with NaOH. Resinous portions are separated and the aqueous solution is extracted with ethyl acetate. The organic phase is washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. The viscous residue is separated on a silica gel column. The uniform fractions are combined, the solvent distilled off *in vacuo* and the residue recrystallized from ethyl acetate. The colourless crystals obtained melt at 103 to 107°C. The thin-layer chromatogram is uniform, the R_f -value being identical to the substance prepared by Example 7. 20

30 Production of the intermediates of general formula X is illustrated by the following Examples. 30

EXAMPLE α

35 **1-(2-Chloroethyl)-2-(4-chlorophenyl)-imidazolidinone** 35
22.4 g (0.15 mol) of N-2-chloroethyloxazolidinone-(2) are heated with 23 g (0.15 mol) of 4-chlorophenylisocyanate in the presence of lithium chloride for 5 hours at 160-180°C. The crystals obtained on cooling are recrystallized from ethanol. Yield: 26 g m.p. 105-107°C.

40 **EXAMPLE β** 40
N-2-chloropropyl-benzimidazolone

13.2 g of N-2-hydroxypropylbenzimidazolone are dissolved in 150 ml of dioxan and, after addition of 8 ml of SOCl_2 , refluxed for one hour. After evaporation *in vacuo*, the remaining residue is dissolved in ethyl acetate, washed with bicarbonate solution and water and dried over Na_2SO_4 . After distilling off the solvent, 13.4 g of N-2-chloropropyl-benzimidazolone are obtained. 45

EXAMPLE I

50 **Tablets** 50

1-(2-cyanophenoxy)-3-[1,1-dimethyl-4-(N-benzimidazol-2-yl)-butylamino-1]-propan-2-ol . HCl 40.0 mg

55 corn starch 164.0 mg 55

sec. calcium phosphate 240.0 mg

magnesium stearate 1.0 mg

445.0 mg

45

The individual components are mixed together well and the mixture is granulated in the conventional way. The granulate is pressed into tablets of 445 mg weight, each of which contains 40 mg of active ingredient.

Tablets may also be obtained in the same way using the same quantity of the following active ingredients:-

1-(α -naphthoxy)-3-[1,1-dimethyl-3-(N-benzimidazol-2-yl)propylamino-1]-propan-2-ol hydrochloride monohydrate and 1-(*o*-tolyl-2-(benzimidazol-2-yl)-ethylamino]-propan-2-ol.

EXAMPLE II

Gelatin Capsules

Each capsule comprises:-

1-(4-hydroxyphenoxy)-3-[1,1-dimethyl-3-(3-phenylimidazolidinon-2-yl)-propylamino-1]-propan-2-ol oxalate

25.0 mg

corn starch

175.0 mg

200.0 mg

These components are mixed well and 200 mg-portions of the mixture are filled into gelatin capsules of suitable size. Each capsule contains 25 mg of the active ingredient.

EXAMPLE III

Coated Tablets having sustained release

Core

1-(α -naphthoxy)-3-[1,1-dimethyl-3-(N-benzimidazolone(2)yl)-propylamino-(1)]-propanol(2) . HCl

25.0 g

carboxymethyl cellulose (CMC)

295.0 g

stearic acid

20.0 g

cellulose acetate phthalate (CAP)

40.0 g

380.0 g

The active ingredient, CMC and stearic acid are mixed well together and the mixture is granulated in the usual way, whereby a solution of CAP in 200 ml of a mixture of ethanol/ethyl acetate is used. The granulate is then pressed into cores of 380 mg, the cores being covered in the conventional way by a sugary 5% solution of polyvinylpyrrolidone in water. Each coated tablet contains 25 mg of active ingredient.

EXAMPLE IV

Tablets

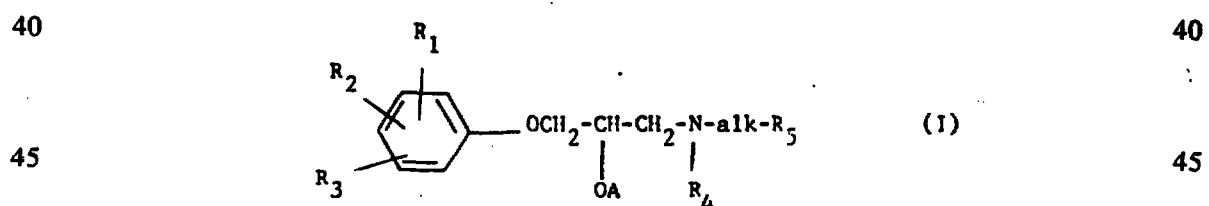
1-(α -naphthoxy)-3-[1,1-dimethyl-3-(N-benzimidazol-2-yl)-propylamino-1]-propan-2-ol : HCl			
5		35.0 g	5
2,6-bis-(diethanolamino)-4,8-dipiperidino-pyrimido-[5,4-d]-pyrimidine			
		75.0 g	
10	lactose	164.0 g	10
	corn starch	194.0 g	
	colloidal silicic acid	14.0 g	
15			15
	polyvinylpyrrolidone	6.0 g	
	magnesium stearate	2.0 g	
20	soluble starch	10.0 g	20
		500.0 g	

