Racemic and optically active compounds of the formula

wherein \( R_1, R_2, R_3, R_4 \), and \( R_5 \) are hydrogen or various substituents, and their physiologically compatible acid addition salts, as well as the process for producing the compounds, therapeutic compositions and methods. The 1-aryloxy-2-hydroxy-3-alkynylamino-propanes have andrenolytic properties and blood-pressure reducing properties.

6 Claims, No Drawings
1-ARYLOXY-2-HYDROXY-3-ALKNYLAMINO-PROPANES

OBJECTS OF THE INVENTION

An object of the present invention is the obtaining of a 1-aryloxy-2-hydroxy-3-alknylamino-propane selected from the group consisting of racemic and optically active compounds having the formula

wherein R₁ is a member selected from the group consisting of hydrogen; halogen; nitro; alkyl having from 1 to 5 carbon atoms; alkoxy having from 1 to 4 carbon atoms; alkenyl having from 2 to 5 carbon atoms; alkynyl having from 2 to 5 carbon atoms; alkylamino having from 1 to 5 carbon atoms; dialkylamino having from 1 to 5 carbon atoms in each alkyl; alkoxyalkyl having from 2 to 6 carbon atoms; alkoxyalkylamino having from 2 to 6 carbon atoms; dialkoxyalkylamino having from 3 to 12 carbon atoms; -(CH₂)ₓ-CN, -(CH₃)₂-NH₂, -(CH₃)₂-CH=CH₂, -(CH₃)₂-CH₂, -(CH₃)₂-NH₂, all where x is an integer from 0 to 3; COOH; COOR, wherein R₄ is an alkyl having from 1 to 4 carbon atoms; alkynylalkoxy having from 3 to 6 carbon atoms; alkynylalkoxy having from 3 to 6 carbon atoms; CO–Rₙ, CO–Rₙ, NH–CO–Rₙ, all where Rₙ is a member selected from the group consisting of alkyl having from 1 to 6 carbon atoms, phenylalkyl having 7 to 10 carbon atoms and phenyl; cycloalkyl having from 3 to 7 carbon atoms; Q–CO–NRₙRₖ where Q is a member selected from the group consisting of a single bond, oxygen, NH, CH₂, and CH₃–NH– and R₁ and R₄ are members selected from the group consisting of hydrogen, lower alkyl and taken together with the nitrogen, pyrrolidino, piperidino and morpholinio; phenyl substituted with a substituent selected from the group consisting of halogen, lower alkyl, lower alkoxy, nitro, cyano, and carboxyl; phenoxy; and phenoxy substituted with a substituent selected from the group consisting of halogen, lower alkyl, lower alkoxy, nitro, cyano, and carboxyl;

R₂ is a member selected from the group consisting of hydrogen, halogen, alkyl having from 1 to 4 carbon atoms, alkoxy having from 1 to 4 carbon atoms, alkenyl having from 1 to 4 carbon atoms, alkenyl having from 2 to 4 carbon atoms, cyano, amino, nitro, and, together with R₁, 3,4-methylenedioxy;

R₃ is a member selected from the group consisting of hydrogen, halogen, alkyl having from 1 to 4 carbon atoms, alkoxy having from 1 to 4 carbon atoms, and, together with R₁ in the ortho position, CH–A–CH–CH–CH–CH–CH– and -(CH₃)ₙ–, where n is an integer from 3 to 5;

R₄ is a member selected from the group consisting of hydrogen and alkyl having from 1 to 3 carbon atoms;

R₅ is a member selected from the group consisting of alkyl having from 1 to 3 carbon atoms and, together with R₄, -(CH₃)ₙ–, where p is an integer from 4 to 6; and its physiologically compatible acid addition salt.

Another object of the invention is the development of methods to produce the above 1-aryloxy-2-hydroxy-3-alknylamino-propanes.

A yet further object of the invention is the development of therapeutic compositions and methods with the above 1-aryloxy-2-hydroxy-3-alknylamino-propanes.

These and other objects of the present invention will become more apparent as the description thereof proceeds.

