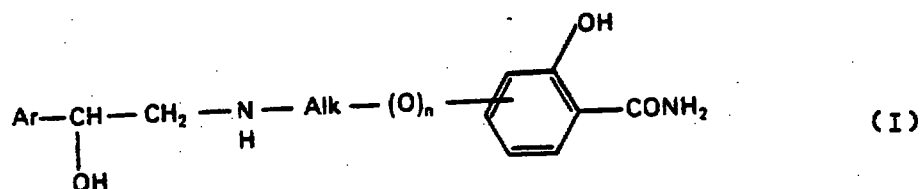


N-Alkylated aminoalcohols and salts thereof, a process for their preparation and pharmaceutical formulations containing them

The present invention relates to new N-alkylated aminoalcohols of the formula



wherein Ar denotes a radical of aromatic character which is unsubstituted or substituted by hydroxyl, n denotes the values zero or 1 and Alk denotes an alkylene radical having 2 to 5 carbon atoms, the nitrogen atom and the oxygen atom, or, if n represents zero, the phenyl radical, being separated from one another by at least two carbon atoms, and to salts thereof, processes for the preparation thereof and to pharmaceutical formulations containing such compounds and the use thereof.

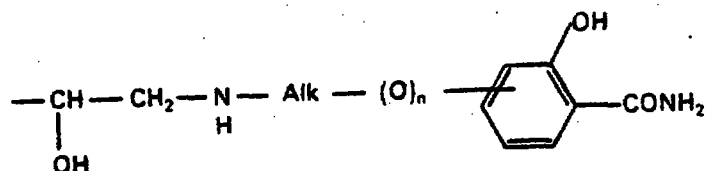
1-Phenyl-2-alkylaminoalkanes and α -aminoalkyl phenyl ketones and especially 1-phenyl-2-alkylaminoalkanols are known from German Offenlegungsschrift 2,135,678; of these the last-mentioned group of compounds differs, in respect of its chemical structure, from the compounds, according to the patent application, of the formula I essentially in the absence of the aromatic hydroxyl group present in the salicylamide group. The known substances have the property of stimulating the β -adrenergic receptors. In particular, they increase the strength of contraction of the heart muscle and can be used for curative treatment or prophylaxis of heart diseases, such as heart failure caused by congestion of blood.

A radical of aromatic character Ar is primarily a monocyclic, carbocyclic or heterocyclic radical of aromatic character having 5 to 6 ring members and not more than 3 hetero-atoms, primarily nitrogen, oxygen and/or sulfur atoms, as ring members. A radical Ar is, therefore, in particular,

phenyl and also pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, furyl, pyrrol, thienyl, oxazolyl, thiazolyl, pyrazolyl, imidazolyl or thiadiazolyl.

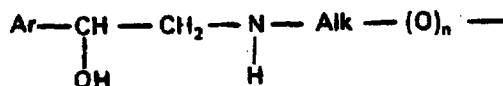
The group of the formula

5



is attached to a carbon atom in a radical Ar and can occupy any of the possible positions. In a phenyl radical substituted by the hydroxyl group, the said group is preferably in the 4-position. The radical of the formula

10



can be a substituent in the salicylamide ring in any of the possible positions.

15

Alkylene Alk can be linear or branched and is, for example, 1,2-ethylene, 1,2-, 2,3- or 1,3-propylene, 1,4-butylene, 2,4-butylene or 2-methyl-2,4-butylene, and the carbon atom attached to the nitrogen atom is preferably branched.

20

Pyridyl is 2-, 3- or 4-pyridyl; pyridazinyl is 3-pyridazinyl or 4-pyridazinyl; pyrimidinyl is 2-, 4- or 5-pyrimidinyl, while pyrazinyl represents 2-pyrazinyl. Furyl is 2-furyl or 3-furyl; pyrrol is 2-pyrrol or 3-pyrrol; thienyl is 2-thienyl or 3-thienyl, while oxazolyl represents 2-oxazolyl or 4-oxazolyl, thiazolyl represents 2-, 4- or 5-thiazolyl, pyrazolyl represents 3-pyrazolyl or 4-pyrazolyl, imidazolyl represents 2-imidazolyl or 4-imidazolyl and thiadiazolyl represents 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl or 1,3,4-thiadiazol-2-yl.

25

Salts of compounds of the formula I are primarily acid addition salts and, in particular, pharmaceutically acceptable, non-toxic acid addition salts with suitable

30

inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid or phosphoric acid, or with suitable organic aliphatic, cycloaliphatic, aromatic, araliphatic or heterocyclic carboxylic or sulfonic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycollic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, fumaric acid, pyruvic acid, benzoic acid, anthranilic acid, 4-hydroxybenzoic acid, salicylic acid, phenylacetic acid, embonic acid, methanesulfonic acid, ethanesulfonic acid, hydroxyethanesulfonic acid, ethylenesulfonic acid, 4-chlorobenzenesulfonic acid, toluenesulfonic acid, naphthalenesulfonic acid, sulfanilic acid or cyclohexylaminesulfonic acid.

Because of the close relationships between the new compounds in the free form and in the form of their salts, what is stated in this text in respect of the free compounds and their salts also applies by analogy to the corresponding salts and free compounds.

The new compounds possess valuable pharmacological properties. The main action of the new compounds consists in stimulation of cardiac β -receptors, which can be demonstrated, for example on the heart, as a positive inotropic or positive chronotropic action. Thus in concentrations from about 0.3 ng/ml an increase in the rate and strength of concentration (sic) is produced on an isolated guinea pig atrium.

The positive isotropic and chronotropic action can also be demonstrated in vivo (anaesthetised cats) in the form of an increase in the maximum rate of pressure rise in the left ventricle (dp/dt) and of the heart rate, from about 0.3 μ g/kg administered intravenously. Individual compounds display a marked preferential inotropic action in this respect. The new compounds also produce a blockade of adrenergic α -receptors, which can be demonstrated, for example from about 100 ng/ml, in the form of an inhibition of noradrenaline contraction on an isolated seminal duct of a rat. The new compounds also produce a reduction in blood pressure, which can be demonstrated from about 0.003 mg/kg after intra-

venous application to anaesthetised cats. Some of the new compounds exhibit a pronounced preferential stimulation of the β_1 -receptors of the heart compared with the β_2 -receptors in the blood vessels and trachea, and can accordingly be regarded as cardioselective β -stimulators.

The new compounds can thus be used as β -stimulators, in particular as agents having a positive inotropic action for the treatment of cardiac insufficiency, on their own or in combination with other formulations, such as for, example, heart glycosides.

It has now been found, surprisingly, that the new compounds are superior to the substances known from the German Offenlegungsschrift mentioned, 2,135,678, which are very closely related in structure, in respect of their stimulating activity on β -adrenergic receptors, as can be seen from the following comparative tests:

Test report

The following compounds were tested to determine their stimulating activity on beta-adrenergic receptors:

- I: α -[N-[2-(3-Carbamoyl-4-hydroxyphenoxy)-1-methyl-ethyl]-aminomethyl]-4-hydroxybenzyl alcohol;
- II: α -[N-[2-(4-Carbamoylphenoxy)-ethyl]-aminomethyl]-4-hydroxybenzyl alcohol; (known from Example 5 on page 17 of German Offenlegungsschrift 2,135,678);
- III: DL-Isoproterenol sulfate.
- A) Positive inotropic and chronotropic effects on an isolated guinea pig atrium.

Guinea pigs of both sexes weighing 250 - 450 g were anaesthetised intraperitoneally with urethane (1.5 g/kg), and the atria were fixed in an organ bath. A continuous registration (isometric contraction under 0.5 g of diastolic pre-tension) was made of the rate of the right atria, beating spontaneously, and of the force of contraction of the left atria, stimulated electrically at a constant rate of 2.5 Hz. The organ bath contained 50 ml of Krebs-henseliet solution at 32°C, oxygenated with a mixture of 95% of O₂ and 5% of CO₂. The substances were added cumulatively.

B) Positive inotropic and chronotropic effects and influence on the blood pressure of anaesthetised cats.

Cats of both sexes were anaesthetised with Nembutal^(R) (35 mg/kg intraperitoneally + 5 mg/kg/hour intravenously) and were vagotomised bilaterally. A microtop insertion transducer (Miller C 350/5F) was advanced through the right carotid artery into the left ventricle. The following parameters of measurement were recorded continuously: the left ventricular pressure, dp/dt in the left ventricle, the mean arterial blood pressure (right axillary artery) and the heart rate. The compounds were administered intravenously in increasing doses until the maximum effect was reached. At the end of the tests, increasing doses of DL-isoproterenol sulfate were administered intravenously until the maximum effect was reached. The maximum effects of the substances were expressed as a % of the isoproterenol maximum, and the doses for half-maximum effects (ED₅₀) were determined.

Table 1

Action on the force of contraction and rate of isolated guinea pig atria

Compound	Increase in force of contraction (= positive inotropic action)		Increase in rate (= positive chronotropic action)		Ratio of chronotropic to inotropic activity
	Activity (EC ₅₀ ; ng/mL) ¹⁾	Relative extent of the action as % of the action of isoproterenol (sic) ²⁾	Activity (EC ₅₀ ; ng/mL) ¹⁾	Relative extent of the action as % of the action of isoproterenol ²⁾	
I	0.3	100	0.1	100	3:1
II	60	85	30	75	2:1
III	1.0	100	0.7	100	1:1

1) EC₅₀ = the concentration which produces half the maximum effect,

2) the maximum effect of isoproterenol = 100%.

Table 2

Action on the maximum rate of pressure rise in the left ventricle dp/dt_{max} , heart rate and blood pressure on anaesthetised cats

Compound	Increase in dp/dt_{max}		Increase in heart rate		Reduction in blood pressure	
	Activity (ED_{50} : $\mu g/kg$ administered intravenously) ¹⁾	Relative extent of the action (% of isoproterenol)	Activity (ED_{50} : $\mu g/kg$ administered intravenously)	Relative extent of the action (% of isoproterenol)	Activity (ED_{50} : $\mu g/kg$ administered intravenously)	Relative extent of the action (% of isoproterenol)
I.	0.03	100	0.05	100	0.3	60
II.	1	100	7.5	100	~ 120	60
DL-isopro- terenol	0.07	100	0.09	100	0.04	100

1) ED_{50} = dose producing half the maximum effect;

2) maximum effect of isoproterenol = 100%.

Discussion:

A) Isolated guinea pig atria

The inotropic activity substance I, which is listed in Table 1 and can be prepared in accordance with the present application is, in conformity with the reciprocal ratio of the particular EC_{50} values, about 200 times greater than that of the comparison substance II. The extent of inotropic stimulation of substance I is greater than that of the comparison substance II and corresponds essentially to that of full stimulation caused by isoproterenol.

The chronotropic activity of compound I is about 300 times greater than that of the comparison substance II, while the extent of chronotropic stimulation is somewhat higher than that of the comparison substance II.

The comparison compound II exhibits a slightly preferential stimulation of chronotropic receptors, as can be seen from the ratio of chronotropic to inotropic activity, which is 2:1. The same applies to compound I.

20 B) Anaesthetised cats

The inotropic activity (increase in dp/dt_{max}) of substance I listed in Table 2 is about 30 times greater, and

its chronotropic activity is about 150 times greater, than those of the comparison compound II. The extent of the effects on the heart is the same for compounds I and II and corresponds to that of full stimulation caused by isoproterenol.

With the exception (sic) of isoproterenol, the doses required for reduction in blood pressure are markedly higher for compound I than the doses which have an action on the heart, which means that this compound, in contrast with isoproterenol, has a cardioselective action. The cardioselective activity of the compounds tested also expresses itself in the fact that the extent of the reduction in blood pressure achieved with this compound is less than that caused by isoproterenol.

The invention relates especially to compounds of the formula I wherein Ar denotes phenyl or pyridyl, for example 2-, 3- or 4-pyridyl, or pyridazinyl, for example 3-, 4- or 6-pyridazinyl, or pyrimidinyl, for example 2-, 4- or 5-pyrimidinyl, or pyrazinyl, for example 2-pyrazinyl, or furyl, for example 2-furyl or 3-furyl, or pyrrolyl, for example 2-pyrrolyl or 3-pyrrolyl, or thienyl, for example 2-thienyl or 3-thienyl, or oxazolyl, for example 2-oxazolyl or 4-oxazolyl, or thiazolyl, for example 2-thiazolyl or 4-thiazolyl, or pyrazolyl, for example 3-pyrazolyl or 5-pyrazolyl, or imidazolyl, for example 2-imidazolyl or 4-imidazolyl, or thiadiazolyl, such as 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl or 1,3,4-thiadiazol-2-yl, each of which is unsubstituted or substituted by 1 or 2 hydroxyl groups, and Alk denotes an alkylene radical having 2 to 4 carbon atoms, and the nitrogen atom and the oxygen atom, or, if n represents zero, the phenyl radical are separated from one another by 2 to 3 carbon atoms, and n represents zero or 1, or to salts thereof, in particular pharmaceutically acceptable, non-toxic acid addition salts thereof.

The invention relates primarily to compounds of the formula I wherein Ar denotes phenyl, 2-pyridyl, 3-pyridyl, 2-furyl, 3-furyl, 2-thienyl or 3-thienyl, each of which is

unsubstituted or substituted by 1 or 2 hydroxyl groups, and Alk denotes an alkylene radical having 2 or 3 carbon atoms, and the nitrogen atom and the oxygen atom, or, if n represents zero, the phenyl radical, are separated from one another by 2 to 3 carbon atoms, and n represents zero or 1, or to salts thereof, in particular pharmaceutically acceptable, non-toxic acid addition salts thereof:

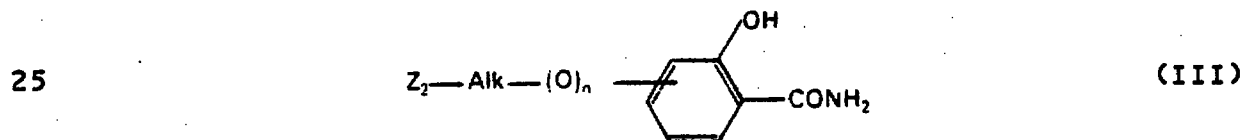
The invention also relates, in particular, to the following compounds of the formula I wherein Ar denotes phenyl, 2-pyridyl, 3-pyridyl, 2-furyl or 2-thienyl, each of which is unsubstituted or substituted by 1 or 2 hydroxyl groups, and Alk denotes an alkylene radical having 2 to 3 carbon atoms, and n represents zero or 1, or to salts thereof, in particular to pharmaceutically acceptable, non-toxic acid addition salts thereof.

The invention relates especially to the compounds of the formula I mentioned in the examples, or to salts thereof, in particular pharmaceutically acceptable, non-toxic acid addition salts thereof.

The new compounds of the formula I are prepared in a manner which is in itself known. They can be obtained, for example, by reacting a compound of the formula



with a compound of the formula



wherein one of the groups Z_1 and Z_2 represents a reactive esterified hydroxyl group and the other represents the primary amino group, and X_1 denotes hydroxyl, or wherein X_1 and Z_1 together denote the epoxy group and Z_2 represents the primary amino group, and Ar, Alk and n have the above meaning,

and/or, if desired, by converting a resulting free compound into a salt or a resulting salt into a free compound, and/or, if desired, separating a resulting mixture of isomers into the isomers or resolving a resulting racemate into its antipodes.

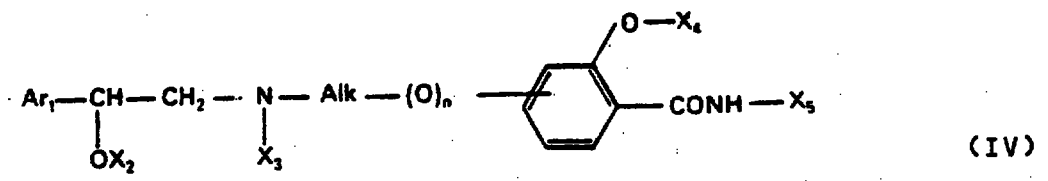
5 A reactive esterified hydroxyl group Z_1 or Z_2 is a hydroxyl group which has been esterified by a strong acid, in particular a strong inorganic acid, such as a hydrogen halide acid, in particular hydrochloric, hydrobromic or hydri-
10 odic acid, or sulfuric acid, or a strong organic acid, in particular a strong organic sulfonic acid, such as an aliphatic or aromatic sulfonic acid, for example methanesulfonic acid, 4-methylphenylsulfonic acid or 4-bromophenylsulfonic acid, and represents primarily halogen, for example chlorine,
15 bromine or iodine, or sulfonyloxy containing aliphatic or aromatic substituents, for example methylsulfonyloxy or 4-methylphenylsulfonyloxy.

The above reaction is carried out in a manner which is in itself known, being carried out, particularly if a
20 starting material containing a reactive esterified hydroxyl group is used, advantageously in the presence of a basic agent, such as an inorganic base, for example an alkali metal carbonate or hydroxide or an alkaline earth metal carbonate or hydroxide, or an organic basic agent, such as an alkali
25 metal lower alkanolate, and/or an excess of the basic reactant, and usually in the presence of a solvent or mixture of solvents, and, if necessary, with cooling or heating, for example within a temperature range from about -20°C to about $+150^{\circ}\text{C}$, in an open or closed vessel and/or in an inert gas
30 atmosphere, for example in an atmosphere of nitrogen.

Starting materials of the formula II or III are known or can be prepared in a manner which is in itself known. Thus a compound of the formula Ar-H wherein hydroxyl groups which may be present can be protected by means of a protect-
35 ive group, for example one of the groups described below, can be halogenoacetylated by the Friedel-Crafts method on a carbon atom of the radical Ar by means of a halogenoacetyl

halide, for example chloroacetyl chloride, in the presence of a suitable Lewis acid, for example aluminium chloride, and the carbonyl group in the Ar-halogenoacetyl compound thus obtainable can be reduced to the carbinol group, for example by treatment with a suitable hydride reducing agent; if desired, a halogen Z₁ can be converted into the primary amino group Z₁, for example by treatment with ammonia or a suitable derivative thereof, such as hexamethylenetetramine, and decomposition of the resulting compound with dilute mineral acid, or by reaction with an alkali metal salt of phthalimide and scission of the resulting N-phthalimide compound, for example by means of hydrazine. Starting materials of the formula II wherein X₁ and Z₁ together denote epoxy can be obtained, for example, by cyclising a compound of the formula II wherein H₁ (sic) represents hydroxyl and Z₁ represents a reactive esterified hydroxyl group, for instance chlorine or methanesulfonyloxy, by means of alkaline reagents, for example a mixture of dilute sodium hydroxide solution and tetrabutylammonium chloride in a suitable solvent, for example methylene chloride. Starting materials of the formula III can be obtained, for example, by reacting a hydroxysalicylamide with a dihalogenoalkane corresponding to the meaning of Alk, for example a chlorobromoalkane or dibromoalkane, in the presence of an alkaline condensation agent, such as an alkali metal carbonate. These reactions are carried out in a customary manner, protective groups attached to the hydroxyl groups being split off at the same time or as described below.

The compounds of the formula I can also be prepared by a process in which, in a compound of the formula



wherein Ar₁ has the meaning of Ar or denotes a radical Ar which is substituted by 1 or 2 groups which can be converted

into hydroxyl, X_2 , X_3 and X_4 each denote hydrogen or a substituent which can be replaced by hydrogen, and X_5 represents hydrogen, or X_2 and X_3 and/or X_4 and X_5 together denote a divalent radical which can be replaced by two hydrogen atoms, subject to the proviso that at least one of the radicals X_2 , X_3 and X_4 is other than hydrogen, or at least Ar_1 denotes a radical Ar which is substituted by 1 or 2 groups which can be converted into hydroxyl, or at least X_2 and X_3 together, or X_4 and X_5 together, represent a divalent radical which can be replaced by two hydrogen atoms, or in a salt thereof, the groups X_2 , X_3 and X_4 , or X_4 and X_5 together, which are other than hydrogen are replaced by hydrogen, and/or substituted hydroxyl present in a radical Ar_1 is converted into free hydroxyl, and, if desired, the additional process stages are carried out.

The removal of the groups X_2 , X_3 or X_4 or X_2 and X_3 together, or X_4 and X_5 together, respectively, and of the hydroxyl substituent present in a radical Ar_1 , is effected by means of solvolysis, such as hydrolysis, alcoholysis or acidolysis, or by means of reduction, including hydrogenolysis.