25 Instead of the β -adrenolytically active substance mentioned in this Example, there may be similarly used in an equal quantity the substances 1-(2,4-dichlorophenoxy)-3-[1,1-dimethyl-2-(3-phenylimidazolidon-2-yl)-ethylamino-1]-propan-2-ol and 1-(2-propargyloxyphenoxy)-3-[1,1-dimethyl-N-benzimidazol-2-yl-ethylamino-1]-propan-2-ol . HCl

30 After admixing the active ingredients thoroughly with lactose, corn starch, colloidal silicic acid and polyvinylpyrrolidone, the mixture is granulated in a conventional manner, whereby an aqueous solution of the soluble starch is used. The granulate is admixed with magnesium stearate and pressed to 1000 tablets, each of 500 mg weight, the tablets each comprise 35 mg of the first and 75 mg of the second active ingredient.

35 WHAT WE CLAIM IS:-

1. Compounds of general formula



[wherein R_1 represents a hydrogen or halogen atom, a trifluoromethyl or nitro group, a straight-chained or branched alkyl group having from 1 to 8 carbon atoms, a straight-chained or branched alkoxy group having from 1 to 4 carbon atoms, an alkoxyalkyl group having from 2 to 8 carbon atoms, an alkenyl or alkynyl group having from 2 to 5 carbon atoms, an alkenyloxy or alkynyloxy group having from 3 to 6 carbon atoms, an optionally bridged and/or unsaturated cycloalkyl or cycloalkoxy group having from 3 to 12 carbon atoms, a group of formula $-(CH_2)_x-A'$ (in which x is zero or an integer from 1 to 3 and A' represents a cyano, amino, carboxamido or hydroxy group), a group of formula $-COOR_6$ (in which R_6 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms), a C_1 to C_6 aliphatic, araliphatic or aromatic acyl, acyloxy or acylamino group, a group of formula $-NH-CO-NR_7R_8$ or $-O-CO-NR_7R_8$ (in which R_7 and R_8 , which may be the same or different, each represents a hydrogen atom, or an alkyl group or, together with the nitrogen atom to which they are attached, represent a heterocyclic group), an aryl, aryloxy or aralkoxy group (optionally substituted by one or more halogen atoms, alkyl, nitro, cyano and/or carboxyl groups), a group of formula $NH-R_9$ or $N-alkyl-R_9$ (in which R_9 represents a C_1 to C_6 alkyl group or acyl group such as a group CH_3SO_2- , $(CH_3)_2N-SO_2$ or $alkyl-O-CO-$) or a group of formula $-CONH-alkyl-$, $-CON(alkyl)_2$, $-CONH-NH_2$, $-CH_2SO_2CH_3$ or $-CO-NH-OH$;



EXAMPLE IV

Tablets

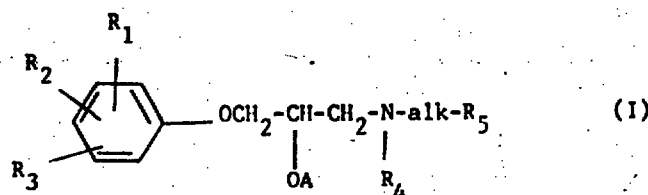
5	1-(α -naphthoxy)-3-[1,1-dimethyl-3-(N-benzimidazol-2-yl)-propylamino-1]-propan-2-ol . HCl	35.0 g	5
	2,6-bis-(diethanolamino)-4,8-dipiperidino-pyrimido-[5,4-d]-pyrimidine	75.0 g	
10	lactose	164.0 g	10
	corn starch	194.0 g	
15	colloidal silicic acid	14.0 g	15
	polyvinylpyrrolidone	6.0 g	
	magnesium stearate	2.0 g	
20	soluble starch	10.0 g	20
		500.0 g	

25 Instead of the β -adrenolytically active substance mentioned in this Example, there may be similarly used in an equal quantity the substances 1-(2,4-dichlorophenoxy)-3-[1,1-dimethyl-2-(3-phenylimidazolidon-2-yl)-ethylamino-1]-propan-2-ol and 1-(2-propargyloxyphenoxy)-3-[1,1-dimethyl-N-benzimidazol-2-yl-ethylamino-1]-propan-2-ol . HCl

30 After admixing the active ingredients thoroughly with lactose, corn starch, colloidal silicic acid and polyvinylpyrrolidone, the mixture is granulated in a conventional manner, whereby an aqueous solution of the soluble starch is used. The granulate is admixed with magnesium stearate and pressed to 1000 tablets, each of 500 mg weight, the tablets each comprise 35 mg of the first and 75 mg of the second active ingredient.