DESCRIPTION OF THE INVENTION

The invention is concerned with novel substituted racemic or optically active 1-aryloxy-2-hydroxy-3-alknylamino-propanes and the acid addition salts thereof, the use of these novel compounds as active ingredients in pharmaceuticals and processes for production thereof.

The novel compounds correspond to general formula

wherein, in the formula

R₁ is a hydrogen or halogen atom, a nitro group, an alkyl group with 1 to 5 carbon atoms, an alkoxy group with 1 to 4 carbon atoms, an alkynyl or alkynyl group with 2 to 5 carbon atoms, a lower alkyl (or di-lower alkyl) amino group, a lower alkylamido group or a lower alkyl (or di-lower alkyl) amino-lower alkyl group, a group of the partial formula -(CH₃)ₓ-CN, -(CH₃)ₓ-NH₂ or -(CH₃)ₓ-CH₃, all where x is an integer from 1 to 3, COOH, COORₙ, where Rₙ means an alkyl group of 1 to 4 carbon atoms, an alkynylamino or alkynylalkoxy group with 3 to 6 carbon atoms, a lower aliphatic, alicyclic or aromatic acyl, acetyloxy or acylamino group, a cycloalkyl group with 3 to 7 carbon atoms, the group -Q--CO–NRₙRₖ where Q is a single bond, an oxygen atom, a NH, CH₂ or CH₃–NH– group, and R₇ and R₈ are hydrogen, lower alkyl or together with the nitrogen atom a heterocycle, such as the pyrrolidino, piperidino or morpholinio group, or an aryl or aryloxy (preferably phenyl or phenoxy) group optionally substituted by halogen, alkyl, alkoxy, a nitro, cyano or carboxyl group;

R₂ is a hydrogen or halogen atom, an alkyl or alkox group with 1 to 4 carbon atoms, an acyl or alkenyl group with 2 to 4 carbon atoms, a cyano, amino or nitro group or together with R₀ the 3,4-methylenedioxo group;

R₃ is a hydrogen or halogen atom, an alkyl or alkox group with 1 to 4 carbon atoms or, together with R₅, the group -(CH₃)ₓ–CH–CH–CH–CH– or -(CH₃)ₓ–(n= an integer from 3 to 5) with a bond of the free valencies in o-position towards each other;

R₄ is hydrogen or an alkyl group with 1 to 3 carbon atoms, and

R₅ is an alkyl group with 1 to 3 carbon atoms or, together with R₆, the group -(CH₃)ₓ–, where p means one of the integers 4 to 6.
If $R_1$ represents a lower aliphatic acyl group, lower alkanoyl, such as the acetyl, propionyl, butyryl or isobutyryl group, may, for example, be considered here. As aliphatic acyl group $R_1$ may represent phenylalkanoyl, such as the phenacyl group, which is optionally substituted at the phenyl with one or several halogen atoms, alkyl groups, nitro, cyano or carboxyl groups. If $R_1$ represents aromatic acyl, it may be, for example, a benzoyl group optionally substituted once or several times by halogen, lower alkyl, nitro, cyano or carboxyl.

If $R_1$ represents an acyloxy or acylamino group, the acyl group therein may as well be represented by the acyl groups individually listed in the above paragraph.

The novel compounds may be produced in a number of ways, in which the following are representative:

a. Reacting a compound of general formula II

\[
\begin{align*}
R_1 & \quad \text{OCH}_2 \quad Z \\
R_2 & \quad R_3
\end{align*}
\]

where $R_1$ to $R_3$ are defined as in formula I and $Z$ is

\[
\begin{align*}
\text{CH} & \quad \text{CH} \\
\text{O}
\end{align*}
\]

or $\text{-CHOH-CH}_2\text{-Hal}$ (Hal = halogen), with an amine of general formula

\[
\begin{align*}
\text{NH}_2 & \quad \text{C-} \quad \text{C=CH} \\
R_4 & \quad R_5
\end{align*}
\]

where $R_4$ and $R_5$ have the meanings indicated in formula I;

b. Cleaving an easily removable protective group off compounds of general formula IV

\[
\begin{align*}
\text{OCH}_2 \quad \text{CH}_2 \quad \text{NH} & \quad \text{C-} \quad \text{C=CH} \\
R_1 & \quad R_2 \quad R_3
\end{align*}
\]

where $R_1$ to $R_3$ are defined as in formula I and $G$ is an easily hydrogenolytically removable group, for example, an acyl or an acetal group.