A particularly suitable removable group X_3 and X_4 and also hydroxyl protective groups in a radical Ar_1 is primarily an α -aryl-lower alkyl group which can be removed by hydrogenolysis, such as an optionally substituted 1-phenyl-lower alkyl or 1-phenyl-lower alkyl group wherein substituents, particularly in the phenyl moiety, can be, for example, lower alkyl, such as methyl, or lower alkoxy, such as methoxy, and is primarily benzyl. A group X_3 , and especially X_2 and X_4 , and also hydroxyl protective groups in a radical Ar_1 , can also represent a radical which can be removed by solvolysis, such as hydrolysis or acidolysis, and also by reduction, including hydrogenolysis, in particular an appropriate acyl radical, such as the acyl radical of an organic carboxylic acid, for example lower alkanoyl, such as acetyl, or aroyl, such as benzoyl, and also the acyl radical of a half-ester of carbonic acid, such as lower alkoxycarbonyl, for example methoxycarbonyl, ethoxycarbonyl or tert.-butoxy-

carbonyl, 2-halogeno-lower alkoxy carbonyl, for example 2,2,2-trichloroethoxycarbonyl or 2-iodoethoxycarbonyl, optionally substituted 1-phenyl-lower alkoxy carbonyl, for example benzyl-oxycarbonyl or diphenylmethoxycarbonyl, or aroyl methoxycarbonyl, for example phenacyloxycarbonyl, and also an optionally substituted 1-polyphenol-lower alkyl group in which substituents, primarily in the phenyl moiety, have, for example, the meaning given above, and can also represent primarily trityl.

- 10 A removable radical formed jointly by X_2 and X_3 and/or X_4 and X_5 is primarily a group which can be removed by hydrogenolysis, such as optionally substituted 1-phenyl-lower alkylidene, wherein substituents, especially in the phenyl moiety, can be, for example, lower alkyl or lower alkoxy, and especially benzylidene, and also groups which can be removed by solvolysis, in particular hydrolysis, such as lower alkylidene, for example methylene or isopropylidene, or 1-phenyl-lower alkylidene in which the phenyl moiety is optionally substituted by lower alkyl, such as methyl, or lower alkoxy, such as methoxy, and especially benzylidene or cycloalkylidene, for example cyclopentylidene or cyclohexylidene.
- 15
- 20

25 Starting materials which can be used in the form of salts are used primarily in the form of acid addition salts, for example salts with mineral acids and also with organic acids.

- 30 Radicals X_2 , X_3 and/or X_4 which can be removed by hydrogenolysis, in particular optionally substituted 1-phenyl-lower alkyl groups, and also suitable acyl groups, such as optionally substituted 1-phenyl-lower alkoxy carbonyl, and also optionally substituted 1-phenyl-lower alkylidene groups which are jointly formed by the groups X_2 and X_3 and X_4 and X_5 , and also hydroxyl protective groups of this type present in a radical Ar_1 , can be removed by treatment with catalytically activated hydrogen, for example with hydrogen in the presence of a nickel catalyst, such as Raney nickel, or a suitable noble metal catalyst.
- 35

Groups X_2 , X_3 and/or X_4 which can be removed by

hydrolysis, such as acyl radicals of organic carboxylic acids, for example lower alkanoyl, and half-esters of carbonic acid, for example lower alkoxycarbonyl, and also, for example, tri-
5 tyl radicals, and lower alkylidene, 1-phenyl-lower alkyl-
 idene or cycloalkylidene groups which are jointly formed by
 the radicals X_2 and X_3 and/or X_4 and X_5 , and also hydroxyl
 protective groups of this type present in a radical Ar_1 can,
 depending on the nature of such radicals, be removed by
10 treatment with water under acid or basic conditions, for
 example in the presence of a mineral acid, such as hydro-
 chloric or sulfuric acid, or of an alkali metal hydroxide
 or carbonate or an alkaline earth metal hydroxide or carbonate
 or an amine, such as isopropylamine.

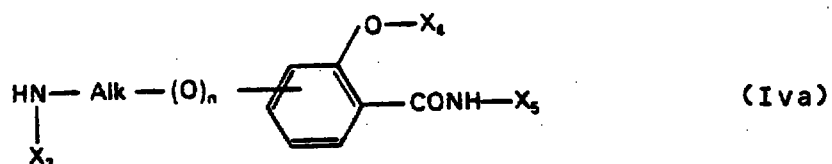
 Radicals X_2 , X_3 and/or X_4 , and/or hydroxyl protec-
15 tive groups in a radical Ar_1 , which can be removed by acid-
 olysis are, in particular, certain acyl radicals of half-
 esters of carbonic acid, such as, for example, tert.-lower
 alkoxycarbonyl or optionally substituted diphenylmethoxy-
 carbonyl radicals, and also tert.-lower alkyl radicals;
20 these can be removed by treatment with suitable strong orga-
 nic carboxylic acids, such as lower alkanecarboxylic acids
 which are optionally substituted by halogen, in particular
 fluorine, primarily trifluoroacetic acid (if necessary in
 the presence of an activating agent, such as anisole), and
25 also with formic acid.

 Radicals X_2 , X_3 and/or X_4 , and/or hydroxyl protec-
 tive groups in a radical Ar_1 , which can be removed by reduc-
 tion are also understood to mean groups which are removed by
 treatment with a chemical reducing agent (in particular a
30 reducing metal or a reducing metal compound). Such radicals
 are, in particular, 2-halogeno-lower alkoxycarbonyl or aryl-
 methoxycarbonyl, which can be removed, for example, by treat-
 ment with a reducing heavy metal, such as zinc, or with a
 reducing heavy metal salt, such as a chromium-(II) salt, for
35 example chromium chloride or acetate, usually in the presence
 of an organic carboxylic acid, such as formic acid or acetic
 acid, and water.

Protective groups attached to hydroxyl groups which are optionally present in a radical Ar_1 correspond to the groups mentioned above which can be removed and replaced by hydrogen by means of the methods described, groups of this type being removed in the course of the process described, simultaneously with other groups, or subsequently in a separate process step.

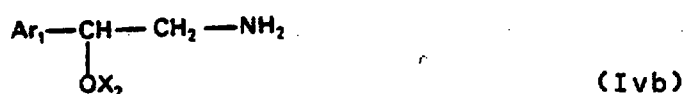
The above reactions are usually carried out in the presence of a solvent or solvent mixture, it being also possible for suitable reactants to function as the latter at the same time, and are carried out, if necessary, with cooling or heating, for example in an open or closed vessel and/or in an atmosphere of an inert gas, for example nitrogen.

The starting materials of the formula Iv can be obtained in a manner which is in itself known by reacting a compound of the formula Ar_1-H with a halogenoacetyl halide, for example chloroacetyl chloride, in the presence of a suitable Lewis acid, for example aluminium chloride, by the Friedel-Crafts process, reducing the carbonyl group in the Ar_1 -halogenoacetyl compound thus obtained, or obtained in another, customary manner, to give the carbinol group, for example by means of sodium borohydride, and reacting the resulting compound with an amine of the formula

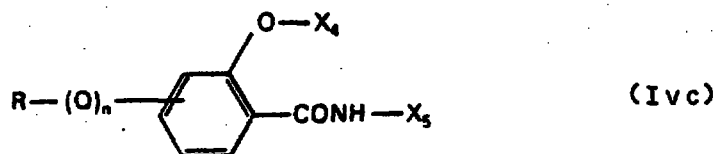


wherein X_3 has the meaning indicated and X_4 or X_4 and X_5 together are other than hydrogen.

It is also possible, for example, to reduce, by means of a borohydride, for instance sodium borohydride, the Schiff's base formed by reacting a compound of the formula

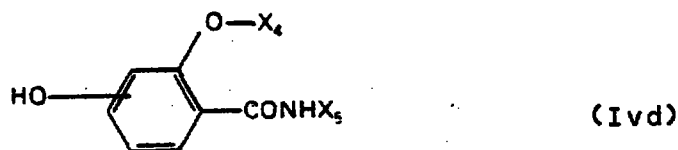


with a carbonyl compound of the formula



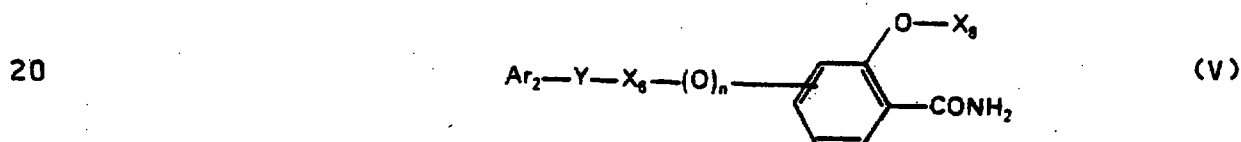
wherein R denotes an alkyl radical corresponding to the alkyl-
ene radical Alk and containing a carbonyl grouping which is
5 separated from the oxygen atom or the phenyl radical by at
least one carbon atom, and X₄ or X₄ and X₅ together denote
one of the protective groups indicated, to give the compound
of the formula IV. The reduction can also be effected by
means of activated hydrogen in the presence of a hydrogen-
10 ation catalyst, for example a platinum-on-charcoal catalyst.

Carbonyl compounds of the formula (Ivc) can, in turn,
be obtained in a customary manner by reacting a compound of
the formula



15 with a compound of the formula R-Hal (Ive) wherein R has the
above meaning, and a compound (Ive) represents, for example,
a halogenoketone, for example chloroacetone.

The new compounds of the formula I can also be ob-
tained by a procedure in which, in a compound of the formula



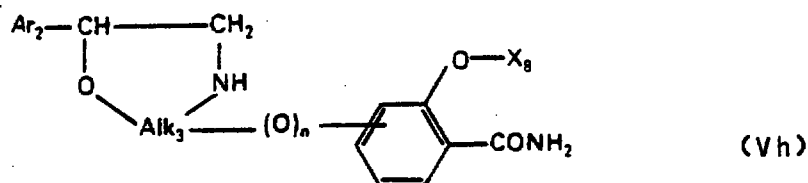
20 wherein X₆ is a reduceable group of the formulae
-CH=N-Alk-(Va) or -CH₂-N=Alk₁-(Vb) or -C(=X₇)-N(X₈)-Alk-(Vc)
or -CH₂-N(X₈)-C(=X₇)-Alk₂-(Vd) or a group -CH₂-N(X₈)-Alk-
(Ve), in which Alk₁ represents the alkyl-ylidene radical cor-
25 responding to a radical Alk and Alk₂ corresponds to a radical

Alk which has been shortened by a methylene group attached to the nitrogen atom, X_7 represents the oxo or thioxo radical and X_8 represents hydrogen or a radical which can be replaced by hydrogen under the conditions for the reduction of X_6 and/or Y, and Y represents a radical of the formula -CO-
5 (Vf) or -CH(OX_8)-(Vg) in which X_8 has the meaning indicated above, Ar_2 corresponds to a radical Ar, but, if appropriate, carries, instead of one or two hydroxyl groups, one or two groups OX_8 in which X_8 has the meaning indicated above, and n denotes zero or 1, X_6 being in all cases a reduceable
10 group Va to Vd and/or Y being a carbonyl group Vf, this/these group(s) is/are reduced and, in the same operation, the groups X_8 other than hydrogen are replaced by hydrogen and, if desired, the additional process stages are carried out.

A group X_8 which can be removed by hydrogenolysis is
15 primarily an α -aryl-lower alkyl group, such as an optionally substituted 1-phenyl-lower alkyl group wherein there can be substituents, for example lower alkoxy, such as methoxy, and is very particularly benzyl.

Protective groups attached to the optionally substituted hydroxyl groups ... (sic) the radical Ar_2 correspond
20 to those mentioned above for X_8 and to the groups which can be removed and replaced by hydrogen by means of the methods described, such groups being removed in the course of the process described simultaneously with other groups or subsequently in a separate process step.
25

Starting materials of the formula V containing a group X_6 of the formula Vb can also exist in the isomeric form of ring tautomers of the formula



30 wherein Alk_3 corresponds to the meaning of Alk_1 and the oxygen and nitrogen atom are attached to the same carbon atom.

An alkyl-ylidene group Alk_1 is, for example, methine

or acethyl-ylidene (sic), while an alkylidene group Alk_2 represents, for example, methylene, ethylidene or 1-methylethylidene.

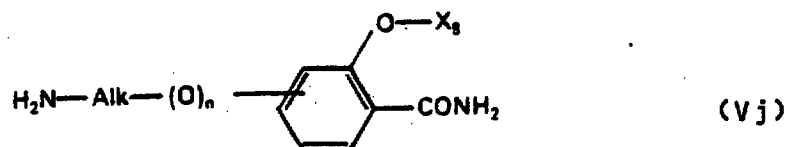
5 The reduction of the nitrogen-carbon double bond in starting materials of the formula V containing, as X_6 , a group Va or Vb, while Ar_2 , Y, X_8 and n have the meaning indicated under formula V (or, in the isomeric compounds of the formula Vg, the oxygen-carbon-nitrogen bond) to give a nitrogen-carbon single bond can be effected in a manner which is
10 in itself known, for example by treatment with catalytically activated hydrogen, such as hydrogen in the presence of a suitable hydrogenation catalyst, for example a nickel, platinum or palladium catalyst, in the course of which groups X_8 which can be removed by hydrogenolysis are at the same
15 time removed and replaced by hydrogen; or the reaction is carried out with a suitable hydride reducing agent, such as an alkali metal borohydride, for example sodium borohydride. In all cases a carbonyl radical Y, if present, is also reduced to give the hydroxymethylene radical at the same time
20 as the group Va or Vb, and, if hydride reducing agents are used, it is also possible for acyl radicals of carboxylic acids, such as, for example, acetic acid, which are attached to oxygen to be present in the form of radicals X_8 and to be removed in the same operation.

25 The reduction of the carbonyl group Y in starting materials of the general formula V containing a group Ve as the radical X_6 , while Ar_2 , X_8 and n have the meaning indicated under the formula V, can be effected in the manner indicated above for the reduction of the groups Va and Vb,
30 and it is again possible for corresponding radicals X_8 to be removed by hydrogenolysis in the course of the catalytic hydrogenation.

Hydride reducing agents, such as, for example, sodium borohydride or diborane, are particularly suitable for the
35 reduction of compounds of the formula V containing a group of the formula Ve or Vd and the conditions applying to Ar_2 , Y and n which are defined under the formula V.

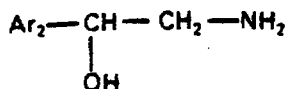
The reduction of a carbonyl group Y, if this group is present, and also the removal, as radicals X₈, of acyl radicals of carboxylic acids, such as, for example, acetic acid, attached to oxygen, takes place at the same time as the reduction of a group Vc or Vd. On the other hand, care must be taken, by limiting the amount of reducing agent and by suitable choice of the reduction conditions, that the aromatically linked carboxamide group is not reduced. Group-
 5 ings of the formulae Ve and Vd wherein X₇ denotes in each case a thioxo group are converted into the grouping of the formula -CH₂-NH-Alk- by reductive desulfurisation, for example by treatment with a hydrogenation catalyst, such as Raney nickel. The above reduction reactions are carried out in a manner which is in itself known, usually in the presence
 10 of an inert solvent and, if necessary, with cooling or heating, for example within a temperature range from about -20°C to about +150°C, and/or in a closed vessel under pressure and/or in an atmosphere of an inert gas, for example nitrogen.

A starting material of the formula V can be prepared in a manner which is in itself known, if appropriate in situ, that is to say under the conditions of the process described. Thus it is possible to acetylate a compound of the formula Ar₂-H (Vi) with a halide or anhydride of acetic acid in the
 20 presence of a Lewis acid and then to convert the acetyl group in the resulting intermediate product into the glyoxyl-
 25 oyl group, for example by treatment with a suitable oxidising agent, such as selenium dioxide. A glyoxyl compound of this type or, if desired, a suitable derivative thereof, for instance an acetal, can then be reacted with an amine of the
 30 formula



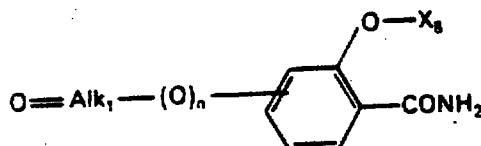
to give a starting product of the formula V containing the

group X_6 of the formula Va wherein Y represents the carbonyl group. It is also possible to halogenoacetylate a compound of the formula (Vi) with a halogenoacetyl halide, for example chloroacetyl chloride, by the Friedel-Crafts method, in the presence of a suitable Lewis acid, for example aluminium chloride, to give the corresponding Ar_2 -chloroacetyl compound, to reduce the carbonyl group in the halogenoacetyl compound obtainable thus or in another manner, to give the carbinol group by treatment with a suitable hydride reducing agent, and to convert the halogen atom into the primary amino group by treatment with ammonia or a suitable derivative thereof, such as hexamethylenetetramine, and decomposition of the resulting reaction product with dilute acid, for example aqueous hydrochloric acid. By reacting the intermediate product thus obtainable of the formula



(Vk)

with a carbonyl compound of the formula

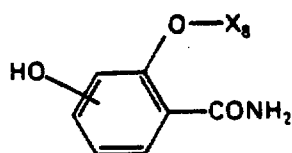


(Vl)

it is possible to obtain starting materials of the formula V containing a group X_6 of the formula (Vb). A modification of these reactions consists in a procedure in which the halogen atom in the intermediate product described above, instead of being replaced by the primary amino group by treatment with ammonia etc., is replaced, by treatment with a 1-aryl-lower alkylamine, for example benzylamine, or a di-(1-aryl-lower alkyl)-amine, for example dibenzylamine, by the corresponding 1-aryl-lower alkylamino or di-(1-aryl-lower alkyl)-amino group, and the resulting compound, for instance the corresponding dibenzylamino compound, is reacted with the oxo compound of the formula (Vl) under the reducing conditions

of the process. The reducing agent used in this modification is primarily catalytically activated hydrogen, for example hydrogen in the presence of a heavy metal hydrogenation catalyst or a mixture of such catalysts, such as palladium catalyst and/or platinum catalyst. Under such reaction conditions, groups X_8 which can be removed by hydrogenolysis, for example benzyl groups, are removed, a carbonyl group which may be present is reduced to give the carbinol group and at the same time the nitrogen-carbon double bond is reduced to give the corresponding nitrogen-carbon single bond.

Oxo compounds of the formula (VI) wherein n represents 1, are in turn obtainable, for example, by reacting a dihydroxy compound of the formula



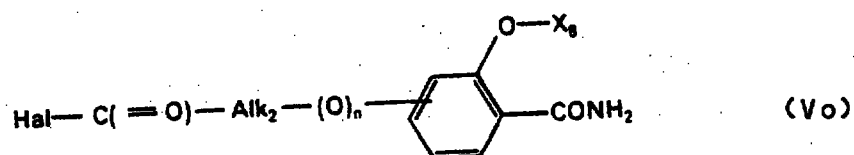
(Vm)

with a halogenoalkanone compound of the formula R-Hal mentioned above (Ive), for example chloroacetone, in the presence of an alkaline condensation agent, for instance potassium carbonate, or an organic base, such as triethylamine.

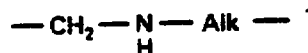
Starting materials of the formula V containing a group X_6 of the formulae Vc or Vd can be prepared in a manner in itself known, for example by reacting a formyl compound of the formula Ar_2-CHO (Vn) with hydrogen cyanide and hydrolysing, for example under acid conditions, the cyano group in the cyanohydrin intermediate product thus obtained, to give the carboxyl group. The Ar_2-2 -hydroxyacetic acid obtained in this manner or via the intermediate stages of imide-chloride, imido-lower alkyl ester and lower alkyl ester, is then reacted with an amine of the formula (Vj) in the presence of a suitable condensation agent, for example a carbodiimide, such as dicyclohexylcarbodiimide, whereupon a starting material of the formula V containing the group X_6 of the formula (Vc) is obtained.