35 WHAT WE CLAIM IS:-

1. Compounds of general formula



40 [wherein R_1 represents a hydrogen or halogen atom, a trifluoromethyl or nitro group, a straight-chained or branched alkyl group having from 1 to 8 carbon atoms, a straight-
 45 chained or branched alkoxy group having from 1 to 4 carbon atoms, an alkoxyalkyl group having from 2 to 8 carbon atoms, an alkenyl or alkynyl group having from 2 to 5 carbon atoms, an alkenyloxy or alkynyloxy group having from 3 to 6 carbon atoms, an optionally bridged and/or unsaturated cycloalkyl or cycloalkoxy group having from 3 to 12 carbon atoms, a group of formula $-(\text{CH}_2)_x-\text{A}'$ (in which x is zero or an integer from 1 to 3 and A' represents a cyano, amino, carboxamido or hydroxy group), a group of formula $-\text{COOR}_6$
 50 (in which R_6 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms), a C_1 to C_6 aliphatic, araliphatic or aromatic acyl, acyloxy or acylamino group, a group of formula $-\text{NH}-\text{CO}-\text{NR}_7\text{R}_8$ or $-\text{O}-\text{CO}-\text{NR}_7\text{R}_8$ (in which R_7 and R_8 , which may be the same or different, each represents a hydrogen atom, or an alkyl group or,
 55 together with the nitrogen atom to which they are attached, represent a heterocyclic group), an aryl, aryloxy or aralkoxy group (optionally substituted by one or more halogen atoms, alkyl, nitro, cyano and/or carboxyl groups), a group of formula $\text{NH}-\text{R}_9$ or $\text{N-alkyl}-\text{R}_9$ (in which R_9 represents a C_1 to C_6 alkyl group or acyl group such as a group CH_3SO_2- , $(\text{CH}_3)_2\text{N}-\text{SO}_2$ or $\text{alkyl}-\text{O}-\text{CO}-$) or a group of formula $-\text{CONH-alkyl-CON(alkyl)}_2$, $-\text{CONH-NH}_2$, $-\text{CH}_2\text{SO}_2\text{CH}_3$ or $-\text{CO-NH-OH}$;
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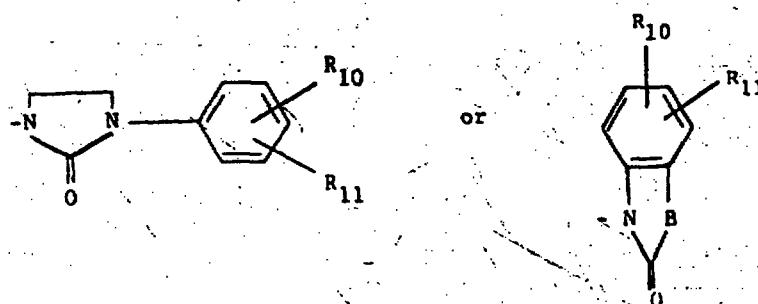
47

R_2 represents a hydrogen or a halogen atom, a straight-chained or branched alkyl or alkoxy group having from 1 to 4 carbon atoms, an aralkoxy group having from 7 to 14 carbon atoms, an alkenyl group having from 2 to 4 carbon atoms or a cyano, nitro, hydroxy or amino group; and

5 R_3 represents a hydrogen or halogen atom, a straight-chained or branched alkyl or alkoxy group having from 1 to 4 carbon atoms, an aralkoxy group having from 7 to 14 carbon atoms, or a hydroxy group; or R_2 and R_3 together represent a divalent group of formula

10 $-O-CH_2-O-$, $-O-(CH_2)_2-O-$, $-CH=CH-CH=CH-$, $-OCH_2-CONH-$, $-(CH_2)_2-CONH-$, $-CH=CH-NH-$, $-O-CO-NH-$, $-CH_2-CH=CH-CH_2-$, $-O-CH=CH-$, $-CH_2-CH_2-CH_2-$, $-O-(CH_2)_3-$, $-S-(CH_2)_3-$ or $-CO(CH_2)_3-$; R_4 represents a hydrogen atom, an alkyl group having from 1 to 5 carbon atoms or an optionally substituted aralkyl group having from 7 to 14 carbon atoms;