c. Cleaving a protective group of general formula V

\[
\begin{align*}
\text{OCH}_2 \quad \text{CH}_2 \quad \text{NH} & \quad \text{C-} \quad \text{C=CH} \\
R_1 & \quad R_2 \quad R_3
\end{align*}
\]

where $R_1$ to $R_3$ are defined as in formula I and $A$ is a group convertible in line with conventional methods, such as the $\text{-CONH}_2$ or $\text{-COOR}$ group (whereby $R_4$ is defined as in formula I), an alkoxy, $\text{O-acyl}$ or $\text{NO}_2$ group, or compounds of general formula VIIb

\[
\begin{align*}
\text{OCH}_2 \quad \text{CH}_2 \quad \text{NH} & \quad \text{C-} \quad \text{C=CH} \\
R_1 & \quad R_2 \quad R_3
\end{align*}
\]

where $R_1$ to $R_3$ are defined as in formula I and $G$ is a group convertible in line with conventional methods, such as the $\text{-CONH}_2$ or $\text{-COOR}$ group (whereby $R_4$ is defined as in formula I), an alkoxy, $\text{O-acyl}$ or $\text{NO}_2$ group, or compounds of general formula VIIb

\[
\begin{align*}
\text{OCH}_2 \quad \text{CH}_2 \quad \text{NH} & \quad \text{C-} \quad \text{C=CH} \\
R_1 & \quad R_2 \quad R_3
\end{align*}
\]

where $R_1$ to $R_3$ are defined as in formula I and $G$ is an easily hydrogenolytically removable group, for example, an acyl or an acetal group.

d. Hydrolyzing an oxazolidine derivative of general formula VI

\[
\begin{align*}
\text{OCH}_2 \quad \text{CH}_2 \quad \text{NH} & \quad \text{C-} \quad \text{C=CH} \\
R_1 & \quad R_2 \quad R_3
\end{align*}
\]

where $R_1$ to $R_3$ are defined as in formula I and $\text{Sch}$ is an easily removable protective group, for example, an acyl group or the carboxenzyloxy group.

e. Converting compounds of formula VIIa

\[
\begin{align*}
\text{OCH}_2 \quad \text{CH}_2 \quad \text{NH} & \quad \text{C-} \quad \text{C=CH} \\
R_1 & \quad R_2 \quad R_3
\end{align*}
\]

where $R_1$ to $R_3$ are defined as in formula I, and $X$ represents $\text{-CO-}$, $\text{-CH}_2$- or a $\text{-CH}$-lower alkyl group, for example, with sodium hydroxide or potassium hydroxide solution in water or in an alcohol/water mixture.

In addition, other processes for the production of compounds of formula I are possible, such as converting a compound having already the 3-alkynylamino-propanol-2 side chain, but not having one of the substituents $R_1$, $R_2$ or $R_3$ on the phenyl ring and in place thereof another substituent convertible to the desired substituent, to the desired substituent $R_1$, $R_2$ or $R_3$ by conventional methods.

\[
\begin{align*}
\text{OCH}_2 \quad \text{CH}_2 \quad \text{NH} & \quad \text{C-} \quad \text{C=CH} \\
R_1 & \quad R_2 \quad R_3
\end{align*}
\]

where $R_1$ to $R_3$ are defined as in formula I and $A$ is a group convertible in line with conventional methods, such as the $\text{-CONH}_2$ or $\text{-COOR}$ group (whereby $R_4$ is defined as in formula I), an alkoxy, $\text{O-acyl}$ or $\text{NO}_2$ group, or compounds of general formula VIIb
where $R_1$, $R_2$ to $R_5$ are defined as in formula I and $B$ is a group convertible into $R_2$ in line with conventional methods, into compounds of formula I, using the method required in each case (splitting off water, reducing, saponifying, cleaving an ether, alkylation).