Furthermore, by reacting a compound of the formula

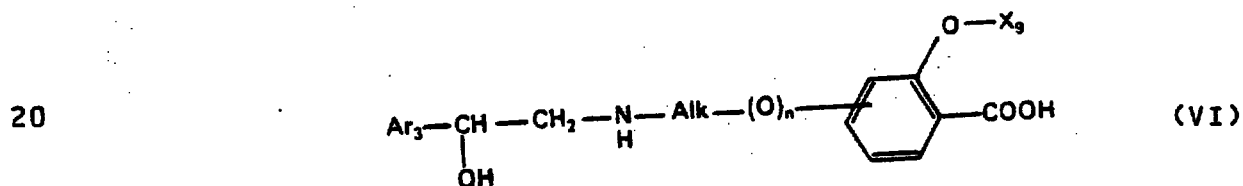
Vk with a compound of the formula



wherein Hal represents halogen and, in particular, chlorine, it is possible to obtain a starting material of the formula (V) containing the group X_6 of the formula (Vd). It is also possible to replace the chlorine in the Ar_2 -chloroacetyl compound indicated above by the primary amino group, for instance by reaction with hexamethylenetetramine, and to react a compound thus obtained with a halogeno compound of the formula (Vo). In a starting material of the formula V thus obtained, containing a group X_6 of the formula Vd and wherein Y represents the carbonyl group, it is possible to reduce simultaneously, for example by means of a hydride reducing agent, in particular diborane, the carbonyl group to give the carbinol group and the aliphatically linked carbamoyl group to give the group of the formula



The new compounds of the formula I can also be obtained by reacting, with ammonia, a compound of the formula



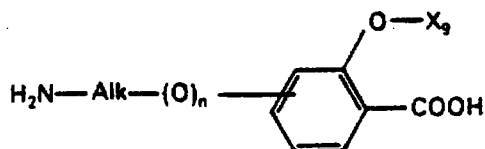
wherein Ar_3 has the meaning of Ar or represents a radical Ar which is substituted by 1 or 2 groups which can be converted into hydroxyl by ammonolysis, and X_9 denotes hydrogen or a group which can be removed by ammonolysis, or a reactive derivative of one of the carboxylic acids defined in formula VI, and at the same time removing, and replacing by hydrogen, radicals X_9 which may be present.

Radicals X_2 which can be removed by hydrolysis and, in particular, by ammonolysis are acyl radicals of organic carboxylic acids, for example aroyl, such as benzoyl, or lower alkanoyl, such as acetyl.

5 Examples of reactive derivatives of the carboxylic acids defined in formula VI are the halides, such as the chlorides or bromides, and also the azides and acid anhydrides, in particular mixed acid anhydrides with, for example, lower alkanecarboxylic acids, such as acetic or propionic
10 acid, or lower alkoxyalkanecarboxylic acids, such as 2-methoxyacetic acid. Reactive derivatives of the formula VI are, in particular, esters, for example esters with lower alkanols, such as methanol, ethanol, isopropanol and tert.-butanol, and also with aryl-lower alkanols, for example benzyl alcohol
15 which is optionally substituted by lower alkyl, for example methyl, or lower alkoxy, for example methoxy, or phenols which are optionally activated by suitable substituents, for example by halogen, for instance 4-halogen, such as 4-chlorine, lower alkoxy, for instance 4-lower alkoxy, such
20 as 4-methoxy, 4-nitro or 2,4-dinitro, such as, for instance, 4-chlorophenol, 4-methoxyphenol, 4-nitrophenol or 2,4-dinitrophenol, and also with cycloalkanols, such as, for instance, cyclopentanol or cyclohexanol, which can, if appropriate, be substituted by lower alkyl, for example methyl.
25 The reaction is carried out in a manner which is in itself known, usually in the presence of an inert solvent, for example within a temperature range from about -10° to $+50^{\circ}\text{C}$ and in a closed vessel.

30 The starting materials of the formula VI can be prepared in a manner which is in itself known by brominating a compound of the formula $\text{Ar}_3\text{-COCH}_3$, reducing, for example by means of diborane, the carbonyl group in the Ar_3 -halogenoacetyl compound thus obtained to give the carbinol group, and reacting the latter with an amine of the formula

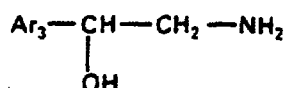
35



(VIa)

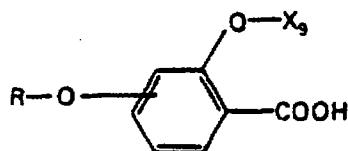
wherein X_9 has the meaning indicated, or with a reactive derivative thereof. It is also possible to react the Ar_3 -halogenoacetyl compound with the amine of the formula VIa and subsequently to convert the carbonyl group into the carbinol group.

It is also possible to reduce, by means of a borohydride, for instance sodium borohydride, the Schiff's base formed by reacting a compound of the formula



(VIb)

with a carbonyl compound of the formula

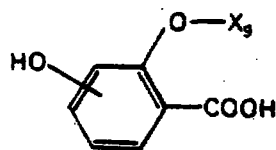


(VIc)

wherein R corresponds to the alkyl radical corresponding to an alkylene radical Alk and containing a carbonyl group.

The reduction can also be effected by means of activated hydrogen in the presence of a hydrogenation catalyst, for example a platinum-on-charcoal catalyst.

Carbonyl compounds of the formula (VIc) wherein n denotes 1 can, in turn, be obtained in a manner which is in itself known by reacting a compound of the formula



with a compound of the formula R-Hal (Ive) wherein Hal represents halogen, in particular chlorine.

Depending on the process conditions and the starting materials, the new compounds are obtained in the free form or in the form, which is also embraced by the invention, of their salts, it being also possible for the new compounds or salts thereof to exist as hemihydrates, monohydrates, sesqui-

hydrates or polyhydrates thereof. Acid addition salts of the new compounds can be converted into the free compounds in a manner which is in itself known, for example by treatment with basic agents, such as alkali metal hydroxides, carbonates of bicarbonates or ion exchangers. On the other hand, resulting free bases can form acid addition salts with organic or inorganic acids, for example with the acids mentioned, the acids used for the preparation thereof being, in particular, those which are suitable for the formation of pharmaceutically acceptable salts.

These or other salts, in particular acid addition salts of the new compounds, such as, for example, oxalates or perchlorates, can also be used to purify the free bases obtained, by converting the free bases into salts, separating off the latter and purifying them and liberating the bases again from the salts.

Depending on the choice of starting materials and procedures, the new compounds can be in the form of optical antipodes or racemates or, if they contain at least two asymmetric carbon atoms, also in the form of mixtures of racemates. The starting materials can also be employed in the form of optical antipodes.

Resulting mixtures of racemates can be separated into the two stereoisomeric (diastereomeric) racemates on the basis of the physico-chemical differences between the diastereoisomers, in a known manner, for example by chromatography and/or fractional crystallisation.

Resulting racemates can be resolved into the antipodes by methods which are in themselves known, for example by recrystallisation from an optically active solvent, by treatment with suitable microorganisms or by reaction with an optically active substance, in particular acids, which form salts with the racemic compound and separation, for example on the basis of different solubilities, of the mixture of salts obtained in this manner, into the diastereomeric salts, from which the free antipodes can be liberated by the action of suitable agents. Examples of optically active

acids which are particularly customary are the D- and L-forms of tartaric acid, di-o-toluytl tartaric acid, malic acid, mandelic acid, camphorsulfonic acid, glutamic acid, aspartic acid or quinic acid. It is advantageous to isolate
5 the more active of the two antipodes.

The invention also relates to embodiments of the process in which a compound which can be obtained as an intermediate product at any stage of the process is used as the starting material and the missing process stages are
10 carried out, or the process is discontinued at any stage, or in which a starting material is formed under the reaction conditions, or in which a reaction component is optionally present in the form of its salts.

For carrying out the reactions according to the invention it is preferable to use starting materials which lead to the groups of final substances specially mentioned at the outset and, in particular, to the final substances which have been specially described or singled out.
15

The starting materials are known or, if they are new, can be obtained by methods which are in themselves known, as above, for example analogously to the methods described in the Examples.
20

The new compounds can be used, for example, in the form of pharmaceutical formulations containing a pharmacologically effective amount of the active substance, if
25 appropriate together with pharmaceutically usable excipients which are suitable for enteral administration, for example oral or parenteral administration and can be inorganic or organic and solid or liquid. Thus tablets or gelatine capsules containing the active compound together with diluents,
30 for example lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycerol and/or lubricants, for example silica, talc or stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol, are used. Tablets can also contain binders, for example magnesium aluminium silicate, starches, such as maize, wheat, rice or arrowroot starch, gelatine, tragacanth,
35

5 methylcellulose, sodium carboxymethylcellulose and/or poly-
vinylpyrrolidone, and, if desired, disintegrators, for ex-
ample starches, agar or alginic acid or a salt thereof,
such as sodium alginate, and/or effervescent mixtures or
10 adsorbents, dyestuffs, flavouring substances and sweeteners.
It is also possible to use the new pharmacologically active
compounds in the form of formulations which can be adminis-
tered parenterally or in fusion solutions. Such solutions
are preferably isotonic aqueous solutions or suspensions,
15 it being possible, for example in the case of lyophilised
formulations containing the active substance on its own or
together with an excipient, for example mannitol, to prepare
this (sic) before use. The pharmaceutical formulations can
be sterilised and/or can contain auxiliary substances, for
20 example preservatives, stabilisers, wetting agents and/or
emulsifiers, solubilisers, salts for regulating the osmotic
pressure and/or buffers. The present pharmaceutical formu-
lations, which, if desired, can contain further pharmacolo-
gically active substances, are prepared in a manner which
25 is in itself known, for example by conventional mixing,
granulating, tablet-coating, dissolving or lyophilising
processes, and contain from about 0.1% to 100%, in particu-
lar from about 1% to about 50%, of lyophilisates up to 100%
of the active compound.

25 The dosage can depend on various factors, such as
the mode of application, the species, the age and/or the
individual condition. Thus the doses to be administered
daily in the case of oral administration to warm-blooded
animals of about 70 kg are preferably between about 0.005
30 and 0.1 g.

The following examples serve to illustrate the in-
vention. Temperatures are quoted in degrees Centigrade.
Example 1

35 100 ml of isopropylamine are added to a solution of
40 g of crude χ -[N-[2-(2,3-dihydro-2,2-dimethyl-4-oxo-4H-
1,3-benzoxazin-6-yl-oxy)-1-methylethyl]-aminomethyl]-benzyl
alcohol in 450 ml of methanol, and the mixture is boiled

74

under reflux for 1.5 hours. Evaporating the reaction mixture leaves a foam, which is dissolved in the smallest quantity possible of hot isopropanol. The crystals formed are filtered off with suction after standing for several days, and constitute a mixture of the diastereoisomers of α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol having a melting range of approx. 120-150°. The pure pairs of enantiomers, which melt at 166-168° and 152-154°, are obtained by fractional recrystallisation from isopropanol.

The starting material is prepared in the following manner:

a) 2,5-dihydroxybenzamide is converted, by the method described by Irvine et al., Synthesis 1972, 568, using an excess of acetone, into 2,3-dihydro-2,2-dimethyl-6-hydroxy-4H-1,3-benzoxazin-4-one of melting point 215-216°.

b) 70 g of 2,3-dihydro-2,2-dimethyl-6-hydroxy-4H-1,3-benzoxazin-4-one in 400 ml of acetonitrile are stirred with 100 g of potassium carbonate and 32 ml of chloroacetone for 30 hours under reflux. After a further 3.2 ml of chloroacetone have been added, the reaction mixture is heated for a further 15-20 hours. The reaction mixture is filtered while still warm, the residue is thoroughly washed with acetone, and the combined filtrate is evaporated. The crystalline residue is recrystallised from toluene, giving 2,3-dihydro-2,2-dimethyl-6-(2-oxopropoxy)-4H-1,3-benzoxazin-4-one of melting point 125-126°.

c) A solution of 26.6 g of 2,3-dihydro-2,2-dimethyl-6-(2-oxopropoxy)-4H-1,3-benzoxazin-4-one and 14.6 g of α -(aminomethyl)-benzyl alcohol in 450 ml of methanol is hydrogenated under normal conditions with the addition of 50 mg of concentrated sulfuric acid and 4 g of a platinum-on-charcoal catalyst until 1 mol.-equivalent of hydrogen has been taken up. The solution obtained after filtering off the catalyst, which contains crude α -[N-[2-(2,3-dihydro-2,2-dimethyl-4-oxo-4H-1,3-benzoxazine-6-yloxy)-1-methylethyl]-aminomethyl]-benzyl alcohol, is hydrolysed without being worked up.

d) The compound used in Example 1 can also be obtained, analogously to Example 2c, by reducing, by means of sodium borohydride, the ketone obtained in accordance with Example 1b and the Schiff's base obtained ... (sic) α -(amino-methyl)-benzyl alcohol.

Example 2

18 g of crude α -[N-[2-(2,3-dihydro-2,2-dimethyl-4-oxo-4H-1,3-benzoxazine-7-yloxy)-1-methylethyl]-aminomethyl]-benzyl alcohol are dissolved in 100 ml of isopropanol, 50 ml of isopropylamine are added and the mixture is boiled under reflux for 1.5 hours. After being evaporated, the reaction mixture is partitioned between 50 ml of 2N hydrochloric acid and 100 ml of ether, and the water phase is separated off, rendered alkaline with concentrated ammonia solution and extracted with 3 times 150 ml of ethyl acetate.

Evaporation gives a foam which crystallises after isopropanol has been added. α -[N-[2-(4-carbamoyl-3-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol is obtained as a mixture of diastereomers of melting range 140-156°. The two pairs of enantiomers of melting point 171-173° and 149-151° are obtained by fractional crystallisation from methanol.

The starting material is prepared in the following manner:

a) 2,3-dihydro-2,2-dimethyl-7-hydroxy-4H-1,3-benzoxazin-4-one of melting point 249-251° is obtained from 2,4-dihydroxybenzamide analogously to Example 1a.

b) 2,3-dihydro-2,2-dimethyl-7-(2-oxopropoxy)-4H-1,3-benzoxazin-4-one of melting point 160-162° (from isopropanol) is obtained, analogously to Example 1b, from 168 g of 2,3-dihydro-2,2-dimethyl-7-hydroxy-4H-1,3-benzoxazin-4-one, 305 g of potassium carbonate and 88 ml of chloroacetone in 1.2 litres of acetonitrile by boiling for 28 hours and working up subsequently.

c) A mixture of 13.0 g of 2,3-dihydro-2,2-dimethyl-7-(2-oxopropoxy)-4H-1,3-benzoxazin-4-one and 6.9 g of

α -(aminomethyl)-benzyl alcohol is boiled under reflux with 100 ml of ethanol for 5 hours. 5.7 g of sodium borohydride are then added in portions, with ice-cooling and stirring, and the mixture is then stirred overnight at room temperature. The excess sodium borohydride is then decomposed with 2 N hydrochloric acid (approx. 75 ml) with ice-cooling, and the reaction mixture is concentrated. The aqueous phase is rendered alkaline with concentrated ammonia solution, and the precipitated product is extracted with twice 500 ml of ethyl acetate.

The crude α -[N-[2-(2,3-dihydro-2,2-dimethyl-4-oxo-4H-1,3-benzoxazin-7-yloxy)-1-methylethyl]-aminomethyl]-benzyl alcohol obtained by evaporation is hydrolysed without further purification.

Example 3

A mixture of 25.4 g of α -(aminomethyl)-benzyl alcohol and 11.1 g of 2,3-dihydro-2,2-dimethyl-6-(2-bromoethoxy)-4H-1,3-benzoxazin-4-one is melted and stirred for 3 hours in a bath at 130°. After cooling, the reaction mixture is dissolved in 50 ml of isopropanol, and the solution is diluted with approx. 50 ml of ethyl acetate, whereupon α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol of melting point 172-174° crystallises out. After recrystallisation from 300 ml of ethanol the product melts at 174-175°.

The starting material is prepared in the following manner:

a) A mixture of 48.2 g of 2,3-dihydro-2,2-dimethyl-6-hydroxy-4H-1,3-benzoxazin-4-one, 70 g of potassium carbonate and 250 ml of 1,2-dibromoethane is boiled under reflux, with stirring, for 4 hours. The semifluid reaction mixture is extracted with 3-4 times 1 litre of hot methanol, the combined methanol extracts are evaporated and the residue is recrystallised from methanol. 55 g of 2,3-dihydro-2,2-dimethyl-6-(2-bromoethoxy)-4H-1,3-benzoxazin-4-one of melting point 190-195° are obtained.

Example 4

A solution of 15 g of crude N-[2-(4-carbamoyl-3-hydroxyphenoxy)-ethyl]-N-(2-hydroxy-2-phenylethyl)-benzylamine in 150 ml of methanol is hydrogenated under normal conditions, with the addition of 3 g of 5% strength palladium-on-charcoal catalyst, until absorption ceases. The catalyst is filtered off, the solvent is removed by evaporation and the residue is recrystallised from isopropanol. This gives α -[N-[2-(4-carbamoyl-3-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol of melting point 141-142°. The compound forms a hydrochloride of melting point 240-242°.

The starting material is prepared in the following manner:

a) 16.2 g of 2,3-dihydro-2,2-dimethyl-7-hydroxy-4H-1,3-benzoxazin-4-one are reacted with 84 ml of 1,2-dibromoethane analogously to Example 3a to give 2,3-dihydro-2,2-dimethyl-7-(2-bromoethoxy)-4H-1,3-benzoxazin-4-one of melting point 156-158° (from isopropanol).

b) 53 g of 2,3-dihydro-2,2-dimethyl-7-(2-bromoethoxy)-4H-1,3-benzoxazin-4-one and 94 g of benzylamine are boiled for 3 hours, with stirring. The reaction mixture is rendered alkaline with concentrated ammonia, and the organic phase is evaporated at a maximum of 50°.

The N-[2-(4-carbamoyl-3-hydroxyphenoxy)-ethyl]-benzylamine thus obtained is an oil having a hydrochloride melting at 252-254° (from methanol).

c) A mixture of 11.0 g of phenylethylene oxide, 9.2 g of N-[2-(4-carbamoyl-3-hydroxyphenoxy)-ethyl]-benzylamine and 100 ml of isopropanol is boiled under reflux for 10 hours. The reaction mixture is evaporated, and the residue is stirred with 50 ml of hexane. The oil insoluble in the hexane consists essentially of N-[2-(4-carbamoyl-3-hydroxyphenoxy)-ethyl]-N-(2-hydroxy-2-phenylethyl)-benzylamine, which is hydrogenated in the crude state.

Example 5

A solution of 13.0 g of α -(aminomethyl)-3-pyridinemethanol and 26.5 g of 2,3-dihydro-2,2-dimethyl-6-(2-oxo-

propoxy)-4H-1,3-benzoxazin-4-one in 400 ml of methanol is hydrogenated at 30° and under normal pressure, with the addition of 0.1 ml of concentrated sulfuric acid and 1 g of 5% strength platinum-on-charcoal catalyst. 2 further additions of 1 g and 2 g, respectively, of the same catalyst are necessary before the calculated amount of hydrogen is absorbed. After the catalyst has been filtered off, 50 ml of isopropylamine are added to the filtrate, and the mixture is boiled under reflux for 1 hour and evaporated. The residue, a dark-brown foam, is dissolved in 50 ml of methanol, 6.1 g of fumaric acid are added, and the mixture is warmed until solution takes place. α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-3-pyridinemethanol crystallises out after a fairly long time in the form of the neutral fumarate of melting point 192-196° (sinters from 187°) in which there is a considerable concentration (~80%) of one pair of enantiomers.

Example 6

Crude α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-2-pyridinemethanol is obtained as a brown oil analogously to the procedure described in Example 5, but using 13.0 g of α -(aminomethyl)-2-pyridinemethanol. It forms a neutral fumarate (from methanol) which melts at 147-165° and constitutes a mixture of the diastereomers.

Example 7

A solution of 15.2 g of 4-benzyloxy- α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol in 500 ml of methanol is hydrogenated under normal conditions in the presence of 2 g of 5% strength palladium-on-charcoal catalyst until 1 mol.-equivalent of hydrogen has been taken up. The catalyst is filtered off and the filtrate is evaporated. The foam which remains is partitioned between 300 ml of ethyl acetate and 50 ml of potassium bicarbonate solution, and the organic phase is separated off, dried and evaporated. The crude α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-4-

hydroxybenzyl alcohol thus obtained forms, with a half equivalent amount of fumaric acid in methanol, a neutral fumarate which, after a fairly long time, crystallises from acetone in the form of a mixture of diastereomers, melting point 185-195°. A single-substance pair of enantiomers of melting point 209-212° (decomposition) can be obtained from this by fractional crystallisation from methanol.