R_5 represents a heterocyclic group of the formula



15 [in which R_{10} and R_{11} , which may be the same or different, each represents a hydrogen or halogen atom, a straight-chained or branched alkyl or alkoxy group having from 1 to 4 carbon atoms, a trifluoromethyl or carboxamido group or a divalent group having the formula $-O-(CH_2)_y-O-$ (wherein y is 1 or 2) bonded with the two free bonds in the *ortho*-position relative to each other; and B represents a divalent group of the formula $\geq NR_{12}$ (in which R_{12} represents a hydrogen atom or a C_1 to C_6 alkyl, alkenyl, alkynyl, cycloalkyl or optionally substituted aryl group), a group $-OCH_2-$ (wherein the oxygen atom is attached to the phenyl nucleus) or a group $-(CH_2)_2$];

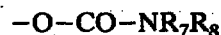
alk represents a straight-chained or branched alkylene group having from 1 to 12 carbon atoms; and

40 A represents a hydrogen atom or an acyl group or a group of formula $-CONH-$ alkyl, $-CON(alkyl)_2$, $-CONHNH_2$, $-CH_2SO_2CH_3$ or $-CONHOH$] and acid addition salts thereof.

2. Compounds as claimed in claim 1 wherein R_1 represents a group of the formula



or



50 (in which R_7 and R_8 , together with the nitrogen atom to which they are attached, form a pyrrolidino, piperidino or morpholino group), a phenyl, phenoxy or benzyloxy group.

3. Compounds as claimed in either of claims 1 and 2 wherein R_2 represents a benzyloxy group or, together with the group R_3 , forms a divalent group in which the two free bonds are bonded to the phenyl nucleus in an *ortho*-position relative to each other.

55 4. Compounds as claimed in any of the preceding claims wherein R_3 represents a benzyloxy or hydroxy group.

5. Compounds as claimed in any of the preceding claims wherein A represents an acyl group or a group of the formula $-CONH-$ alkyl, $-CON(alkyl)_2$, $-CONH-NH_2$, $-CH_2SO_2CH_3$ or $-CO-NH-OH$.

60 6. Compounds as claimed in claim 1 wherein R_1 represents a methyl, methoxy, ethyl, ethoxy, isopropyl, isopropoxy, vinyl, allyl, ethynyl, allyloxy, propargyloxy, cyclopropyl, cyclopentyl, cyclopentyloxy, adamantyl, acetyl, propionyl, butyryl or isobutyryl group, or a phenacetyl, benzoyl or naphthoyl group (optionally substituted in the aromatic nucleus by one or more halogen atoms, or C_1 to C_6 alkyl, nitro, cyano or carboxyl groups), or an



acetoxo, propionyloxy, butyryloxy or isobutyryloxy group or a phenacetoxo, benzoyloxy or naphthoyloxy group (optionally substituted in the aromatic nucleus by one or more halogen atoms or C₁ to C₆ alkyl, nitro, cyano or carboxyl groups), or a fluorine, chlorine, bromine or iodine atom.