Furthermore, the following process is suitable for producing compounds of general formula I, where $R_2$ or $R_3$ is a halogen atom:

f. Introducing a halogen atom into compounds of formula VIII

$$
Ar-O-CH_2-CHOH-CH_2-NH-C-C=CH
$$

where $R_4$ and $R_5$ are defined as in formula I, and $Ar$ is a group of the partial formula

$$(\text{where } R_1, R_2 \text{ and } R_3 \text{ have the above meanings}), \text{ for example, with a mixture of hydrogen halide and hydrogen peroxide at elevated temperature.}
$$

Furthermore, the following process is suitable for producing compounds of general formula I, where $R_1$ and/or $R_2$ represent a $\text{--CN}$:

g. Introducing a $\text{--CN}$ group into compound of general formula IXa

$$
M-O-CH_2-CHOH-CH_2-NH-C=C=CH
$$

where $R_4$ and $R_5$ are defined as in formula I, and $M$ represents a group of the partial formula

$$(\text{where } R_1, R_2 \text{ and } R_3 \text{ are defined as in formula I}) \text{ and } C \text{ is an amino group or halogen.}
$$

This may be effected, in case $C$ is an amino group, by means of diazotizing and boiling in the presence of cyanides such as KCN and in case $C$ is halogen by reaction with Cu(I)CN in a high boiling solvent.

The starting compounds required for carrying out the processes (a) to (g) have already been partly known. The remainder can be obtained by known processes. Thus, the epoxides of formula II may be produced easily by reaction with a corresponding phenol or phenolate of formula $X$

where $R_1$ to $R_6$ have the meanings mentioned above and $Kt$ is hydrogen or a cation (e.g., an alkali metal cation). The epoxides may be used for production of further starting materials; for instance, the halogen hydride of formula II may be produced by reacting the epoxides with the corresponding hydrogen halide.

Amines of formula III have been known and represent mostly commercial products. Compounds of formula IV may be obtained by reacting a halohydrin of formula II with a compound (such as vinyl ether or dihydropyran) to give the protective group $G$ and, subsequently, reacting the obtained compound of formula

with a compound of general formula III.

The tertiary amines of formula V are obtained by reacting a compound of general formula $X$ with a compound of general formula

$$(\text{where } R_4, R_5 \text{ and } \text{Sch} \text{ have the above-mentioned meanings and } Z \text{ is a halide.})
$$

The oxazolidinones of formula VI (e.g., compounds where $X = CO$) are producible, for example, starting from the epoxides of formula II, by reacting the latter with a urethane (producing from a chloroethyl formate and an amine of formula II) of formula

$$(\text{where } R_1, R_2 \text{ to } R_6 \text{ are defined as in formula I, } C \text{ is an amino group or halogen.})$$
where \( R_1 \) and \( R_2 \) have the meanings mentioned above.

The compounds of formulas VIIa, VIIb, VIII, IXa and IXb already contain the complete 1-phenoxyl-2-hydroxy-3-alkylaminoligo-propane structure and may, therefore, be produced analogously to the process (a) described above, starting from the corresponding phenol, via the corresponding 1-phenoxyl-2,3-epoxypropane (produces by reaction with epichlorhydrin) by reaction with an alkylamine of formula III.

The compounds according to the invention possess an asymmetric carbon atom at the CHOH group and can occur, therefore, as racemate as well as in the form of optical antipodes. The latter may be obtained by separation of racemates with the conventional optically active acids, such as dibenzoyl- (or di-p-tolyl-)-D-tartaric acid or D-3-bromocamphor-8-sulfonic acid or by using optically active starting materials as well.

The 1-aryloxy-2-hydroxy-3-alkylaminoligo-propanes of general formula I according to the invention may be converted into the physiologically compatible acid addition salts thereof in the conventional way. Suitable acids are, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, methane-sulfonic acid, maleic acid, acetic acid, oxalic acid, lactic acid, tartaric acid or 8-chlorotrichlorpropylene.