The starting material is prepared in the following manner:

10 a) A solution of 9.6 g of 2,3-dihydro-2,2-dimethyl-6-(2-oxopropoxy)-4H-1,3-benzoxazin-4-one and 9.37 g of 4-benzyloxy- α -(aminomethyl)-benzyl alcohol in 250 ml of methanol is hydrogenated analogously to Example 1 until 1 equivalent of hydrogen has been taken up. The catalyst is filtered off, 40 ml of isopropylamine are added to the solution, and the mixture is boiled under reflux for 1 hour. Evaporating the reaction mixture gives 4-benzyloxy- α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl-benzyl alcohol in the form of a crystalline mass which can be hydrogenated without further purification.

20 Example 8

A solution of 26.8 g of 5-(2-oxopropoxy)-salicylamide and 17.6 g of α -(aminomethyl)-benzyl alcohol in 450 ml of methanol is hydrogenated under normal conditions, after 0.32 g of concentrated sulfuric acid and 3 g of 5% strength platinum-on-charcoal catalyst have been added, until 1 mol.-equivalent of hydrogen has been taken up. The catalyst is filtered off, the solvent is removed by evaporation and the crude α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol thus obtained is dissolved in the minimum quantity of hot methanol, and the solution is cooled and inoculated with crystals of the higher-melting pair of enantiomers. The crystals of melting point 160-163° which are obtained after standing for several days produce, after a further crystallisation from methanol, one pure pair of enantiomers of melting point 166-168°. The lower-melting pair of enantiomers of melting

point 152-154° is isolated from the first mother liquor, after the solvent has been removed by evaporation, by fractional crystallisation using ethyl acetate and/or isopropanol.

5 The 5-(2-oxopropoxy)-salicylamide required as the starting material is prepared in the following manner:

8a) 74 g of crude 2,3-dihydro-2,2-dimethyl-6-(2-oxopropoxy)-4H-1,3-benzoxazin-4-one, obtained in accordance with Example 1b, in a mixture of 150 ml of dioxane and 450
10 ml of 2 N hydrochloric acid are heated on a water bath for 45 minutes. The solvent is removed by evaporation and the crystalline residue is triturated with water and then suction-drained. Recrystallisation from isopropanol gives 5-(2-oxopropoxy)-salicylamide of melting point 152-154°.

15 Example 9

A solution of 8.0 g of R-(-)- α -(aminomethyl)-benzyl alcohol and 12.2 g of 5-(2-oxopropoxy)-salicylamide in 220 ml of methanol is hydrogenated and worked up analogously to Example 8. Neutralising the crude base with 5 N hydrochloric acid in methanol gives, after recrystallisation from
20 methanol/ether, the hydrochloride of R-(-)- α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol in the form of a pure enantiomer of melting point 180-184° ($[\alpha]_D^{20}$ -31 $\pm$ 1° (1% strength in methanol)).

25 A mixture of diastereomers of melting point 165-180° crystallises out from the mother liquor on concentrating the latter.

Example 10

A solution of 7.2 g of 4-benzyloxy- α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol
30 in 200 ml of methanol is hydrogenated analogously to Example 7 in the presence of 5% strength palladium-on-charcoal catalyst. Evaporating the filtered solution gives crude α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-4-hydroxybenzyl alcohol which, after recrystallisation from
35 methanol/isopropanol, melts at 194-196°.

The starting material is prepared in the following

manner:

5 a) A mixture of 21 g of α -(aminomethyl)-4-benzyloxy-benzyl alcohol and 12 g of 6-(2-bromoethoxy)-2,3-dihydro-2,2-dimethyl-4H-1,3-benzoxazin-4-one is stirred for 1 hour in an oil bath at 130°. The reaction mixture is partitioned between 500 ml of ethyl acetate and 50 ml of 2 N aqueous ammonia solution, the organic phase is separated off and evaporated and the residue is recrystallised from isopropanol. 4-benzyloxy- α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-benzylalcohol of melting point 160-162° is obtained.

Example 11

15 A molten mixture of 5.0 g of 6-(2-bromoethoxy)-salicylamide and 13.0 g of α -(aminomethyl)-benzyl alcohol is stirred for 1 hour in a bath at 130°. The reaction mixture is dissolved, while still warm, in 250 ml of ethyl acetate, and the solution is washed successively with 50 ml of saturated potassium bicarbonate solution, 100 ml of water and 100 ml of saturated aqueous sodium chloride solution, 20 dried over magnesium sulfate and evaporated. The residue is dissolved in 30 ml of hot ethanol from which, on cooling, α -[N-[2-(2-carbamoyl-3-hydroxy-phenoxy)-ethyl]-aminomethyl]-benzyl alcohol of melting point 122-123° crystallises out. The compound forms a hydrochloride of melting point 190-191° 25 (from methanol/isopropanol).

The starting material is prepared as follows:

30 a) A mixture of 23.0 g of 2,6-dihydroxybenzamide, 20.7 g of potassium carbonate and 28.2 g of 1,2-dibromoethane in 300 ml of acetonitrile is stirred under reflux for 2-3 hours. The reaction mixture is filtered while still warm, the filtrate is evaporated and the residue is recrystallised from a little methanol. 6-(2-bromoethoxy)-salicylamide of melting point 120-121° is obtained.

Example 12

35 16.6 g of crude N-[3-(4-carbamoyl-3-hydroxyphenoxy)-propyl]-N-(2-hydroxy-2-phenylethyl)-benzylamine are hydrogenated and worked up analogously to Example 4. α -[N-[3-

(4-carbamoyl-3-hydroxyphenoxy)-propyl]-aminomethyl]-benzyl alcohol of melting point 208-210° is obtained by recrystallisation from isopropanol.

5 The starting material is prepared via the following stages:

a) A mixture of 38.6 g of 2,3-dihydro-2,2-dimethyl-7-hydroxy-4H-1,3-benzoxazin-4-one, 55.2 g of potassium carbonate, 47.2 g of 1-bromo-3-chloropropane and 600 ml of acetone is boiled under reflux for 24 hours. Filtration, concentrating the filtrate to 1/3 of its original volume and cooling gives 7-(3-bromopropoxy)-2,3-dihydro-2,2-dimethyl-4H-1,3-benzoxazin-4-one of melting point 111-113°.

10 b) 13.6 g of this compound, together with 32 g of benzylamine, are heated at 100° for 1 1/2 hours, with stirring. Working up on a basis analogous to Example 4b and removing the excess benzylamine in a high vacuum gives, after recrystallising the residue from toluene, N-[3-(4-carbamoyl-3-hydroxyphenoxy)-propyl]-benzylamine of melting point 131-135°.

20 c) A solution of 12.7 g of N-[3-(4-carbamoyl-3-hydroxyphenoxy)-propyl]-benzylamine and 7.6 g of phenylethylene oxide in 80 ml of isopropanol is boiled under reflux for 16 hours. The reaction mixture is evaporated, the residue is partitioned between 100 ml of 6 N hydrochloric acid and 100 ml of ether, and the aqueous phase is separated off and rendered alkaline with 2 N ammonia solution. The N-[3-(4-carbamoyl-3-hydroxyphenoxy)-propyl]-N-(2-hydroxy-2-phenylethyl)-benzylamine thus obtained is isolated by extraction with ethyl acetate and is debenzylated in the form of the crude product.

30 Example 13

20 ml of concentrated ammonia solution are added to a solution of 1.7 g of crude α -[N-[2-(3-carbomethoxy-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol in 10 ml of dioxane, and the mixture is allowed to stand at room temperature for 60-70 hours. The reaction mixture is evaporated and the residue is dissolved in 75 ml of ethyl

acetate and washed with 10 ml of saturated aqueous sodium chloride solution. Evaporating the organic phase gives crude α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol as a mixture of diastereoisomers in the form of an oil, which is crystallised from a little ethyl acetate and is identical with the product obtained, for example, in Example 1; melting point 120-140°.

The starting material is obtained in the following manner:

10 a) A solution of 3.4 g of methyl 2,5-dihydroxybenzoate, 4.0 g of triethylamine and 2.8 g of chloroacetone in 40 ml of acetonitrile is boiled under reflux for 16 hours. After 1.4 g of chloroacetone and 1.3 g of triethylamine have been added, the reaction mixture is boiled for a further 5
15 hours and is then evaporated, the residue is dissolved in 50 ml of toluene, and the solution is washed with 10 ml of water and then with 10 ml of saturated aqueous sodium chloride solution, and is chromatographed over 200 g of silica gel. The fractions first eluted with toluene contain methyl
20 5-(2-oxopropoxy)-salicylate, which is recrystallised from isopropanol and melts at 80-82°.

b) A solution of 0.8 g of α -aminomethylbenzyl alcohol and 1.2 g of methyl 5-(2-oxopropoxy)-salicylate in 40 ml of methanol is hydrogenated analogously to Example 8.

25 Filtration and evaporation gives crude α -[N-[2-(3-carbomethoxy-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol in the form of a yellowish oil, which is processed further in the crude state.

Example 14

30 A solution of 13.4 g of phenylglyoxal and 19.6 g of 5-(2-aminoethoxy)-salicylamide in 100 ml of methanol is heated under reflux for 1 hour and 7 g of sodium borohydride are then added in portions, with stirring and cooling in ice. The reaction mixture is stirred overnight at approx. 20°,
35 decomposed with 2 N hydrochloric acid with ice-cooling and filtered. The filtrate is concentrated, rendered alkaline with concentrated ammonia solution and extracted with

ethyl acetate.

The crude product obtained by evaporation is crystallised from ethanol, giving α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol of melting point 174-175°.

14a) The 5-(2-aminoethoxy)-salicylamide of melting point 140° which is required as the starting material is obtained analogously to Example 21 by catalytic debenzylation of 5-(2-benzylaminoethoxy)-salicylamide by means of 5% strength palladium-on-charcoal catalyst in methanol.

Example 15

α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-2-pyridinemethanol of melting point 169-170° (from ethanol/methanol) is obtained analogously to Example 3 by melting 5.0 g of α -(aminomethyl)-2-pyridinemethanol and 2.2 g of 2,3-dihydro-2,2-dimethyl-6-(2-bromoethoxy)-4H-1,3-benzoxazin-4-one.

Example 16

A mixture of 0.96 g of phenylethylene oxide and 2.1 g of 4-(2-aminopropoxy)-salicylamide in 25 ml of 2-propanol is boiled under reflux for 15 hours. The reaction mixture is then evaporated, the residue is partitioned between 10 ml of water and 100 ml of ethyl acetate, and the organic phase is washed three times with water. Drying the organic phase over magnesium sulfate and evaporating it gives crude α -[N-[2-(4-carbamoyl-3-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol, which is recrystallised analogously to Example 2 and affords in this manner the two pairs of enantiomers of melting point 171-173° and 149-151°.

The starting material is prepared in the following manner:

a) Approx. 5 g of Raney nickel catalyst are added to a solution of 25 g of 2,3-dihydro-2,2-dimethyl-7-(2-oxopropoxy)-4H-1,3-benzoxazin-4-one in 500 ml of methanol, the mixture is put into an autoclave and ammonia gas is then injected until the pressure is 5 bar. Hydrogenation is then carried out at 50° and 100 bar of hydrogen pressure until

absorption ceases. Filtering off the catalyst and evaporating the solution gives crude 4-(2-aminopropoxy)-salicylamide which, after recrystallisation from methanol, melts at 185-187°.

5 Example 17

A mixture of 7.0 g of α -(aminomethyl)-2-furanmethanol and 7.5 g of 2,3-dihydro-2,2-dimethyl-6-(2-bromoethoxy)-4H-1,3-benzoxazin-4-one is melted and stirred for 1 hour in a bath at approx. 110°. 50 ml of isopropanol and 2 ml of concentrated ammonia solution are added to the reaction mixture while it is still warm, and the mixture is boiled for 5 minutes, filtered and allowed to cool. Working up gives α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-2-furanmethanol of melting point 169-171°.

15 Example 18

A mixture of 2.7 g of α -(aminomethyl)-2-thiophenemethanol and 3.6 g of 2,3-dihydro-2,2-dimethyl-6-(2-bromoethoxy)-4H-1,3-benzoxazin-4-one is stirred, together with 2 ml of triethylamine, for 1 hour in a bath at 100-110°. The reaction mixture is partitioned between 100 ml of ethyl acetate and 10 ml of 2 N aqueous potassium bicarbonate solution, and the organic phase is separated off, dried over magnesium sulfate and evaporated, giving crude α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-2-thiophenemethanol in the form of a crystalline mass which, after recrystallisation from a little isopropanol, melts at 158-161°; repeated recrystallisation raises the melting point to 171-172°.

Example 19

0.26 g of concentrated sulfuric acid are added to a solution of 14.1 g of S-(+)- α -(aminomethyl)-benzyl alcohol and 21.5 g of 5-(2-oxopropoxy)-salicylamide in 400 ml of methanol, and the mixture is hydrogenated over 2 g of 5% strength platinum-on-charcoal catalyst analogously to Example 8 and worked up. The evaporation residue, obtained in the form of a foam, crystallises from ethyl acetate as a mixture of diastereomers of melting point 146-161°.

Fractional crystallisation from isopropanol gives a pure enantiomer of S-(+)- α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol of melting point 160-162°. Neutralisation with methanolic hydrochloric acid of the basic mother liquor obtained in the fractional crystallisation, and fractional crystallisation of the hydrochloride from methanol gives the other enantiomer in the form of the hydrochloride, melting point 181-183°. In the form of their hydrochlorides, both enantiomers exhibit the same specific rotation $[\alpha]_D^{20} = +33^\circ \pm 1^\circ$ (C = 1, methanol), but have different C-NMR spectra.

Example 20

A solution of 8.7 g of 4-benzyloxy- α -[N-[2-(4-carbamoyl-3-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol in 100 ml of dioxane is hydrogenated under normal conditions, with the addition of 2 g of 5% strength palladium-on-charcoal catalyst, until 1 equivalent of hydrogen has been taken up. The precipitated product is brought into solution by warming, after adding 200 ml of methanol, the catalyst is filtered off and the filtrate is evaporated. Recrystallisation on (sic) isopropanol gives crystalline α -[N-[2-(4-carbamoyl-3-hydroxyphenoxy)-ethyl]-aminomethyl]-4-hydroxybenzyl alcohol of melting point 181-182°.

20a) The starting material can be prepared analogously to Example 10a using 7-(2-bromoethoxy)-2,3-dihydro-2,2-dimethyl-4H-1,3-benzoxazin-4-one. The 4-benzyloxy- α -[N-[2-(4-carbamoyl-3-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol thus obtained melts at 181-183°.

Example 21

5 g of 5% strength palladium-on-charcoal catalyst are added to a solution of 45 g of crude α -[N-benzyl-N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol in 500 ml of methanol, and the mixture is hydrogenated and worked up analogously to Example 4. α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol of melting point 174-175° (from ethanol) is obtained. The methanesulfonate melts at 182-183° (from methanol).

The starting material is prepared in the following manner:

21a) A suspension of 60 g of 6-(2-bromoethoxy)-2,3-dihydro-2,2-dimethyl-4H-1,3-benzoxazin-4-one in 110 ml of benzylamine is heated, with stirring, for 30 minutes in a bath at 80°. The pH of the reaction mixture is then adjusted to approx. 3 with concentrated hydrochloric acid while cooling with ice is applied, and the mixture is allowed to stand in order to crystallise. The crystals are filtered off with suction after 4 hours, washed with 10 ml of water and 10 ml of ethyl acetate and dried. The crude 5-(2-benzylaminoethoxy)-salicylamide hydrochloride thus obtained melts at 214-216°. The base liberated therefrom melts at 107-108° (from ethylacetate/ether).

21b) A solution of 13.2 g of phenylethylene oxide and 28.6 g of 5-(2-benzylaminoethoxy)-salicylamide in 100 ml of isopropanol is heated under reflux for 24 hours. Removing the solvent by evaporation gives crude α -[N-benzyl-N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol in the form of an oil which can be employed for debenzylation without further purification.

Example 22

A mixture of 13.7 g of α -(aminomethyl)-benzyl alcohol and 9.4 g of 6-(3-bromopropoxy)-2,3-dihydro-2,2-dimethyl-4H-1,3-benzoxazin-4-one is heated, with stirring, for 45 minutes in a bath at 120°. The reaction mixture is cooled, 250 ml of ethyl acetate are added and the solution is washed successively with twice 50 ml of aqueous, saturated potassium bicarbonate solution, 50 ml of water and 50 ml of saturated sodium chloride solution, dried over magnesium sulfate and evaporated. The oily residue is dissolved in a little isopropanol and neutralised with a solution (~5 N) of hydrogen chloride in methanol. α -[N-[3-(3-carbamoyl-4-hydroxyphenoxy)-propyl]-aminomethyl]-benzyl alcohol is obtained in this way in the form of the hydrochloride of melting point 189-192°.

The starting material is prepared in the following

manner:

22a) A mixture of 9.7 g of 2,3-dihydro-2,2-dimethyl-6-hydroxy-4H-1,3-benzoxazin-4-one, 41 g of 1,3-dibromopropane and 10.4 g of potassium carbonate is stirred under reflux for 2 1/2 hours. The reaction mixture is diluted with toluene and filtered, and the filtrate is evaporated. 20 ml of ether are added to the residue and the sludge precipitated is filtered off. The filtrate is evaporated again and the residue is triturated with 50 ml of petroleum ether to give 14 g of crude 6-(3-bromopropoxy)-2,3-dihydro-2,2-dimethyl-4H-1,3-benzoxazin-4-one in the form of a crystalline mass. After recrystallisation from a little petroleum ether, the product melts at 115-118°.

Example 23

15 A solution of 13.9 g of crude α -[N-benzyl-N-[3-(3-carbamoyl-4-hydroxyphenyl)-propyl]-aminomethyl]-benzyl alcohol in 150 ml of methanol is hydrogenated under normal conditions, in the presence of 1.4 g of 5% strength palladium-on-charcoal catalyst, until the absorption of hydrogen ceases. Filtering the solution, evaporating the filtrate and triturating the residue with ether gives a solid which, after recrystallisation from a little isopropanol, affords α -[N-[3-(3-carbamoyl-4-hydroxyphenyl)-propyl]-aminomethyl]-benzyl alcohol of melting point 151-153°.

25 The starting materials can be obtained in the manner described below:

23a) 3-(4-hydroxyphenyl)-propionic acid is converted via the mixed anhydride obtained with methyl chloroformate and by means of benzylamine into N-benzyl-3-(4-hydroxyphenyl)-propionamide of melting point 115-116°.

23b) N-benzyl-3-(3-carboxy-4-hydroxyphenyl)-propionamide of melting point 180-181° is obtained under the conditions of the Kolbe synthesis by reacting the sodium salt of N-benzyl-3-(4-hydroxyphenyl)-propionamide and carbon dioxide at a temperature of 180° for 4 hours under a pressure of 55 bar.

23c) Esterifying N-benzyl-3-(3-carboxy-4-hydroxy-

phenyl)-propionamide by boiling under reflux for 48 hours with a mixture of methanol and concentrated sulfuric acid gives N-benzyl-3-(3-methoxycarbonyl-4-hydroxyphenyl)-propionamide of melting point 139-140° (from ethyl acetate).

5 23d) Reacting N-benzyl-3-(3-methoxycarbonyl-4-hydroxyphenyl)-propionamide with benzyl bromide in the presence of potassium carbonate, in acetone as the solvent, by boiling under reflux for 15 hours gives N-benzyl-3-(4-benzyloxy-3-methoxycarbonylphenyl)-propionamide in the form
10 of a yellowish oil.

 23e) Selective reduction of the amide group in N-benzyl-3-(4-benzyloxy-3-methoxycarbonylphenyl)-propionamide by means of diborane in tetrahydrofuran for 48 hours at a temperature of 20-25° gives N-[3-(4-benzyloxy-3-methoxycarbonylphenyl)-propyl]-benzylamine, which is converted, in
15 the form of the crude product, by means of hydrogen, in the presence of 50% strength palladium-on-charcoal catalyst, in methanol as solvent and at a temperature of 15-20°, into N-[3-(4-hydroxy-3-methoxycarbonylphenyl)-propyl]-benzylamide
20 (sic) of melting point 75-77° (from isopropanol).