- 5 7. Compounds as claimed in either of claims 1 and 6 wherein R₂ represents a methyl, methoxy, ethyl or ethoxy group, or, together with the group R₃, forms a 3,4-methylenedioxy group. 5
8. Compounds as claimed in any of claims 1, 6 and 7 wherein R₃ represents a methyl, methoxy, ethyl or ethoxy group.
- 10 9. Compounds as claimed in any of claims 1 and 6 to 8 wherein A represents an acetyl, propionyl, butyryl or isobutyryl group, or a phenacetyl, benzoyl or naphthoyl group (optionally substituted in the aromatic nucleus by one or more halogen atoms or C₁ to C₆ alkyl, nitro, cyano or carboxyl groups). 10
10. Compounds as claimed in any of the preceding claims wherein alk represents an ethylene, trimethylene, tetramethylene, hexamethylene, dodecamethylene, 1-methylethylene, 2-methylethylene, 1,1-dimethylethylene, 1,1-dimethylpropylene, 1,1-dimethylbutylene or 1,1,4,4-tetramethylbutylene group. 15
11. 1-(3,3-Dimethyl-3-(3-*o*-chlorophenoxy-2-hydroxypropyl)-propylamino]-3-phenylimidazolidin-2-one, and acid addition salts thereof.
- 20 12. 1-(2-Chlorophenoxy)-3-[1,1-dimethyl-3-(benzimidazolidinon-2-yl)-propylamino]-propan-2-ol, and acid addition salts thereof. 20
13. 1-[1,1-Dimethyl-3-(3-phenylimidazolidinon-2-yl)propylamino]-3-(2-methylphenoxy)-propan-2-ol, and acid addition salts thereof.
- 25 14. 1-(2-Allylphenoxy)-3-(N-benzimidazolonyl-3-propylamino)-propan-2-ol, and acid addition salts thereof. 25
15. 1-(3-Methylphenoxy)-3-(N-benzimidazolonyl-3-propylamino)-propan-2-ol, and acid addition salts thereof.
16. 1-(3-Methoxyphenoxy)-3-[1,1-dimethyl-3-(3-phenylimidazolidinonyl)propylamino]-1-propan-2-ol, and acid addition salts thereof.
- 30 17. 1-(2-Propargyloxyphenoxy)-3-[1,1-dimethyl-3-(3-phenylimidazolidinonyl)propylamino]-1-propan-2-ol, and acid addition salts thereof. 30
18. 1-(2-Acetyl-4-aminobutyrylphenoxy)-3-(3-N-benzimidazolonyl-1,1-dimethyl-1-propylamino)propan-2-ol, and acid addition salts thereof.
- 35 19. 1-(2-Chloro-5-methylphenoxy)-3-(3-N-benzimidazolonyl-1,1-dimethyl-1-propylamino)-propan-2-ol, and acid addition salts thereof. 35
20. 1-(2-Chlorophenoxy)-3-[1,1-dimethyl-3-(benzimidazolidinon-2-yl)-propylamino]-propan-2-ol, and acid addition salts thereof.
21. 1-[1,1-Dimethyl-3-(3,4-dihydro-1,4-2H-benzoxaz-3-onyl)-propylamino]-propan-2-ol, and acid addition salts thereof.
- 40 22. 1-[1,1-Dimethyl-3-(3-phenylimidazolidinon-2-yl)-propylamino]-3(3-methylphenoxy)-propan-2-ol, and acid addition salts thereof. 40
23. 1-(3-Methylphenoxy)-3-[N-(1,2,3,4-tetrahydroquinol-2-one)-1,1-dimethylpropylamino]-propan-2-ol, and acid addition salts thereof.
- 45 24. 1-(2-n-Propylphenoxy)-3-[1,1-dimethyl-3-(3-phenylimidazolidinonyl)propylamino]propan-2-ol, and acid addition salts thereof. 45
25. 1-(4-Methoxyphenoxy)-3-[1,1-dimethyl-3-(3-phenylimidazolonyl)-propylamino-1]-propan-2-ol, and acid addition salts thereof.
26. 1-(2-Allylphenoxy)-3-[1,1-dimethyl-2-(3-phenylimidazolidinonyl)ethylamino-1]-propan-2-ol, and acid addition salts thereof.
- 50 27. 1-(3-Trifluoromethylphenoxy)-3-[1,1-dimethyl-2-(3-phenylimidazolidinonyl)ethylamino-1]-propan-2-ol, and acid addition salts thereof. 50
28. 1-(Indanyloxy)-3-[1,1-dimethyl-3-(3-phenylimidazolidinonyl)-propylamino-1]-propan-2-ol, and acid addition salts thereof.
29. 1-(3,5-Dimethylphenoxy)-3-[1,1-dimethyl-3-(3-phenylimidazolidinonyl)-propylamino-1]-propan-2-ol, and acid addition salts thereof. 55
30. 1-(2-Propargyloxyphenoxy)-3-[1,1-dimethyl-3-(3-phenylimidazolidinonyl)propylamino]-1-propan-2-ol, and acid addition salts thereof.
31. 1-(3-Methoxyphenoxy)-3-[1,1-dimethyl-3-(3-phenylimidazolidinonyl)propylamino-1]propan-2-ol, and acid addition salts thereof.
- 60 32. 1-(3,5-Dimethylphenoxy)-3-[2-(3-phenylimidazolidinonyl)-ethylamino-1]propan-2-ol, and acid addition salts thereof. 60
33. 1-(3-Methylphenoxy)-3-[2-(3-phenylimidazolidinonyl)ethylamino-1]-propan-2-ol, and acid addition salts thereof.
34. 1-(3,5-Dimethylphenoxy)-3-[3-(3-phenylimidazolidinonyl)-propylamino-1]-propan-2-ol, and acid addition salts thereof. 65

36. 1-(3,5-Dimethylphenoxy)-3-[1,1-dimethyl-3-(N-benzimidazolonyl)-propylamino-1]-propan-2-ol, and acid addition salts thereof.

38. 1-(3-Methylphenoxy)-3-[1-methyl-2-(N-benzimidazolonyl)-ethylamino-1]propan-2-ol, and acid addition salts thereof.

39. 1-(2,4-Dichlorophenoxy)-3-[1-methyl-2-(N-benzimidazolonyl)-ethylamino-1]propan-2-ol, and acid addition salts thereof.

40. 1-(4-Chlorophenoxy)-3-[1,1-dimethyl-N-(1,2,3,4-tetrahydroquinolonyl)-propylamino]-propan-2-ol, and acid addition salts thereof.

41. 1-(2,6-Dichlorophenoxy-3-(N-benzimidazolonyl-3-propylamino-1)propan-2-ol, or acid addition salts thereof.

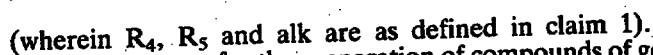
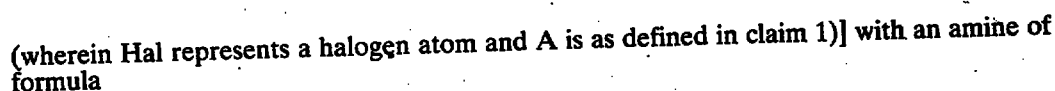
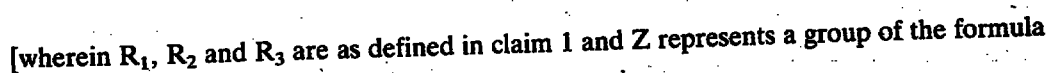
acid addition salts thereof.

43. 1-(2-Bromophenoxy)-3-(N-benzimidazolonyl-3-propylamino)-propan-2-ol, and acid addition salts thereof.

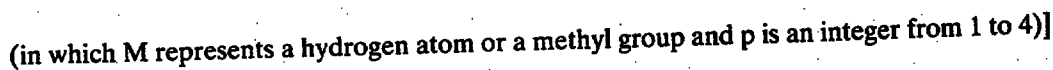
44. 1-(2,4-Dichlorophenoxy)-3-[1,1-dimethyl-2-(3-phenylimidazolidinon-2-yl) ethylamino]-1-propan-2-ol and acid addition salts thereof.

45. Compounds of general formula I and salts thereof as defined in claim 1 as herein specifically described, with the exception of the compounds claimed in claims 11 to 44

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



47. A process for the preparation of compounds of general formula I as defined in claim 1 [wherein R₄ represents a hydrogen atom and alk represents a group of the formula

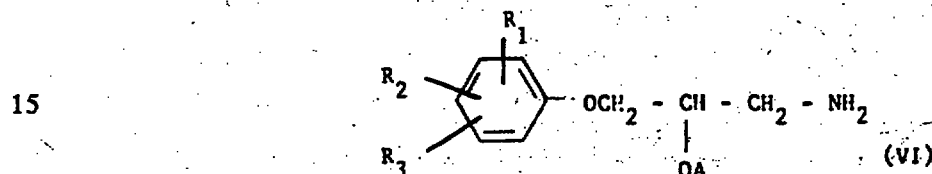




which comprises reductively aminating a compound of formula



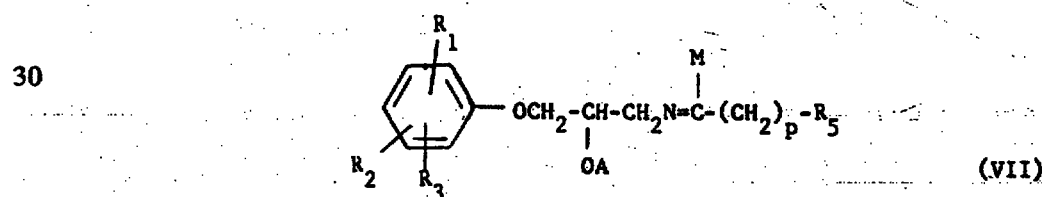
(wherein R_5 is as defined in claim 1, and M and p are as herein defined) with a compound of formula



(wherein R_1 , R_2 , R_3 and A are as defined in claim 1).

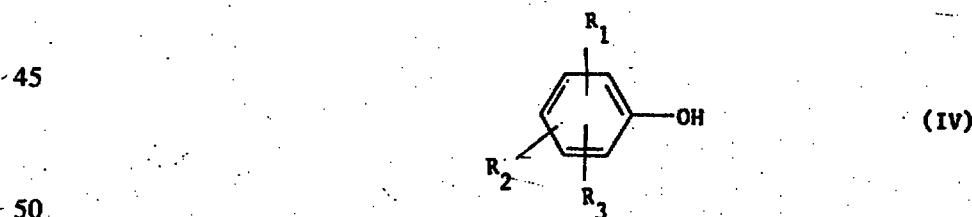
48. A process as claimed in claim 47 wherein the reductive amination is effected in the presence of a reducing agent comprising LiAlH_4 or SDMA, or under conditions of catalytic hydrogenation.