 23f) A solution of 27 g of N-[3-(4-hydroxy-3-methoxycarbonylphenyl)-propyl]-benzylamine in 100 ml of dioxane is esterified (sic) with 200 ml of concentrated ammonia, the mixture being allowed to stand for 3-4 days at 20-
25 30°. The reaction mixture is evaporated, the residue is partitioned between water and ethyl acetate, and the organic phase is separated off. Working up in the customary manner gives 14.5 g of crude N-[3-carbamoyl-4-hydroxyphenyl)-propyl]-benzylamine in the form of an oil, which is processed further without further purification.
30

 23g) A solution of 8.5 g of crude N-[3-(3-carbamoyl-4-hydroxyphenyl)-propyl]-benzylamine and 10 g of phenylethylene oxide in 100 ml of isopropanol is boiled under reflux for 8 hours and is then evaporated. The oily residue is
35 freed from excess phenylethylene oxide by being stirred with petroleum ether. The crude, oily α -[N-benzyl-N-[3-(3-carbamoyl-4-hydroxyphenyl)-propyl]-aminomethyl]-benzyl alcohol

which is sparingly soluble in petroleum ether is processed further in the form of the crude product, without further purification.

Example 24

5 A solution of 31 g of crude N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-N-[2-(3,5-dibenzyloxyphenyl)-2-hydroxyethyl]-benzylamine in 300 ml of methanol is hydrogenated under normal conditions over 6 g of 5% strength palladium-on-charcoal catalyst until 3 mol.-equivalents of hydrogen
10 have been taken up. The catalyst is filtered off, the filtrate is evaporated and the residue is dissolved in 200 ml of isopropanol. The solution is filtered through silica gel, and the filtrate is evaporated, to give α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-3,5-dihydroxybenzyl alcohol in the form of a brownish foam. The compound is characterised by the following signals in the proton nuclear magnetic resonance spectrum, using hexadeuterio-dimethyl sulfoxide as the solvent:

20 Chemical shift: 2.74 (d, 2H); 3.0 (t, 2H); 4.05 (t, 2H); 4.5 (t, 1H); 6.1 (d, 1H); 6.24 (d, 2H); 6.8 (d, 1H); 7.05 (g, 1H); 7.47 (d, 1H).

 The starting material can be prepared in the following manner:

25 24a) 28.6 g of 5-(2-benzylaminoethoxy)-salicylamide are added, in portions and with stirring, to a solution of 20.6 g of ω -bromo-3,5-dibenzyloxyacetophenone in 300 ml of acetone, and the reaction mixture is stirred overnight at room temperature. The precipitated crystals are filtered off with suction, and the filtrate is evaporated, giving
30 crude ω -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethoxyethyl]-benzylamino-3,5-dibenzyloxyacetophenone.

35 24b) 4 portions of sodium borohydride, each of 3 g, are added at intervals of 2-3 hours to a solution of 39 g of the resulting crude product in a mixture of 200 ml of ethanol and 200 ml of methanol, and the whole mixture is then stirred overnight. The pH of the mixture is adjusted to 4 by adding 2 N hydrochloric acid dropwise with ice-

cooling, and the mixture is then evaporated. 200 ml of water are added to the residue from evaporation, and the mixture is rendered alkaline with concentrated ammonia solution and extracted with 400 ml of ethyl acetate. The organic phase is separated off, dried over magnesium sulfate and evaporated, giving N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-N-[2-(3,5-dibenzyloxyphenyl)-2-hydroxyethyl]-benzylamine in the form of a viscous crude product, which is processed further as such.

10 Example 25

A suspension of 21.9 g of 5-(2-aminoethoxy)-salicylamide, 36.0 ... (sic) α -(bromomethyl)-benzyl alcohol and 30 g of potassium bicarbonate in 240 ml of ethanol is heated to reflux temperature, with stirring, for 15 hours. The reaction mixture is then cooled, filtered and evaporated. The residue from evaporation is partitioned between 300 ml of ethyl acetate and 100 ml of water, and the organic phase is separated off, dried over magnesium sulfate and evaporated. The residue is dissolved in the minimum amount of hot ethanol and induced to crystallise, giving α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol of melting point 174-175° (from ethanol).

Example 26

A suspension of 14.5 g of phenylethylene oxide and 19.6 g of the 5-(2-aminoethoxy)-salicylamide obtained in Example 14a in 50 ml of isopropanol is boiled under reflux for 30 minutes. After cooling, α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol crystallises out slowly, and after recrystallisation from ethanol it melts at 174-175°.

Example 27

Tablets containing 20 mg of active substance are prepared in a customary manner with the following composition:

35 Composition:

α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol of melting point

(92)

	152-154°	20 mg
	Wheat starch	60 mg
	Lactose	50 mg
	Colloidal silica	5 mg
5	Talc	9 mg
	Magnesium stearate	1 mg
		145 mg

Preparation:

10 α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methyl-ethyl]-aminomethyl]-benzyl alcohol of melting point 152-154° is mixed with part of the wheat starch and with the lactose and colloidal silica, and the mixture is rubbed through a sieve. A further part of the wheat starch is made into a paste with 5 times its quantity of water on a water bath, 15 and the powder mixture is kneaded with this paste until a slightly plastic composition has been formed.

The plastic composition is forced through a sieve of approx. 3 mm mesh width and is dried, and the resulting dry granules are again forced through a sieve. The remainder of 20 the wheat starch, the talc and the magnesium stearate are then mixed in, and the mixture is compressed to give tablets weighing 145 mg, with a breaking groove.

Example 28

25 Capsules containing 20 mg of active substance are prepared in a customary manner as follows:

α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-amino-methyl]-benzyl alcohol of melting point 152-154° 2500 mg
Talc 80 mg
Colloidal silica 20 mg

30 Preparation:

The active substance is intimately mixed with the talc and colloidal silica, the mixture is forced through a sieve of 0.5 mm mesh width, and the product is filled in portions of 21 mg in each case into hard gelatine capsules 35 of a suitable size.

Example 29

A syrup containing 2% weight/volume of active substance is prepared in a customary manner as follows:

Composition:

5	α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol of melting point 152-154°	2.0 g
	Saccharin	0.6 g
	Sugar	30.0 g
	Glycerol	5.0 g
10	Flavouring substances	0.1 g
	Ethanol (86%)	10.0 ml
	Distilled H ₂ O	add 100 ml

Preparation:

15 The sugar, the saccharin and the glycerol are dissolved in 60 g of water. A solution of the active compound and the flavouring substance in the ethanol is added, with stirring. The mixture is then made up to 100 ml with distilled water.

Example 30

20 Instead of the compounds used as the active substance in Examples 27 to 29, it is also possible to use the following compounds of the formula I, or pharmaceutically acceptable, non-toxic acid addition salts thereof, as the active compounds in tablets, coated tablets, capsules etc.: α -[N-[2-(4-carbamoyl-3-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol in the form of the pair of enantiomers of melting point 171-173° and also in the form of the pair of enantiomers of melting point 149-151°;

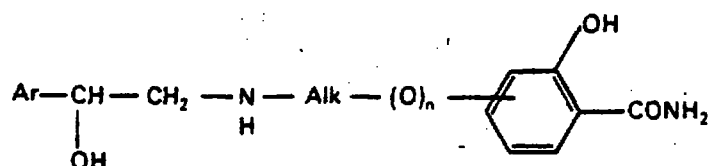
25 α -[N-[2-(4-carbamoyl-3-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol,
30 α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-3-pyridinemethanol,
 α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-4-hydroxybenzyl alcohol,
35 R-(-)- α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol,
 α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-

- 4-hydroxybenzyl alcohol,
 α -[N-[2-(2-carbamoyl-3-hydroxyphenoxy)-ethyl]-aminomethyl]-
benzyl alcohol,
 α -[N-[3-(4-carbamoyl-3-hydroxyphenoxy)-propyl]-aminomethyl]-
5 benzyl alcohol,
 α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-
benzyl alcohol,
 α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-
2-pyridinemethanol,
10 α -[N-[3-(3-carbamoyl-4-hydroxyphenoxy)-propyl]-aminomethyl]-
benzyl alcohol,
 α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-
2-furanmethanol,
 α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-
15 2-thiophenemethanol,
enantiomer of
S(+)- α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-
aminomethyl]-benzyl alcohol of melting point 160-162°
(hydrochloride melting point 189-191°) and also the enan-
20 tiomer having a hydrochloride of melting point 181-183°,
 α -[N-[2-(4-carbamoyl-3-hydroxyphenoxy)-ethyl]-aminomethyl]-
4-hydroxybenzyl alcohol,
 α -[4-[3-(3-carbamoyl-4-hydroxyphenoxy)-propyl]-aminomethyl]-
benzyl alcohol,
25 α -[N-[3-(3-carbamoyl-4-hydroxyphenoxy)-propyl]-aminomethyl]-
benzyl alcohol or
 α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-
3,5-dihydroxybenzyl alcohol.



Patent Claims for the contracting states BE, CH, DE, FR, GB, IT, LU, NL and SE

1. N-alkylated amino alcohols of the formula



wherein Ar denotes a radical of aromatic character which is unsubstituted or substituted by hydroxyl, n denotes the values 0 or 1 and Alk denotes an alkylene radical having 2 to 5 carbon atoms, the nitrogen atom and the oxygen atom or, if n represents 0, the phenyl radical, being separated from one another by at least 2 carbon atoms, in the form of mixtures of racemates, stereoisomeric (diastereomeric) racemates or optical antipodes.

2. Compounds of the formula I wherein Ar denotes phenyl, 2-, 3- or 4-pyridyl, 3-, 4- or 6-pyridazinyl, 2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, 2-furyl or 3-furyl, 2-pyrrolyl or 3-pyrrolyl, 2-thienyl or 3-thienyl, 2-oxazolyl or 4-oxazolyl, 2-thiazolyl or 4-thiazolyl, 3-pyrazolyl or 5-pyrazolyl, 2-imidazolyl or 4-imidazolyl, or 1,2,4-thiadiazol-3-yl, 1,2,4-thiazdiazol-5-yl or 1,3,4-thiadiazol-2-yl, each of which is unsubstituted or substituted by 1 or 2 hydroxyl groups, and Alk denotes an alkylene radical having 2 to 4 carbon atoms, the nitrogen atom and the oxygen atom or, if n represents 0, the phenyl radical, being separated from one another by 2 to 3 carbon atoms, and n represents 0 or 1.

3. Compounds of the formula I wherein Ar denotes phenyl, 2-pyridyl or 3-pyridyl, 2-furyl or 3-furyl or 2-thienyl or 3-thienyl, each of which is unsubstituted or substituted by 1 or 2 hydroxyl groups, and Alk denotes an alkylene radical having 2 to 3 carbon atoms, the nitrogen atom and the oxygen atom or, if n represents 0, the phenyl radical, being separated from one another by 2 to 3 carbon atoms, and n represents 0 or 1.

4. Compounds of the formula I wherein Ar represents phenyl, 2-pyridyl or 3-pyridyl, 2-furyl or 2-thienyl, each

of which is unsubstituted or substituted by 1 or 2 hydroxyl groups, and Alk denotes an alkylene radical having 2 to 3 carbon atoms, the nitrogen atom and the oxygen atom or, if n represents 0, the phenyl radical, being separated from one another by 2 to 3 carbon atoms, and n represents 0 or 1.

5. α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methyl-ethyl]-aminomethyl]-benzyl alcohol in the form of the pair of enantiomers of melting point 166-168°.

6. α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methyl-ethyl]-aminomethyl]-benzyl alcohol in the form of the pair of enantiomers of melting point 152-154°.

7. α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol.

8. α -[N-[2-(4-carbamoyl-3-hydroxyphenoxy)-ethyl]-aminomethyl]-4-hydroxybenzyl alcohol.

9. Salts of compounds of Claims 1 to 8.

10. Pharmaceutically acceptable, non-toxic acid addition salts of compounds of Claims 1 to 8.

11. Pharmaceutical formulations containing a compound of Claims 1 to 8 and 10 together with inert auxiliaries and excipients.

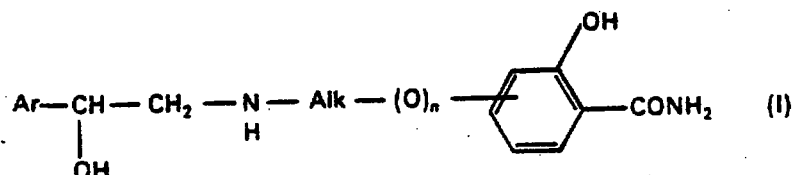
12. Compounds of the formula I as medicaments.

13. Compounds of the formula I as stimulators of cardiac β -receptors.

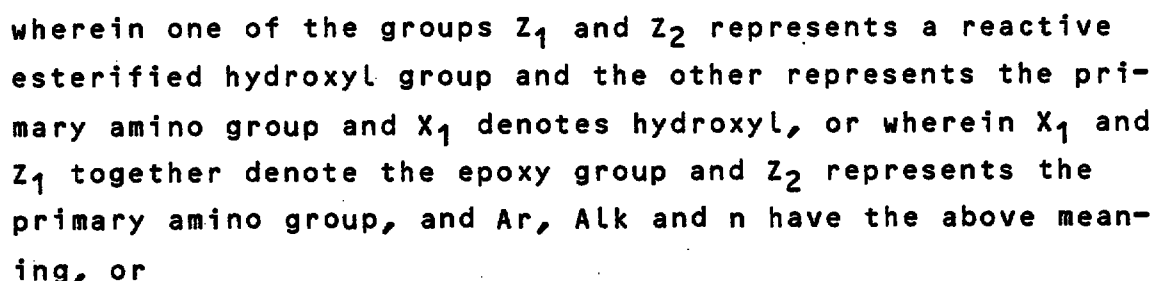
14. The use of compounds of the formula I for the preparation of medicaments.

15. Compounds of the formula I for use in combating cardiac insufficiency.

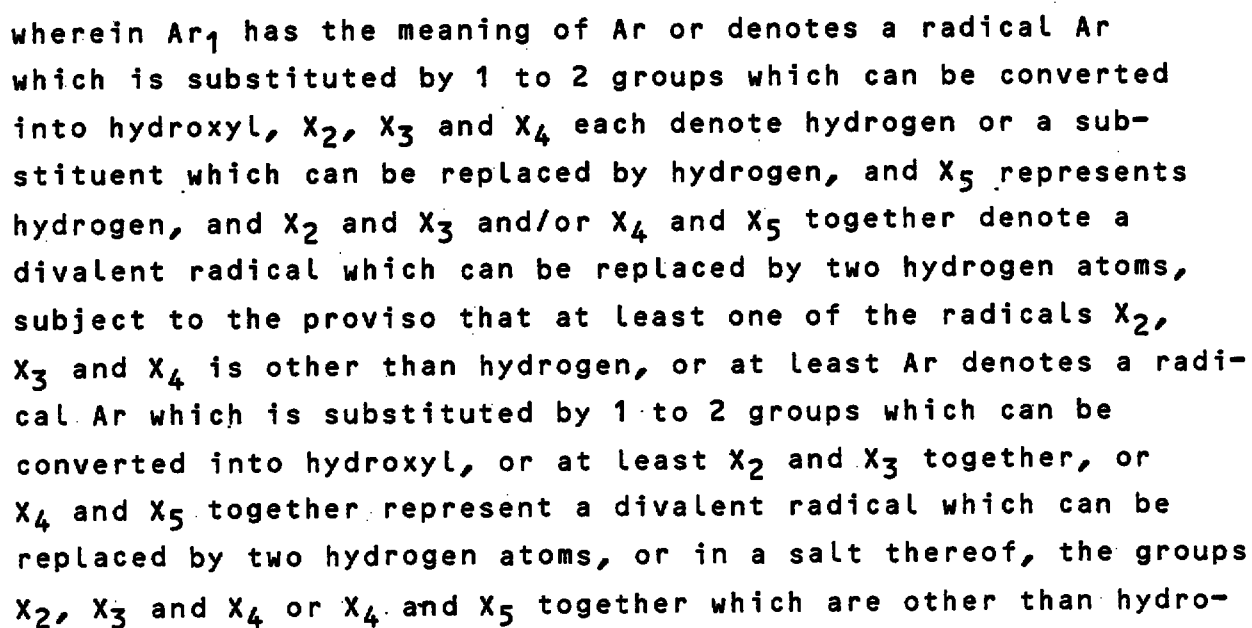
16. Process for the preparation of N-alkylated amino alcohols of the formula



wherein Ar denotes a radical of aromatic character which is unsubstituted or substituted by hydroxyl, n denotes the values 0 or 1 and Alk denotes an alkylene radical having 2



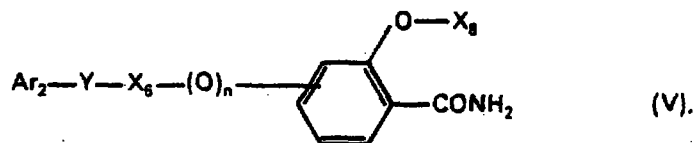
b) in a compound of the formula





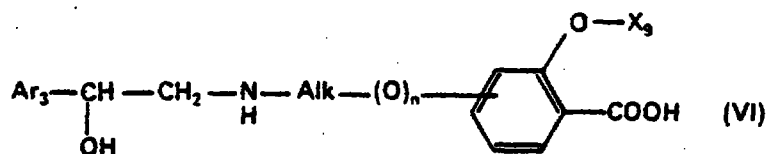
gen are replaced by hydrogen, and/or substituted hydroxyl which is present in a radical Ar_1 is converted into free hydroxyl, or

c) in a compound of the formula



wherein X_6 is a reducible group of the formulae $-\text{CH}=\text{N}-\text{Alk}-$ (Va) or $-\text{CH}_2-\text{N}=\text{Alk}_1-$ (Vb) or $-\text{C}(=\text{X}_7)-\text{N}(\text{X}_8)-\text{Alk}-$ (Vc) or $-\text{CH}_2-\text{N}(\text{X}_8)-\text{C}(=\text{X}_7)-\text{Alk}_2-$ (Vd) or a group $-\text{CH}_2-\text{N}(\text{X}_8)-\text{Alk}-$ (Ve), in which Alk_1 represents the alkyl-ylidine radical corresponding to a radical Alk and Alk_2 corresponds to a radical Alk which has been shortened by one methylene group attached to the nitrogen atom, X_7 represents the oxo or thioxo radical and X_8 represents hydrogen or a radical which can be replaced by hydrogen under the conditions for the reduction of X_6 and/or Y , and Y represents a radical of the formula $-\text{CO}-$ (Vf) or $-\text{CH}(\text{OX}_8)-$ (Vg) in which X_8 has the meaning indicated above, Ar_2 corresponds to a radical Ar , but optionally carries, instead of one or two hydroxyl groups, one or two groups OX_8 in which X_8 has the meaning indicated above, and n denotes zero or 1, X_6 being in all cases a reducible group Va to Vd and/or Y being a carbonyl group Vf, this/these group(s) is/are reduced and the groups X_8 which are other than hydrogen are replaced by hydrogen in the same operation, or

d) a compound of the formula



wherein Ar_3 has the meaning of Ar or represents a radical Ar which is substituted by 1 or 2 groups which can be converted into hydroxyl by ammonolysis, and X_9 denotes hydrogen or a group which can be removed by ammonolysis, or a reactive derivative of one of the carboxylic acids defined in



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formula (VI), is reacted with ammonia, and radicals X_9 which may be present are removed at the same time and replaced by hydrogen, and/or, if desired, the resulting free compound is converted into a salt or a resulting salt is converted into the free compound, and/or, if desired, a resulting mixture of racemates is separated into the two stereoisomeric (diastereomeric) racemates or a resulting racemate is resolved into the optical antipodes.

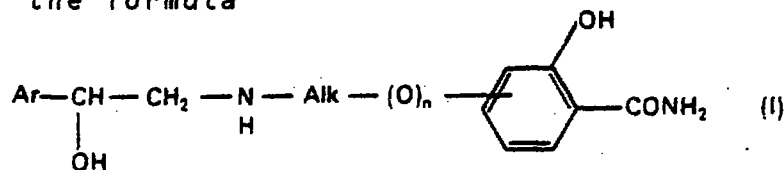
17. Process according to Claim 16, characterised in that a resulting compound of the formula I is converted into a pharmaceutically acceptable, non-toxic acid addition salt.