49. A process for the preparation of compounds of general formula I as defined in claim 47 which comprises reducing a compound of formula



(wherein R_1 , R_2 , R_3 , R_5 and A are as defined in claim 1 and M and p are as defined in claim 47).

50. A process for the preparation of compounds of general formula I as defined in claim 1 (wherein R_4 represents a hydrogen atom) which comprises reacting a compound of formula



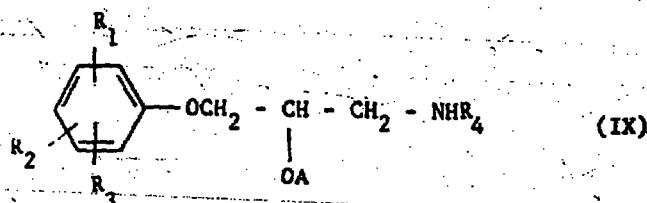
(wherein R_1 , R_2 and R_3 are as defined in claim 1) with a compound of formula



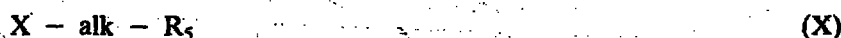
(wherein R_5 alk and A are as defined in claim 1).



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



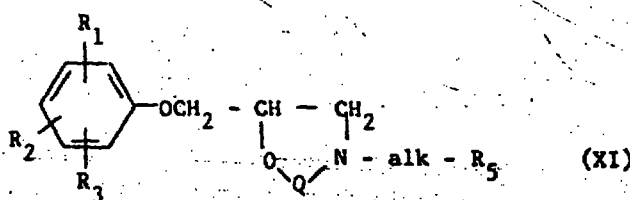
(wherein R_1 , R_2 , R_3 , R_4 and A are as defined in claim 1) with a compound of formula



(wherein R_5 and alk are as defined in claim 1 and X represents a leaving group).

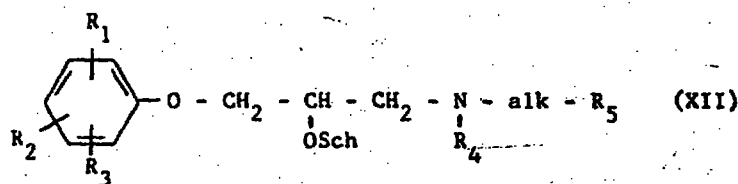
52. A process as claimed in claim 51 wherein a compound of formula X in which X represent a halogen atom or a mesyl or tosyl group is used.

53. A process for the preparation of compounds of general formula I as defined in claim 1 (in which R_4 and A each represent hydrogen atoms) which comprises hydrolytically splitting the oxazolidine ring of a compound of formula



(wherein R_1 , R_2 , R_3 , R_5 and alk are as defined in claim 1 and Q represents a $-\text{CH}_2-$ or $-\text{CO}-$ group).

54. A process for the preparation of compounds of general formula I as defined in claim 1 (wherein A represents a hydrogen atom) which comprises removing the protecting group from a compound of formula



(wherein R_1 , R_2 , R_3 , R_4 , R_5 and alk are as defined in claim 1, and Sch represents a protecting group).

55. A process as claimed in claim 54 wherein a compound in which Sch represents an acyl, benzyl or acetal group is used.

56. A process as claimed in either of claim 54 and 55 wherein the protecting group is removed hydrolytically or hydrogenolytically.

57. A process as claimed in claim 56 wherein the removal of the protecting group is affected in an aqueous alkaline or acid medium or by catalytic hydrogenation.

58. A process for the preparation of compounds of general formula I as defined in claim 1 (wherein R_1 , R_2 , R_3 and R_5 represent groups which are not affected by catalytic hydrogenation, and R_4 represents a hydrogen atom) which comprises catalytically hydrogenating a compound of formula I as defined in claim 1 (in which R_4 represents an arylmethyl group).