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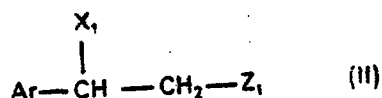
Patent Claims for the contracting state AP

1. Process for the preparation of N-alkylated amino alcohols of the formula

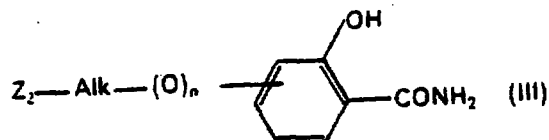


wherein Ar denotes a radical of aromatic character which is unsubstituted or substituted by hydroxyl, n denotes the values 0 or 1 and Alk denotes an alkylene radical having 2 to 5 carbon atoms, the nitrogen atom and the oxygen atom or, if n represents 0, the phenyl radical, being separated from one another by at least 2 carbon atoms, and salts thereof, characterised in that

a) a compound of the formula

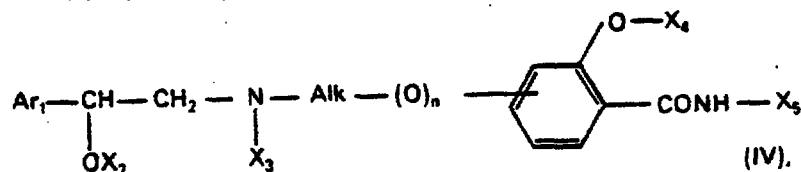


is reacted with a compound of the formula



wherein one of the groups Z₁ and Z₂ represents a reactive esterified hydroxyl group and the other represents the primary amino group and X₁ denotes hydroxyl, or wherein X₁ and Z₁ together denote the epoxy group and Z₂ represents the primary amino group, and Ar, Alk and n have the above meaning, or

b) in a compound of the formula



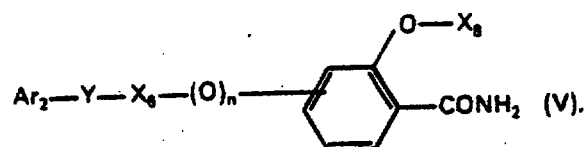
wherein Ar₁ has the meaning of Ar or denotes a radical Ar which is substituted by 1 to 2 groups which can be converted into hydroxyl, X₂, X₃ and X₄ each denote hydrogen or a substituent which can be replaced by hydrogen, and X₅ represents



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hydrogen, and X_2 and X_3 and/or X_4 and X_5 together denote a divalent radical which can be replaced by two hydrogen atoms, subject to the proviso that at least one of the radicals X_2 , X_3 and X_4 is other than hydrogen, or at least Ar denotes a radical Ar which is substituted by 1 to 2 groups which can be converted into hydroxyl, or at least X_2 and X_3 together, or X_4 and X_5 together represent a divalent radical which can be replaced by two hydrogen atoms, or in a salt thereof, the groups X_2 , X_3 and X_4 or X_4 and X_5 together which are other than hydrogen are replaced by hydrogen, and/or substituted hydroxyl which is present in a radical Ar_1 is converted into free hydroxyl, or

c) in a compound of the formula

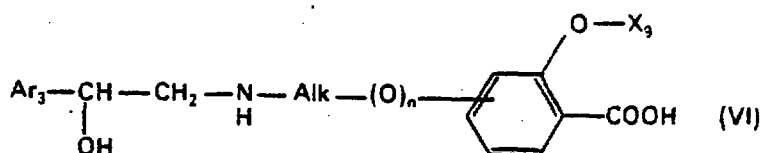


wherein X_6 is a reducible group of the formulae $-\text{CH}=\text{N}-\text{Alk}-$ (Va) or $-\text{CH}_2-\text{N}=\text{Alk}_1-$ (Vb) or $-\text{C}(=\text{X}_7)-\text{N}(\text{X}_8)-\text{Alk}-$ (Vc) or $-\text{CH}_2-\text{N}(\text{X}_8)-\text{C}(=\text{X}_7)-\text{Alk}_2-$ (Vd) or a group $-\text{CH}_2-\text{N}(\text{X}_8)-\text{Alk}-$ (Ve), in which Alk_1 represents the alkyl-ylidine radical corresponding to a radical Alk and Alk_2 corresponds to a radical Alk which has been shortened by one methylene group attached to the nitrogen atom, X_7 represents the oxo or thioxo radical and X_8 represents hydrogen or a radical which can be replaced by hydrogen under the conditions for the reduction of X_6 and/or Y, and Y represents a radical of the formula $-\text{CO}-$ (Vf) or $-\text{CH}(\text{OX}_8)-$ (Vg) in which X_8 has the meaning indicated above, Ar_2 corresponds to a radical Ar, but optionally carries, instead of one or two hydroxyl groups, one or two groups OX_8 in which X_8 has the meaning indicated above, and n denotes zero or 1, X_6 being in all cases a reducible group Va to Vd and/or Y being a carbonyl group Vf, this/these group(s) is/are reduced and the groups X_8 which are other than hydrogen are replaced by hydrogen in the same operation, or

d) a compound of the formula



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wherein Ar_3 has the meaning of Ar or represents a radical Ar which is substituted by 1 or 2 groups which can be converted into hydroxyl by ammonolysis, and X_9 denotes hydrogen or a group which can be removed by ammonolysis, or a reactive derivative of one of the carboxylic acids defined in formula (VI), is reacted with ammonia, and radicals X_9 which may be present are removed at the same time and replaced by hydrogen, and/or, if desired, the resulting free compound is converted into a salt or a resulting salt is converted into the free compound, and/or, if desired, a resulting mixture of racemates is separated into the two stereoisomeric (diastereomeric) racemates or a resulting racemate is resolved into the optical antipodes.

2. Process for the preparation of α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol according to Claim 1, characterised in that α -[N-[2-(2,3-dihydro-2,2-dimethyl-4-oxo-4H-1,3-benzoxazin-6-yloxy)-1-methylethyl]-aminomethyl]benzyl alcohol and isopropylamine are used as the starting materials.

3. Process for the preparation of α -[N-[2-(4-carbamoyl-3-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol according to Claim 1, characterised in that α -[N-[2-(2,3-dihydro-2,2-dimethyl-4-oxo-4H-1,3-benzoxazin-7-yloxy)-1-methylethyl]-aminomethyl]-benzyl alcohol and isopropylamine are used as the starting materials.

4. Process for the preparation of α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol according to Claim 1, characterised in that α -(aminomethyl)-benzyl alcohol and 2,3-dihydro-2,2-dimethyl-6-(2-bromoethoxy)-4H-1,3-benzoxazin-4-one are used as the starting materials.

5. Process for the preparation of α -[N-[2-(4-carbamoyl-3-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol according to Claim 1, characterised in that N-[2-[4-carbamoyl-3-



hydroxyphenoxy)-ethyl]-N-(2-hydroxy-2-phenylethyl)-benzyl-amine is used as the starting materials (sic).

6. Process for the preparation of α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-3-pyridine-methanol according to Claim 1, characterised in that α -(aminomethyl)-3-pyridinemethanol and 2,3-dihydro-2,2-dimethyl-6-(2-oxopropoxy)-4H-1,3-benzoxazin-4-one are used as the starting materials.

7. Process for the preparation of α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-2-pyridine-methanol according to Claim 1, characterised in that α -(aminomethyl)-2-pyridinemethanol and 2,3-dihydro-2,2-dimethyl-6-(2-oxopropoxy)-4H-1,3-benzoxazin-4-one are used as the starting materials.

8. Process for the preparation of α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-4-hydroxybenzyl alcohol according to Claim 1, characterised in that 4-benzyloxy- α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol is used as the starting material.

9. Process for the preparation of α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol according to Claim 1, characterised in that the Schiff's base formed from 5-(2-oxopropoxy)-salicylamide and α -(aminomethyl)-benzyl alcohol is used as the starting material.

10. Process for the preparation of R-(-)- α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol according to Claim 1, characterised in that the Schiff's base formed from R-(-)- α -(aminomethyl)-benzyl alcohol and 5-(2-oxopropoxy)-salicylamide is used as the starting material.

11. Process for the preparation of α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-4-hydroxybenzyl alcohol according to Claim 1, characterised in that 4-benzyloxy- α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol is used as the starting material.

12. Process for the preparation of α -[N-[2-(2-carbamoyl-



-3-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol according to Claim 1, characterised in that 6-(2-bromoethoxy)-salicylamide and α -(aminomethyl)-benzyl alcohol are used as the starting material (sic).

13. Process for the preparation of α -[N-[3-(4-carbamoyl-3-hydroxyphenoxy)-propyl]-aminomethyl]-benzyl alcohol according to Claim 1, characterised in that N-[3-(4-carbamoyl-3-hydroxyphenoxy)-propyl]-N-(2-hydroxy-2-phenylethyl)-benzylamine is used as the starting material.

14. Process for the preparation of α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol according to Claim 1, characterised in that α -[N-[2-(3-carbomethoxy-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol and ammonia are used as the starting materials.

15. Process for the preparation of α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol according to Claim 1, characterised in that phenylglyoxal and 5-(2-aminoethoxy)-salicylamide are used as the starting materials.

16. Process for the preparation of α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-2-pyridinemethanol according to Claim 1, characterised in that α -(aminomethyl)-2-pyridinemethanol and 2,3-dihydro-2,2-dimethyl-6-(2-bromoethoxy)-4H-1,3-benzoxazin-4-one are used as the starting materials.

17. Process for the preparation of α -[N-[2-(4-carbamoyl-3-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol according to Claim 1, characterised in that phenylethylene oxide and 4-(2-aminopropoxy)-salicylamide are used as the starting materials.

18. Process for the preparation of α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-2-furanmethanol according to Claim 1, characterised in that α -(aminomethyl)-2-furanmethanol and 2,3-dihydro-2,2-dimethyl-6-(2-bromoethoxy)-4H-1,3-benzoxazin-4-one are used as the starting materials.



19. Process for the preparation of α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-2-thiophenemethanol according to Claim 1, characterised in that α -(aminomethyl)-2-thiophenemethanol and 2,3-dihydro-2,2-dimethyl-6-(2-bromoethoxy)-4H-1,3-benzoxazin-4-one are used as the starting materials.
20. Process for the preparation of S-(+)- α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-1-methylethyl]-aminomethyl]-benzyl alcohol according to Claim 1, characterised in that S-(+)- α -(aminomethyl)-benzyl alcohol and 5-(2-oxopropoxy)-salicylamide are used as the starting materials.
21. Process for the preparation of α -[N-[2-(4-carbamoyl-3-hydroxyphenoxy)-ethyl]-aminomethyl]-4-hydroxybenzyl alcohol according to Claim 1, characterised in that 4-benzyloxy- α -[N-[2-(4-carbamoyl-3-hydroxyphenoxy)-ethylaminomethyl]-benzyl alcohol is used as the starting material.
22. Process for the preparation of α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol according to Claim 1, characterised in that α -[N-benzyl-N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol is used as the starting material.
23. Process for the preparation of α -[N-[3-(3-carbamoyl-4-hydroxyphenoxy)-propyl]-aminomethyl]-benzyl alcohol according to Claim 1, characterised in that α -(aminomethyl)-benzyl alcohol and 6-(3-bromopropoxy)-2,3-dihydro-2,2-dimethyl-4H-1,3-benzoxazin-4-one are used as the starting materials.
24. Process for the preparation of α -[N-[3-(3-carbamoyl-4-hydroxyphenyl)-propyl]-aminomethyl]-benzyl alcohol according to Claim 1, characterised in that α -[N-benzyl-N-[3-(3-carbamoyl-4-hydroxyphenyl)-propyl]-aminomethyl]-benzyl alcohol is used as the starting material.
25. Process for the preparation of α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-3,5-dihydroxybenzyl alcohol according to Claim 1, characterised in that N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-N-[2-(3,5-dibenzyloxyphenyl)-2-hydroxyethyl]-benzylamine is used as the starting



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material.

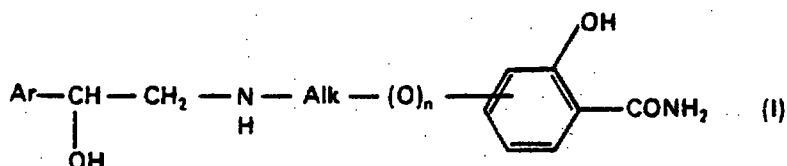
26. Process for the preparation of α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol according to Claim 1, characterised in that 5-(2-aminoethoxy)-salicylamide and α -(bromoethyl)-benzyl alcohol are used as the starting materials.

27. Process for the preparation of α -[N-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethyl]-aminomethyl]-benzyl alcohol according to Claim 1, characterised in that phenylethylene oxide and 5-(2-aminoethoxy)-salicylamide are used as the starting materials.

28. Process according to one of Claims 1-27, characterised in that a resulting compound of the formula I is converted into a pharmaceutically acceptable, non-toxic acid addition salt.



1. A N-alkylated aminoalcohol of the formula



in which Ar is a radical of aromatic character which is unsubstituted or substituted by hydroxyl, n has the values nought or 1 and Alk is an alkylene radical having 2 to 5 carbon atoms and the nitrogen atom and the oxygen atom or, if n is

nought, the phenyl radical are separated from one another by at least 2 carbon atoms, in the form of a mixture of racemates, a stereoisomeric (diastereomeric) racemate or an optical antipode.

2. A compound of the formula I, in which Ar is phenyl, 2- or 3- or 4-pyridyl, 3- or 4- or 6-pyridazinyl, 2- or 4- or 5-pyrimidinyl or 2-pyrazinyl, 2- or 3-furyl, 2- or 3-pyrrolyl, 2- or 3-thienyl, 2- or 4-oxazolyl, 2- or 4-thiazolyl, 3- or 5-pyrazolyl, 2- or 4-imidazolyl, 1,2,4-thiadiazol-3- or 5-yl or 1,3,4-thiadiazol-2-yl, which radicals are in each case unsubstituted or substituted by 1 or 2 hydroxyl groups, and Alk is an alkylene radical having 2 to 4 carbon atoms and the nitrogen atom and the oxygen atom or, if n is nought, the phenyl radical are separated from one another by 2 to 3 carbon atoms, and n is nought or 1.

3. A compound of the formula I in which Ar is phenyl, 2- or 3-pyridyl, 2- or 3-furyl or 2- or 3-thienyl, which radicals are in each case unsubstituted or substituted by 1 or 2 hydroxyl groups, and Alk is an alkylene radical having 2 or 3 carbon atoms, and the nitrogen atom and the oxygen atom or, if n is nought, the phenyl radical are separated from one another by 2 to 3 carbon atoms, and n is nought or 1.

4. A compound of the formula I in which Ar is phenyl, 2- or 3-pyridyl, 2-furyl or 2-thienyl, which radicals are in each case unsubstituted or substituted by 1 or 2 hydroxyl groups, and Alk is an alkylene radical having 2 or 3 carbon atoms, and the nitrogen atom and the oxygen atom or, if n is nought, the phenyl radical are separated from one another by 2 or 3 carbon atoms, and n is

nought or 1.

5. α -[N-[2-(3-Carbamoyl-4-hydroxy-phenoxy)-1-methyl-ethyl]-aminomethyl]-benzyl alcohol as the enantiomer pair with a melting point of 166-168°C.

6. α -[N-[2-(3-Carbamoyl-4-hydroxy-phenoxy)-1-methyl-ethyl]-aminomethyl]-benzyl alcohol as the enantiomer pair with a melting point of 152-154°C.

7. α -[N-[2-(3-Carbamoyl-4-hydroxy-phenoxy)-ethyl]-aminomethyl]-benzyl alcohol.

8. α -[N-[2-(4-Carbamoyl-3-hydroxy-phenoxy)-ethyl]-aminomethyl]-4-hydroxy-benzyl alcohol.

9. A salt of a compound of Claims 1 to 8.

10. A pharmaceutically acceptable, non-toxic acid addition salt of a compound of Claims 1 to 8.

11. A pharmaceutical preparation containing a compound of Claims 1 to 8 and 10, together with inert auxiliaries and carriers.

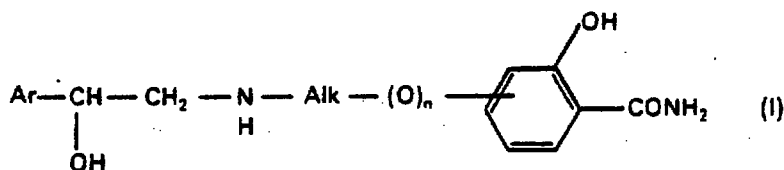
12. A compound of the formula I as a pharmaceutical active substance.

13. A compound of the formula I as stimulator of cardiac β -receptors.

14. The use of a compound of the formula I for producing pharmaceutical preparations.

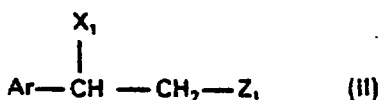
15. A compound of the formula I for use in combating cardiac insufficiency.

16. A process for the preparation of a N-alkylated aminoalcohol of the formula

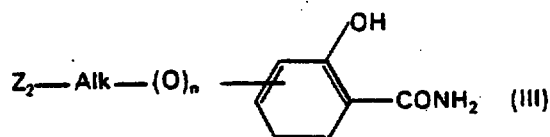


in which Ar is a radical of aromatic character which is unsubstituted or substituted by hydroxyl, n has the values nought or 1 and Alk is an alkylene radical having 2 to 5 carbon atoms and the nitrogen atom and the oxygen atom or, if n is nought, the phenyl radical are separated from one another by at least 2 carbon atoms, or a salt thereof, which comprises

a) reacting a compound of the formula



with a compound of the formula

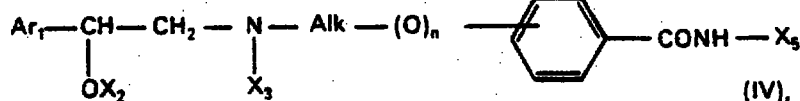


in which formulae one of the groups Z_1 and Z_2 is a reactive esterified hydroxyl group and the other is a primary amino group and X_1 is hydroxyl, or X_1 and Z_1 together are an epoxy group and Z_2 is a primary amino group, and Ar, Alk and n are as defined above, or

b) in a compound of the formula

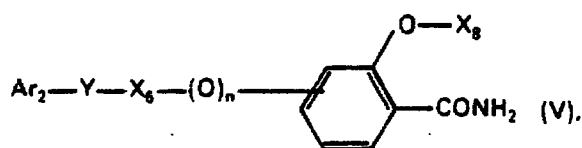


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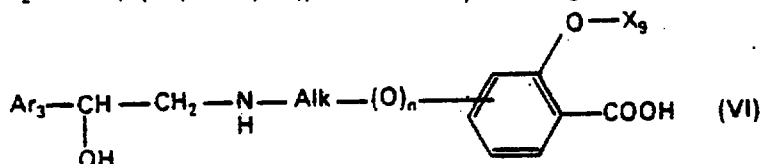


in which Ar₁ has the meaning defined for Ar or is a radical Ar which is substituted by 1 to 2 groups which can be converted to hydroxyl and X₂, X₃ and X₄ are each hydrogen or a substituent re-

and X₄ differs from hydrogen, or at least Ar₁ is a radical Ar which is substituted by 1 to 2 groups which can be converted to hydroxyl, or at least X₂ and X₃ together or X₄ and X₅ together are a divalent radical replaceable by two hydrogen atoms, or in a salt thereof, replacing by hydrogen the X₂, X₃, X₄ or X₅ together which differ from hydrogen and/or converting substituted hydroxyl present in a radical Ar₁ to free hydroxyl, or c) in a compound of the formula



in which X₆ is a reducible group of the formulae -CH=N-Alk (Va) or -CH₂-N=Alk₁- (Vb) or -C(=X₇)-



in which Ar₃ has the meaning defined for Ar or is a radical Ar which is substituted by 1 to 2 groups convertible to hydroxyl by ammonolysis and X₉ is hydrogen or a group detachable by ammonolysis, or a reactive derivative of one of the carboxylic acids defined by formula VI, with ammonia and, at the same time, detaching any radicals X₉ which may be present and replacing these by hydrogen, and/or, if desired, converting the resulting free compound into a salt or converting a resulting salt into the free compound and/or, if desired, separating the resulting mixture of racemates into

placeable by hydrogen and X₅ is hydrogen, or X₂ and X₃ and/or X₄ and X₅ together are a divalent radical replaceable by two hydrogen atoms, with the proviso that at least one of the radicals X₂, X₃

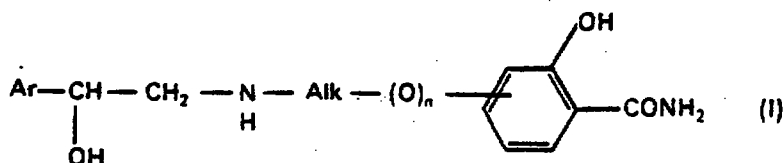
N(X₄)-Alk (Vc) or -CH₂-N(X₄)-C(=X₇)-Alk₂ (Vd) or a group -CH₂-N(X₄)-Alk (Ve), in which formulae Alk₁ is an alkylidene radical corresponding to a radical Alk and Alk₂ corresponds to a radical Alk shortened by a methylene group bonded to the nitrogen atom, X₇ is an oxo or thioxo radical and X₈ is hydrogen or a radical replaceable by hydrogen under the conditions for the reduction of X₆ and/or Y, and Y is a radical of the formula -CO-(Vf) or -CH(OX₈)- (Vg), in which X₈ is as defined above, Ar₂ corresponds to a radical Ar but can carry one or two groups OX₈, in which X₈ is as defined above, in place of one or two hydroxyls, and n is nought or 1 and, in every case, X₉ is a reducible group Va to Vd and/or Y is a carbonyl group Vf, reducing this group or groups and, in the same operation, replacing by hydrogen the groups X₉ which differ from hydrogen, or d) reacting a compound of the formula

the two stereoisomeric (diastereomeric) racemates or resolving a resulting racemate into the optical antipodes.

17. A process according to claim 16, wherein a resulting compound of the formula I is converted to a pharmaceutically acceptable, non-toxic acid addition salt.

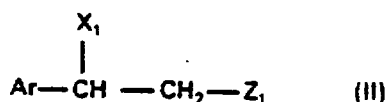
Claims for the Contracting state AT

1. A process for the preparation of a N-alkylated aminoalcohol of the formula

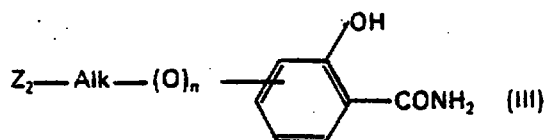


in which Ar is a radical of aromatic character which is unsubstituted or substituted by hydroxyl, n has the values nought or 1 and Alk is an alkylene radical having 2 to 5 carbon atoms and the nitrogen atom and the oxygen atom or, if n is nought, the phenyl radical are separated from one another by at least 2 carbon atoms, or a salt thereof, which comprises

a) reacting a compound of the formula

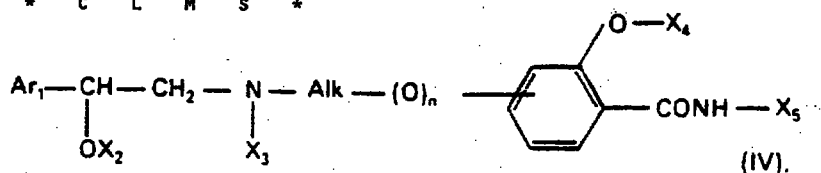


with a compound of the formula



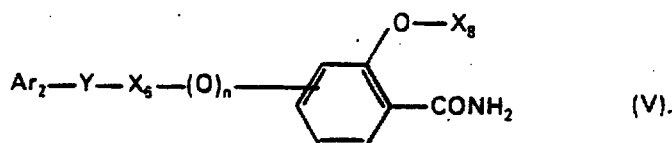
in which formulae one of the groups Z₁ and Z₂ is a reactive esterified hydroxyl group and the other is a primary amino group and X₁ is hydroxyl, or X₁ and Z₁ together are an epoxy group and Z₂ is a primary amino group, and Ar, Alk and n are as defined above, or

b) in a compound of the formula



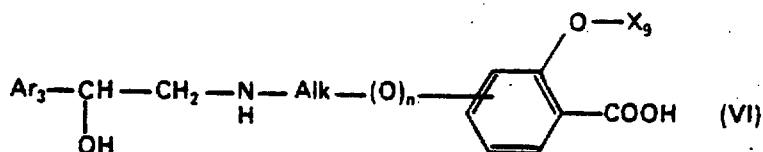
in which Ar₁ has the meaning defined for Ar or is a radical Ar which is substituted by 1 to 2 groups which can be converted to hydroxyl and X₂, X₃ and X₄ are each hydrogen or a substituent replaceable by hydrogen and X₅ is hydrogen, or X₂ and X₃ and/or X₄ and X₅ together are a divalent radical replaceable by two hydrogen atoms, with the proviso that at least one of the radicals X₂, X₃ and X₄ differs from hydrogen, or at least Ar₁ is a

radical Ar which is substituted by 1 to 2 groups which can be converted to hydroxyl, or at least X₂ and X₃ together or X₄ and X₅ together are a divalent radical replaceable by two hydrogen atoms, or in a salt thereof, replacing by hydrogen the X₂, X₃, X₄ or X₅ and X₅ together which differ from hydrogen and/or converting substituted hydroxyl present in a radical Ar₁ to free hydroxyl, or c) in a compound of the formula



in which X₆ is a reducible group of the formulae -CH=N-Alk (Va) or -CH₂-N=Alk₁ (Vb) or -C(=X₇)-N(X₈)-Alk (Vc) or -CH₂-N(X₈)-C(=X₇)-Alk₂ (Vd) or a group -CH₂-N(X₈)-Alk (Ve), in which formulae Alk₁ is an alkylidene radical corresponding to a radical Alk and Alk₂ corresponds to a radical Alk shortened by a methylene group bonded to the nitrogen atom, X₇ is an oxo or thioxo radical and X₈ is hydrogen or a radical replaceable by hydrogen under the conditions for the reduction of X₆ and/or Y, and Y is a radical of the formula -CO-

(Vf) or -CH(OX₉) (Vg), in which X₉ is as defined above, Ar₂ corresponds to a radical Ar but can carry one or two groups OX₉, in which X₉ is as defined above, in place of one or two hydroxyls, and n is nought or 1 and, in every case, X₆ is a reducible group Va to Vd and/or Y is a carbonyl group Vf, reducing this group or groups and, in the same operation, replacing by hydrogen the groups X₈ which differ from hydrogen or d) reacting a compound of the formula



in which Ar₃ has the meaning defined for Ar or is a radical Ar which is substituted by 1 to 2 groups convertible to hydroxyl by ammonolysis and X₉ is hydrogen or a group detachable by ammonolysis, or a reactive derivative of one of the carboxylic acids defined by formula VI, with ammonia and, at the same time, detaching any radicals X₉ which may be present and replacing these by hydrogen, and/or, if desired, converting the resulting free compound into a salt or converting a resulting salt into the free compound and/or, if desired, separating the resulting mixture of racemates into the two stereoisomeric (diastereomeric) racemates or resolving a resulting racemate into the optical antipodes.

2. A process according to Claim 1 for producing α-[N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-1-methyl-ethyl]-aminomethyl]-benzyl alcohol, wherein the starting materials used are α-[N-[2-(2,3-dihydro-2,2-dimethyl-4-oxo-4H-1,3-benzoxazin-6-yloxy)-1-methyl-ethyl]-aminomethyl]-benzyl alcohol and isopropylamine.

3. A process according to Claim 1 for producing α-[N-[2-(4-carbamoyl-3-hydroxyphenoxy)-

1-methyl-ethyl]-aminomethyl]-benzyl alcohol, wherein the starting materials used are α-[N-[2-(2,3-dihydro-2,2-dimethyl-4-oxo-4H-1,3-benzoxazin-7-yloxy)-1-methyl-ethyl]-aminomethyl]-benzyl alcohol and isopropylamine.

4. A process according to Claim 1 for producing α-[N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-ethyl]-aminomethyl]-benzyl alcohol, wherein the starting materials used are α-(aminomethyl)-benzyl alcohol and 2,3-dihydro-2,2-dimethyl-6-(2-bromoethoxy)-4H-1,3-benzoxazin-4-one.

5. A process according to Claim 1 for producing α-[N-[2-(4-carbamoyl-3-hydroxy-phenoxy)-ethyl]-aminomethyl]-benzyl alcohol, wherein the starting materials used are N-[2-(4-carbamoyl-3-hydroxy-phenoxy)-ethyl]-N-(2-hydroxy-2-phenylethyl)-benzylamine.

6. A process according to Claim 1 for producing α-[N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-1-methyl-ethyl]-aminomethyl]-3-pyridinemethanol, wherein the starting materials used are α-(aminomethyl)-3-pyridinemethanol and 2,3-dihydro-2,2-dimethyl-6-(2-oxo-propoxy)-4H-1,3-benzoxazin-4-one.



7. A process according to Claim 1 for producing α -[N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-1-methyl-ethyl]-aminomethyl]-2-pyridinemethanol, wherein the starting materials used are α -(aminomethyl)-2-pyridinemethanol and 2,3-dihydro-2,2-dimethyl-6-(2-oxo-propoxy)-4H-1,3-benzoxazin-4-one.
8. A process according to Claim 1 for producing α -[N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-1-methyl-ethyl]-aminomethyl]-4-hydroxybenzyl alcohol, wherein a starting material used is 4-benzyloxy- α -[N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-1-methyl-ethyl]-aminomethyl]-benzyl alcohol.
9. A process according to Claim 1 for producing α -[N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-1-methyl-ethyl]-aminomethyl]-benzyl alcohol, wherein a starting material used is the Schiff base formed from 5-(2-oxo-propoxy)-salicylamide and α -(aminomethyl)-benzyl alcohol.
10. A process according to Claim 1 for producing R-(-)- α -[N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-1-methyl-ethyl]-aminomethyl]-benzyl alcohol, wherein a starting material used is the Schiff base formed from R-(-)- α -(aminomethyl)-benzyl alcohol and 5-(2-oxo-propoxy)-salicylamide.
11. A process according to Claim 1 for producing α -[N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-ethyl]-aminomethyl]-4-hydroxybenzyl alcohol, wherein a starting material used is 4-benzyloxy- α -[N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-ethyl]-aminomethyl]-benzyl alcohol.
12. A process according to Claim 1 for producing α -[N-[2-(2-carbamoyl-3-hydroxy-phenoxy)-ethyl]-aminomethyl]-benzyl alcohol, wherein a starting material used is 6-(2-bromoethoxy)-salicylamide and α -(aminomethyl)-benzyl alcohol.
13. A process according to Claim 1 for producing α -[N-[3-(4-carbamoyl-3-hydroxy-phenoxy)-propyl]-aminomethyl]-benzyl alcohol, wherein a starting material used is N-[3-(4-carbamoyl-3-hydroxy-phenoxy)-propyl]-N-(2-hydroxy-2-phenyl-ethyl)-benzylamine.
14. A process according to Claim 1 for producing α -[N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-1-methyl-ethyl]-aminomethyl]-benzyl alcohol, wherein the starting materials used are α -[N-[2-(3-carbomethoxy-4-hydroxy-phenoxy)-1-methyl-ethyl]-aminomethyl]-benzyl alcohol and ammonia.
15. A process according to Claim 1 for producing α -[N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-ethyl]-aminomethyl]-benzyl alcohol, wherein the starting materials used are phenylglyoxal and 5-(2-aminoethoxy)-salicylamide.
16. A process according to Claim 1 for producing α -[N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-ethyl]-aminomethyl]-2-pyridinemethanol, wherein the starting materials used are α -(aminomethyl)-2-pyridinemethanol and 2,3-dihydro-2,2-dimethyl-6-(2-bromoethoxy)-4H-1,3-benzoxazin-4-one.
17. A process according to Claim 1 for producing α -[N-[2-(4-carbamoyl-3-hydroxy-phenoxy)-1-methyl-ethyl]-aminomethyl]-benzyl alcohol, wherein the starting materials used are phenylethylene oxide and 4-(2-amino-propoxy)-salicylamide.
18. A process according to Claim 1 for producing α -[N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-ethyl]-aminomethyl]-2-furanmethanol, wherein the starting materials used are α -(aminomethyl)-2-furanmethanol and 2,3-dihydro-2,2-dimethyl-6-(2-bromoethoxy)-4H-1,3-benzoxazin-4-one.
19. A process according to Claim 1 for producing α -[N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-ethyl]-aminomethyl]-2-thiophenemethanol, wherein the starting materials used are α -(aminomethyl)-2-thiophenemethanol and 2,3-dihydro-2,2-dimethyl-6-(2-bromoethoxy)-4H-1,3-benzoxazin-4-one.
20. A process according to Claim 1 for producing S-(+)- α -[N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-1-methyl-ethyl]-aminomethyl]-benzyl alcohol, wherein the starting materials used are S-(+)- α -(aminomethyl)-benzyl alcohol and 5-(2-oxo-propoxy)-salicylamide.
21. A process according to Claim 1 for producing α -[N-[2-(4-carbamoyl-3-hydroxy-phenoxy)-ethyl]-aminomethyl]-4-hydroxybenzyl alcohol, wherein a starting material used is 4-benzyloxy- α -[N-[2-(4-carbamoyl-3-hydroxy-phenoxy)-ethyl]-aminomethyl]-benzyl alcohol.
22. A process according to Claim 1 for producing α -[N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-ethyl]-aminomethyl]-benzyl alcohol, wherein a starting material used is α -[N-benzyl-N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-ethyl]-aminomethyl]-benzyl alcohol.
23. A process according to Claim 1 for producing α -[N-[3-(3-carbamoyl-4-hydroxy-phenoxy)-propyl]-aminomethyl]-benzyl alcohol, wherein the starting materials used are α -(aminomethyl)-benzyl alcohol and 6-(3-bromopropoxy)-2,3-dihydro-2,2-dimethyl-4H-1,3-benzoxazin-4-one.
24. A process according to Claim 1 for producing α -[N-[3-(3-carbamoyl-4-hydroxy-phenyl)-propyl]-aminomethyl]-benzyl alcohol, wherein a starting material used is α -[N-benzyl-N-[3-(3-carbamoyl-4-hydroxy-phenyl)-propyl]-aminomethyl]-benzyl alcohol.
25. A process according to Claim 1 for producing α -[N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-ethyl]-aminomethyl]-3,5-dihydroxybenzyl alcohol, wherein a starting material used is N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-ethyl]-N-[2-(3,5-dibenzyloxyphenyl)-2-hydroxy-ethyl]-benzylamine.
26. A process according to Claim 1 for producing α -[N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-ethyl]-aminomethyl]-benzyl alcohol, wherein the starting materials used are 5-(2-aminoethoxy)-salicylamide and α -(bromomethyl)-benzyl alcohol.
27. A process according to Claim 1 for producing α -[N-[2-(3-carbamoyl-4-hydroxy-phenoxy)-ethyl]-aminomethyl]-benzyl alcohol, wherein the starting materials used are phenylethylene oxide

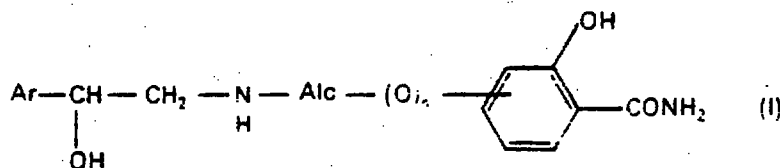


and 5-(2-aminoethoxy)-salicylamide.

28. A process according to any one of Claims 1-27, wherein a resulting compound of the formula I is converted into a pharmaceutically acceptable, non-toxic acid addition salt.

Revendications pour les Etats contractants BE, CH, DE, FR, GB, IT, LU, NL, SE

1 Aminoalcools N-alcylés de formule



où Ar représente un radical non substitué ou substitué par hydroxy de caractère aromatique, n les nombres zéro ou 1 et Alc un radical alcoylène ayant de 2 à 5 atomes de carbone, ou l'atome d'azote et l'atome d'oxygène ou, si n vaut zéro, le radical phényle sont séparés l'un de l'autre par au moins deux atomes de carbone sous forme de mélanges de racémates, de racémates stéréoisomères (diastéréoisomères) ou d'antipodes optiques.

2. Composés de formule I, où Ar représente un phényle non substitué ou substitué par un ou deux groupes hydroxy, un 2-, 3- ou 4-pyridyle, un 3-, 4- ou 6-pyridazinyne, un 2-, 4- ou 5-pyrimidinyle ou un 2-pyrazinyne, un 2-, ou 3-furyle, un 2- ou 3-pyrryle, un 2- ou 3-thiényle, un 2- ou 4-oxazolyle, un 2- ou 4-thiazolyle, un 3- ou 5-pyrazolyle, un 2- ou 4-imidazolyle, un 1,2,4-thiadiazol-3- ou 5-yle ou un 1,3,4-thiadiazol-2-yle et Alc un radical alcoylène ayant de 2 à 4 atomes de carbone, l'atome d'azote et l'atome d'oxygène ou, si n vaut zéro, le radical phényle, étant séparés l'un de l'autre par 2 à 3 atomes de carbone, et n vaut zéro ou 1.

3. Composés de formule I, où Ar représente un phényle non substitué ou substitué par un ou deux groupes hydroxy, un 2- ou 3-pyridyle, un 2- ou 3-furyle ou un 2- ou 3-thiényle et Alc un radical alcoylène ayant de 2 à 3 atomes de carbone, où l'atome d'azote et l'atome d'oxygène ou, si n vaut zéro, le radical phényle, sont séparés l'un de l'autre par 2 à 3 atomes de carbone, et n vaut zéro ou 1.

4. Composés de formule I, où Ar représente un phényle non substitué ou substitué par un ou deux groupes hydroxy; un 2- ou 3-pyridyle, un

2-furyle ou un 2-thiényle et Alc un radical alcoylène ayant de 2 à 3 atomes de carbone. l'atome d'azote et l'atome oxygène ou, si n vaut zéro, le noyau phényle, étant séparés l'un de l'autre par 2 à 3 atomes de carbone, et n vaut zéro ou 1.

5. α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-1-méthyl-éthyl]-aminométhyl]-benzylalcoool sous forme de paire d'énantiomères de P, 166-168°

6. α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-1-méthyl-éthyl]-aminométhyl]-benzylalcoool sous forme de paire d'énantiomères de P, 152-154°.

7. α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-éthyl]-aminométhyl]-benzylalcoool.

8. α -[N-[2-(4-carbamoyl-3-hydroxy-phénoxy)-éthyl]-aminométhyl]-4-hydroxy-benzylalcoool.

9. Les sels des composés des revendications 1 à 8.

10. Sels d'addition acides non toxiques pharmaceutiquement acceptables des composés des revendications 1 à 8.

11. Préparations pharmaceutiques contenant un composé des revendications 1 à 8 et 10 avec des additifs et supports inertes.

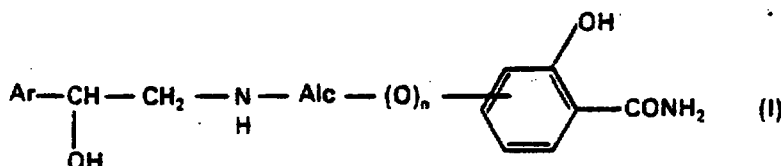
12. Composés de formule I comme médicaments.