59. A process for the preparation of compounds of general formula I as defined in claim 1 (wherein at least one of R_1 , R_2 and R_3 represents a hydroxy group) which comprises splitting the benzyloxy group from a compound of formula I as defined in claim 1 (in which at least one of R_1 , R_2 and R_3 represents a benzyloxy group).
- 5 60. A process as claimed in claim 59 wherein splitting of the benzyloxy group is effected using a hydrohalic acid or borotrihalide, or by catalytic hydrogenation. 5
61. A process for the preparation of compounds of general formula I as defined in claim 1 (wherein R_1 represents a group of the formula $-\text{CONH}_2$, $-\text{CONH-alkyl}$, $-\text{CON-(alkyl)}_2$, $-\text{CO-NHNH}_2$ or $-\text{CONHOH}$) which comprises aminolysing a compound of formula I as defined in claim 1 (wherein R_1 represents a group of the formula $-\text{COO-alkyl}$). 10
62. A process for the preparation of compounds of general formula I as defined in claim 1 (wherein at least one of the groups R_1 , R_2 , R_3 , R_{10} and R_{11} represents a halogen atom) which comprises halogenating a compound of formula I as defined in claim 1 (wherein at least one of R_1 , R_2 , R_3 , R_{10} and R_{11} represents a hydrogen atom). 15
63. A process as claimed in claim 62 wherein the halogenation is effected using a hydrohalic acid in the presence of hydrogen peroxide. 15
64. A process for the preparation of compounds of general formula I as defined in claim 1 (wherein R_4 represents an alkyl group) which comprises alkylating a compound of formula I as defined in claim 1 (wherein R_4 represents a hydrogen atom). 20
65. A process as claimed in claim 64 wherein the alkylation is effected using an alkyl halide, alkyl mesylate or alkyl tosylate, or for the preparation of compounds wherein R_4 represents a methyl group with formaldehyde/formic acid. 20
66. A process for the preparation of compounds of general formula I as defined in claim 1 (in which R_1 represents a halogen atom or a cyano group) which comprises subjecting a compound of formula I as defined in claim 1 (wherein R_1 represents a primary amino group) to a Sandmeyer reaction. 25
67. A process for the preparation of compounds of general formula I as defined in claim 1 (wherein R_1 represents a group which may be prepared by reduction, and R_2 and R_3 are groups which are not affected by reduction) which comprises reducing a compound of formula I as defined in claim 1 (wherein R_1 represents a reducible group). 30
68. A process for the preparation of compounds of general formula I as defined in claim 1 (wherein at least one of the groups R_1 , R_2 and R_3 represents a hydroxy group) which comprises subjecting a compound of formula I as defined in claim 1 (wherein at least one of the groups R_1 , R_2 and R_3 represents a lower alkoxy group) to ether splitting. 35
69. A process as claimed in claim 68 wherein the ether splitting is effected using a concentrated hydrohalic acid. 35
70. A process as claimed in either of claims 68 and 69 wherein a compound of formula I (wherein at least one of the groups R_1 , R_2 and R_3 represents a methoxy group) is subjected to ether splitting. 40
71. A process as claimed in any of claims 46 to 70 wherein the compound of formula I produced is converted to an acid addition salt thereof. 40
72. A process as claimed in any of claims 46 to 71 wherein the compound of formula I produced is resolved into its optical isomers. 45
73. A process as claimed in claim 72 wherein optically active isomers of the compound of formula I are prepared by converting the compound of formula I into its diastereomeric salts with a suitable acid and separating the diastereomeric salts by fractional crystallization. 45
74. A process as claimed in any of claims 46 to 71 wherein an optically active isomer of a compound of formula I is produced using an optically active starting material. 50
75. A process as claimed in any of claims 46 to 74 substantially as herein disclosed. 50
76. A process for the preparation of compounds as claimed in claim 1 substantially as herein described in any of Examples 1 to 20. 50
77. Compounds of general formula I, acid addition salts and optical isomers thereof whenever prepared by a process claimed in any of claims 46 to 76. 55
78. Pharmaceutical compositions comprising as active ingredient at least one compound of formula I as defined in claim 1 or a physiologically acceptable acid addition salt thereof in association with a pharmaceutical carrier or excipient. 55
79. Compositions as claimed in claim 78 in a form suitable for oral, rectal or parenteral administration. 60
80. Compositions as claimed in claim 78 in the form of tablets, coated tablets, solutions, emulsions, powders, capsules, syrups, suppositories or forms adapted to provide sustained release of the active ingredient. 60
81. Compositions as claimed in any of claims 78 to 80 in the form of dosage units. 65
82. Compositions as claimed in claim 81 wherein each dosage unit comprises from 1 to 500 mg of the active ingredient. 65



(53)

83. Compositions as claimed in claim 81 for oral administration wherein each dosage unit comprises from 2 to 200 mg of the active ingredient.

84. Compositions as claimed in claim 81 for parenteral administration wherein each dosage unit comprises from 1 to 20 mg of active ingredient.

5 85. Compositions as claimed in any of claims 78 to 84 comprising at least one further active ingredient. 5

86. Compositions as claimed in claim 85 wherein the further active ingredient comprises a coronary dilator, cardiac glycoside, tranquillizer, vasodilator, diuretic, sympathicomimetic, hypotensive, anti-Parkinson agent or α -blocker.

10 87. Compositions as claimed in claim 78 substantially as herein described. 10

88. Pharmaceutical compositions comprising as active ingredient a compound of formula I as defined in claim 1 or a physiologically acceptable acid addition salt thereof substantially as herein described in any of Examples I to IV.

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