13. Composés de formule I comme stimulateurs des β -récepteurs cardiaques.

14. Application des composés de formule I à la préparation de médicaments.

15. Composés de formule I aux fins d'application dans la lutte contre l'insuffisance cardiaque.

16. Procédé de préparation d'aminoalcools N-alcylés de formule



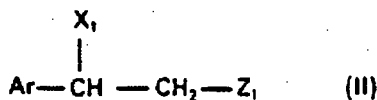
où Ar représente un radical non substitué ou substitué par hydroxy de caractère aromatique, n les nombres zéro ou 1 et Alc un radical alcoylène ayant de 2 à 5 atomes de carbone, où l'atome d'azote et l'atome d'oxygène ou, si n vaut zéro, le

radical phényle sont séparés l'un de l'autre par au moins deux atomes de carbone et de leurs sels, caractérisé en ce qu'on procède

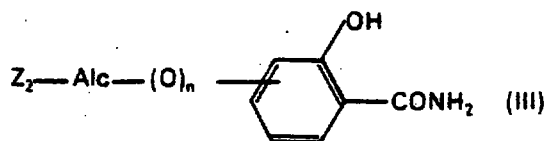
a) en faisant réagir un composé de formule



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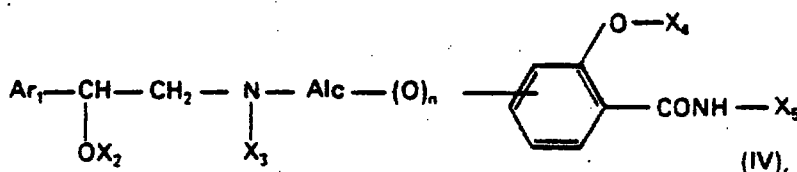


avec un composé de formule



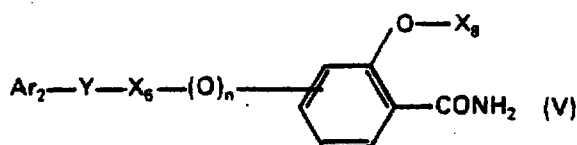
où l'un des groupes Z_1 et Z_2 représente un groupe hydroxy estérifié réactif et l'autre le groupe amino primaire, et X_1 représente un hydroxy, ou bien où X_1 et Z_1 représentent ensemble le groupe

époxy et Z_2 représente le groupe amino primaire, Ar , Alc et n ont la signification donnée ci-dessus, ou
b) dans un composé de formule



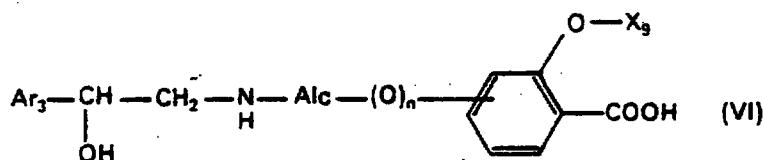
où Ar_1 a la signification d' Ar ou représente un radical Ar substitué par 1 à 2 groupes transformables en hydroxy, X_2 , X_3 et X_4 représentent chacun un hydrogène ou un substituant remplaçable par un hydrogène, et X_5 représente un hydrogène, ou X_2 et X_3 et/ou X_4 et X_5 représentent ensemble un radical bivalent remplaçable par 2 atomes d'hydrogène, avec la précision qu'au moins l'un des radicaux X_2 , X_3 et X_4 est différent d'un hydrogène, ou bien où au moins Ar_1 représente un radical Ar substitué par 1 à 2 groupes transformables en hydroxy, ou bien où au moins X_2 et X_3 ensemble ou X_4 et X_5 ensemble représentent un radical bivalent remplaçable par 2 atomes d'hydrogène, ou dans un de ses sels, au remplacement du X_2 , X_3 ou X_4 qui est différent d'un hydrogène, ou bien de X_4 et X_5 ensemble par un hydrogène, et/ou en transformant dans un radical Ar_1 l'hydroxy substitué présent en un hydroxy libre, ou

c) en réduisant dans un composé de formule



où X_4 est un groupe réductible de formules $-\text{CH}=\text{N}-\text{Alc}_1$ (Va), ou $-\text{CH}_2-\text{N}=\text{Alc}_1$ (Vb) ou $-\text{C}(=\text{X}_7)-\text{N}(\text{X}_8)-\text{Alc}_1$ (Vc) ou $-\text{CH}_2-\text{N}(\text{X}_8)-\text{C}(=\text{X}_7)-\text{Alc}_2$ (Vd) ou un groupe $-\text{CH}_2-\text{N}(\text{X}_8)-\text{Alc}_1$ (Ve), où Alc_1 représente le radical alcoyl-ylidène correspondant à un radical Alc et où Alc_2 correspond à un radical Alc raccourci d'un groupe méthylène lié sur l'atome d'azote, X_7 représente le radical oxo ou thioxo et X_8 un hydrogène ou un radical remplaçable par un hydrogène dans les conditions pour la réduction de X_8 et/ou Y et Y représente un radical de formule $-\text{CO}-$ (Vf) ou $-\text{CH}(\text{OX}_8)-$ (Vg) où X_8 a la signification donnée ci-dessus, Ar_2 correspond à un radical Ar , mais porte cependant éventuellement à la place d'un ou de deux hydroxy un ou deux groupes OX_8 , où X_8 a la signification donnée ci-dessus, et n vaut zéro ou 1, où X_6 est toujours un groupe Va à Vd réductible et/ou Y un groupe carbonyle Vf, en réduisant donc ce ou ces groupe(s) et dans le même mode opératoire en remplaçant les groupes X_8 différents d'un hydrogène par un hydrogène, ou

d) en faisant réagir avec de l'ammoniac un composé de formule



où Ar_3 a la signification de Ar , ou représente un radical Ar , qui est substitué par un à deux groupes transformables en hydroxy au moyen d'une ammonolyse, X_9 représente un hydrogène ou un groupe séparable par ammonolyse, ou un dérivé réactif de l'un des acides carboxyliques définis dans la formule VI, et simultanément en

séparant les radicaux X_9 éventuellement présents et en les remplaçant par de l'hydrogène, et/ou, si on le désire, en dédoublant un mélange de racémates obtenu pour donner les deux racémates stéréoisomères (diastéréoisomères) ou un racémate obtenu pour donner les antipodes optiques.

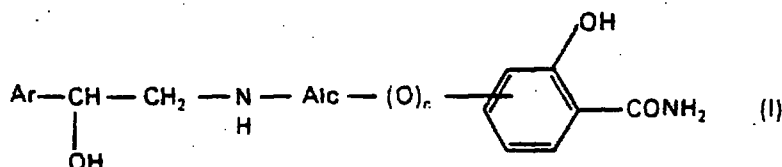
17. Procédé selon la revendication 16 caracté-



risé en ce qu'on transforme un composé de formule I obtenu en un sel d'addition acide non toxique pharmaceutiquement acceptable.

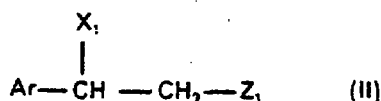
Revendications pour l'Etat contractant AT

1. Procédé de préparation d'aminoalcools N-alcoylés de formule

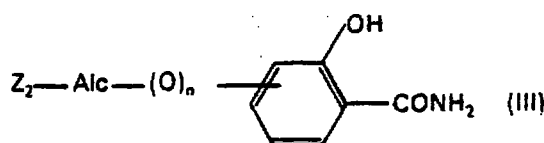


où Ar représente un radical non substitué ou substitué par hydroxy de caractère aromatique, n les nombres zéro ou 1 et Alc un radical alcoylène ayant de 2 à 5 atomes de carbone, où l'atome d'azote et l'atome d'oxygène ou, si n vaut zéro, le radical phényle sont séparés l'un de l'autre par au moins deux atomes de carbone et de leurs sels, caractérisé en ce qu'on procède

a) en faisant réagir un composé de formule

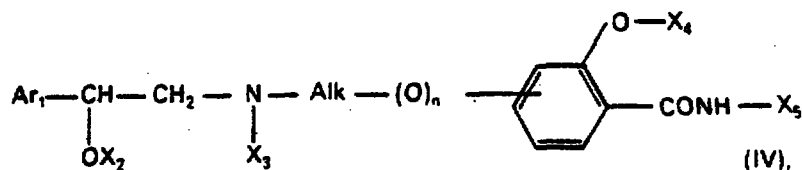


avec un composé de formule



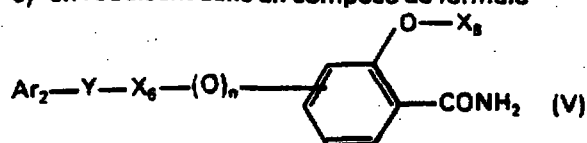
où l'un des groupes Z_1 et Z_2 représente un groupe hydroxy estérifié réactif et l'autre le groupe amino primaire, et X_1 représente un hydroxy, ou bien où X_1 et Z_1 représentent ensemble le groupe

époxy et Z_2 représente le groupe amino primaire, Ar, Alc et n ont la signification donnée ci-dessus, ou
b) dans un composé de formule



où Ar_1 a la signification d'Ar ou représente un radical Ar substitué par 1 à 2 groupes transformables en hydroxy, X_2 , X_3 et X_4 représentent chacun un hydrogène ou un substituant remplaçable par un hydrogène, et X_5 représente un hydrogène, ou X_2 et X_3 et/ou X_4 et X_5 représentent ensemble un radical bivalent remplaçable par 2 atomes d'hydrogène, avec la précision qu'au moins l'un des radicaux X_2 , X_3 et X_4 est différent d'un hydrogène, ou bien où au moins Ar_1 représente un radical Ar substitué par 1 à 2 groupes transformables en hydroxy, ou bien où au moins X_2 et X_3 ensemble ou X_4 et X_5 ensemble représentent un radical bivalent remplaçable par 2 atomes d'hydrogène, ou dans un de ses sels, au remplacement du X_2 , X_3 , ou X_4 qui est différent d'un hydrogène, ou bien de X_4 et X_5 ensemble par un hydrogène, et/ou en transformant dans un radical Ar_1 l'hydroxy substitué présent en un hydroxy libre, ou

c) en réduisant dans un composé de formule



où X_6 est un groupe réductible de formules

$-\text{CH}=\text{N}-\text{Alc}-$ (Va), ou $-\text{CH}_2-\text{N}=\text{Alc}_1-$ (Vb)

ou $-\text{C}(=\text{X}_7)-\text{N}(\text{X}_8)-\text{Alc}-$ (Vc) ou

$-\text{CH}_2-\text{N}(\text{X}_8)-\text{C}(=\text{X}_7)-\text{Alc}_2-$ (Vd) ou un groupe

$-\text{CH}_2-\text{N}(\text{X}_8)-\text{Alc}-$ (Ve), où Alc_1 représente le radical

alcoyl-ylidène correspondant à un radical Alc et

où Alc_2 correspond à un radical Alc raccourci d'un

groupe méthylène lié sur l'atome d'azote, X_7 représente le radical oxo ou thioxo et X_8 un hydrogène

ou un radical remplaçable par un hydrogène

dans les conditions pour la réduction de X_6 et/ou

Y et Y représente un radical de formule $-\text{CO}-$ (Vf)

ou $-\text{CH}(\text{OX}_9)-$ (Vg) où X_9 a la signification donnée

ci-dessus, Ar_2 correspond à un radical Ar, mais

porte cependant éventuellement à la place d'un

ou de deux hydroxy un ou deux groupes OX_9 , où

X_9 a la signification donnée ci-dessus, et n vaut

zéro ou 1, où X_6 est toujours un groupe Va à Vd

réductible et/ou Y un groupe carbonyle Vf, en

réduisant donc ce ou ces groupe(s) et dans le

même mode opératoire en remplaçant les

groupes X_8 différents d'un hydrogène par un

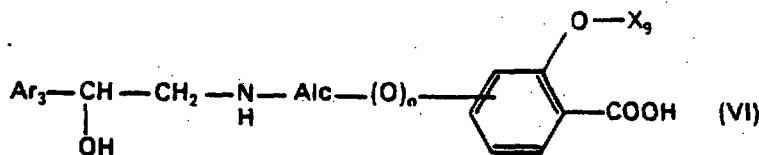
hydrogène, ou

d) en faisant réagir avec de l'ammoniac un

composé de formule



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où Ar_3 a la signification de Ar , ou représente un radical Ar , qui est substitué par un à deux groupes transformables en hydroxy au moyen d'une ammonolyse, X_9 représente un hydrogène ou un groupe séparable par ammonolyse, ou un dérivé réactif de l'un des acides carboxyliques définis dans la formule VI, et simultanément en séparant les radicaux X_9 éventuellement présents et en les remplaçant par de l'hydrogène, et/ou, si on le désire, en dédoublant un mélange de racémates obtenu pour donner les deux racémates stéréoisomères (diastéréoisomères) ou un racémate obtenu pour donner les antipodes optiques.

2. Procédé de préparation d' α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-1-méthyl-éthyl]-aminométhyl]-benzylalcool selon la revendication 1, caractérisé en ce qu'on utilise comme produits de départ l' α -[N-[2-(2,3-dihydro-2,2-diméthyl-4-oxo-4H-1,3-benzoxazin-6-yloxy)-1-méthyl-éthyl]-aminométhyl]-benzylalcool et l'isopropylamine.

3. Procédé de préparation d' α -[N-[2-(4-carbamoyl-3-hydroxy-phénoxy)-1-méthyl-éthyl]-aminométhyl]-benzylalcool selon la revendication 1, caractérisé en ce qu'on utilise comme produits de départ l' α -[N-[2-(2,3-dihydro-2,2-diméthyl-4-oxo-4H-1,3-benzoxazin-7-yloxy)-1-méthyl-éthyl]-aminométhyl]-benzylalcool et l'isopropylamine.

4. Procédé de préparation d' α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-éthyl]-aminométhyl]-benzylalcool selon la revendication 1, caractérisé en ce qu'on utilise comme produits de départ l' α -(aminométhyl)-benzylalcool et la 2,3-dihydro-2,2-diméthyl-6-(2-brométhoxy)-4H-1,3-benzoxazin-4-one.

5. Procédé de préparation d' α -[N-[2-(4-carbamoyl-3-hydroxy-phénoxy)-éthyl]-aminométhyl]-benzylalcool selon la revendication 1, caractérisé en ce qu'on utilise comme produit de départ la N-[2-(4-carbamoyl-3-hydroxy-phénoxy)-éthyl]-N-(2-hydroxy-2-phényl-éthyl)-benzylamine.

6. Procédé de préparation d' α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-1-méthyl-éthyl]-aminométhyl]-3-pyridine méthanol selon la revendication 1, caractérisé en ce qu'on utilise comme produits de départ l' α -(aminométhyl)-3-pyridineméthanol et la 2,3-dihydro-2,2-diméthyl-6-(2-oxo-propoxy)-4H-1,3-benzoxazin-4-one.

7. Procédé de préparation d' α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-1-méthyl-éthyl]-aminométhyl]-2-pyridineméthanol selon la revendication 1, caractérisé en ce qu'on utilise comme produits de départ l' α -(aminométhyl)-2-pyridineméthanol et la 2,3-dihydro-2,2-diméthyl-6-(2-oxo-propoxy)-4H-1,3-benzoxazin-4-one.

8. Procédé de préparation d' α -[N-[2-(3-carba-

moyl-4-hydroxy-phénoxy)-1-méthyl-éthyl]-aminométhyl]-4-hydroxy-benzylalcool selon la revendication 1, caractérisé en ce qu'on utilise comme produit de départ le 4-benzyloxy- α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-1-méthyl-éthyl]-aminométhyl]-benzylalcool.

9. Procédé de préparation d' α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-1-méthyl-éthyl]-aminométhyl]-benzylalcool selon la revendication 1, caractérisé en ce qu'on utilise comme produit de départ la base de Schiff formée à partir du 5-(2-oxo-propoxy)-salicylamide et de l' α -(aminométhyl)-benzylalcool.

10. Procédé de préparation du R-(-)- α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-1-méthyl-éthyl]-aminométhyl]-benzylalcool selon la revendication 1, caractérisé en ce qu'on utilise comme produit de départ la base de Schiff formée à partir du R-(-)- α -(aminométhyl)-benzylalcool et de 5-(2-oxo-propoxy)-salicylamide.

11. Procédé de préparation d' α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-éthyl]-aminométhyl]-4-hydroxybenzylalcool selon la revendication 1, caractérisé en ce qu'on utilise comme produit de départ le 4-benzyloxy- α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-éthyl]-aminométhyl]-benzylalcool.

12. Procédé de préparation du α -[N-[2-(2-carbamoyl-3-hydroxy-phénoxy)-éthyl]-aminométhyl]-benzylalcool selon la revendication 1, caractérisé en ce qu'on utilise comme produit de départ le 6-(2-brométhoxy)-salicylamide et l' α -(aminométhyl)-benzylalcool.

13. Procédé de préparation du α -[N-[3-(4-carbamoyl-3-hydroxy-phénoxy)-propyl]-aminométhyl]-benzylalcool selon la revendication 1, caractérisé en ce qu'on utilise comme produit de départ la N-[3-(4-carbamoyl-3-hydroxy-phénoxy)-propyl]-N-(2-hydroxy-2-phényl-éthyl)-benzylamine.

14. Procédé de préparation du α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-1-méthyl-éthyl]-aminométhyl]-benzylalcool selon la revendication 1, caractérisé en ce qu'on utilise comme produit de départ le α -[N-[2-(3-carbométhoxy-4-hydroxy-phénoxy)-1-méthyl-éthyl]-aminométhyl]-benzylalcool et l'ammoniac.

15. Procédé de préparation du α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-éthyl]-aminométhyl]-benzylalcool selon la revendication 1, caractérisé en ce qu'on utilise comme produits de départ le phénylglyoxal et le 5-(2-aminoéthoxy)-salicylamide.

16. Procédé de préparation de α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-éthyl]-aminométhyl]-2-pyridineméthanol selon la revendication 1, caractérisé en ce qu'on utilise comme produits de départ le α -(aminométhyl)-2-pyridineméthanol

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nol et la 2,3-dihydro-2,2-diméthyl-6-(2-brométhoxy)-4H-1,3-benzoxazin-4-one.

17. Procédé de préparation de α -[N-[2-(4-carbamoyl-3-hydroxy-phénoxy)-1-méthyl-éthyl]-aminométhyl]-benzylalcool selon la revendication 1, caractérisé en ce qu'on utilise comme produits de départ le phényléthylénoxyde et le 4-(2-amino-propoxy)-salicylamide.

18. Procédé de préparation de α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-éthyl]-aminométhyl]-2-furaneméthanol selon la revendication 1, caractérisé en ce qu'on utilise comme produits de départ le α -(aminométhyl)-2-furaneméthanol et la 2,3-dihydro-2,2-diméthyl-6-(2-brométhoxy)-4H-1,3-benzoxazin-4-one.

19. Procédé de préparation de α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-éthyl]-aminométhyl]-2-thiophène-méthanol selon la revendication 1, caractérisé en ce qu'on utilise comme produits de départ le α -(aminométhyl)-2-thiophène-méthanol et la 2,3-dihydro-2,2-diméthyl-6-(2-brométhoxy)-4H-1,3-benzoxazin-4-one.

20. Procédé de préparation de S-(+)- α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-1-méthyl-éthyl]-aminométhyl]-benzylalcool selon la revendication 1, caractérisé en ce qu'on utilise comme produits de départ le S-(+)- α -(aminométhyl)-benzylalcool et le 5-(2-oxo-propoxy)-salicylamide.

21. Procédé de préparation de α -[N-[2-(4-carbamoyl-3-hydroxy-phénoxy)-éthyl]-aminométhyl]-4-hydroxy-benzylalcool selon la revendication 1, caractérisé en ce qu'on utilise comme produit de départ le 4-benzyloxy- α -[N-[2-(4-carbamoyl-3-hydroxy-phénoxy)-éthyl]-aminométhyl]-benzylalcool.

22. Procédé de préparation de α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-éthyl]-aminométhyl]-benzylalcool selon la revendication 1, caractérisé en ce qu'on utilise comme produit de départ le α -[N-benzyl-N-[2-(3-carbamoyl-4-

hydroxy-phénoxy)-éthyl]-aminométhyl]-benzylalcool.

23. Procédé de préparation de α -[N-[3-(3-carbamoyl-4-hydroxy-phénoxy)-propyl]-aminométhyl]-benzylalcool selon la revendication 1, caractérisé en ce qu'on utilise comme produits de départ le α -(aminométhyl)-benzylalcool et la 6-(3-bromopropoxy)-2,3-dihydro-2,2-diméthyl-4H-1,3-benzoxazin-4-one.

24. Procédé de préparation du α -[N-[3-(3-carbamoyl-4-hydroxy-phényl)-propyl]-aminométhyl]-benzylalcool selon la revendication 1, caractérisé en ce qu'on utilise comme produit de départ le α -[N-benzyl-N-[3-(3-carbamoyl-4-hydroxy-phényl)-propyl]-aminométhyl]-benzylalcool.

25. Procédé de préparation de α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-éthyl]-aminométhyl]-3,5-dihydroxy-benzylalcool selon la revendication 1, caractérisé en ce qu'on utilise comme produit de départ la N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-éthyl]-N-[2-(3,5-dibenzyloxy-phényl)-2-hydroxy-éthyl]-benzylamine.

26. Procédé de préparation de α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-éthyl]-aminométhyl]-benzylalcool selon la revendication 1, caractérisé en ce qu'on utilise comme produits de départ le 5-(2-aminoéthoxy)-salicylamide et l' α -(bromométhyl)-benzylalcool.

27. Procédé de préparation de α -[N-[2-(3-carbamoyl-4-hydroxy-phénoxy)-éthyl]-aminométhyl]-benzylalcool selon la revendication 1, caractérisé en ce qu'on utilise comme produit de départ le phényléthylénoxyde et le 5-(2-aminoéthoxy)-salicylamide.

28. Procédé selon l'une des revendications 1-27, caractérisé en ce qu'on transforme un composé de formule I obtenu en un sel d'addition acide non toxique pharmaceutiquement acceptable.



* C L M S *