The compounds of general formula I or the physiologically compatible acid addition salts thereof have shown valuable therapeutic properties, in particular, adrenolytic properties as demonstrated by animal tests in guinea pigs and may, therefore, be used for treatment or prophylaxis of diseases of the coronary and for treatment of cardiac arrhythmia, especially of tachycardia, in human medicine. The blood-pressure decreasing properties of the compounds are therapeutically interesting too. Compared to the known \( \beta \)-receptor blockers, for example, the commercial product 1-(1-naphthoxy)-2-hydroxy-3-isopropylaminopropane (Propanolol), the compounds have the advantage of a considerably decreased toxicity combined with a superior action.

The invention, therefore, also relates to a process for the treatment of coronary diseases, cardiac arrhythmia and high blood pressure in warm-blooded animals comprising administering a safe but effective amount of the 1-aryloxy-2-hydroxy-3-alkylaminoligo-propane compounds of formula I.

Here compounds of general formula I have proved to be valuable, in particular, where \( R_1 \) and \( R_2 \) represent each a methyl group and one of \( R_3 \), \( R_4 \) and \( R_5 \) is other than hydrogen (substituted 1-phenoxyl-2-(2-methylbutynyl-3-amino-2)-2-propanols).

Among the preferred meanings for \( R_1 \) are to be stressed the unsaturated substituents such as alkenyl (e.g., allyl), alkynyl (e.g., ethynyl, propynyl), alkenyloxy (e.g., allyloxy), alkynyl (e.g., propargyloxy) or cyano, in particular, if they stand in the 2-position to the propanolamine side-chain.

\( R_2 \) may represent in this case preferably hydrogen, but furthermore, lower alkyl (e.g., methyl), preferably in the 5-position to the propanolamine side-chain, while \( R_3 \) is hydrogen as a rule. \( R_4 \) and \( R_5 \) are again preferably methyl.

A further preferred sub-group is formed by such substances of general formula I, where \( R_1 \) represents a hydroxalkyl, in particular, the hydroxymethyl group; or an amino or acylamino, especially acetylaminogroup; whereby \( R_4 \) and \( R_5 \) may represent in the first case hydrogen, in the second case hydrogen or else halogen or lower alkyl. \( R_4 \) and \( R_5 \) are again preferably methyl.

Important individual compounds are, in particular: 1-(2-cyano-phenoxyl)-3-(2-methylbutynyl-3-amino-2)-2-propanol and 1-(2-ethynylphenoxyl)-3-(2-methylbutynyl-3-amino-2)-2-propanol, 1-(2-allyloxyphenoxyl)-3-(2-methylbutynyl-3-amino-2)-2-propanol, furthermore, 1-(3,5-dibromo-4-aminophenoxyl)-3-(2-methylbutynyl-3-amino-2)-2-propanol, 1-(2-hydroxymethylphenoxyl)-2-(2-methylbutynyl-3-amino-2)-2-propanol, the 1-(3-chlorophenoxyl)-3-(2-methylbutynyl-3-amino-2)-2-propanol and the 1-(4-acetamidophenoxyl)-3-(2-methylbutynyl-3-amino-2)-2-propanol or the physiologically compatible acid addition salts thereof.

The single dose of the compounds according to the invention lies at 1 to 300 mg, preferably 5 to 100 mg (orally) or 1 to 20 mg (parenterally). When administered to warm-blooded animals, the single dosage is from 0.015 mg to 5 mg/kg.

The active ingredients according to the invention may be incorporated into the conventional galenic forms of administration, such as tablets, coated tablets, solutions, emulsions, powders, capsules or forms of sustained release. For the production of the above, the usual pharmaceutical excipients as well as the conventional methods of production may be applied.

Corresponding tablets may be obtained by mixing the active ingredients with known excipients, for example, with inert diluents, such as calcium carbonate, calcium phosphate or lactose, disintegrants, such as corn starch or alginic acid, binders, such as starch or gelatin, lubricants, such as magnesium stearate or talc and/or agents for obtaining sustained release, such as carbopolymethylene, carboxymethylcellulose, cellulose acetate/phtalate or polyvinylacetate.

The tablets may also be composed of several layers. There may be produced correspondingly coated tablets by means of coating cores, prepared analogous to the tablets, with agents usually applied for tablet-coats, such as polyvinylpyroliidine or shellac, gum arabic, talc, titanium dioxide or sugar. For obtaining sustained release or in order to avoid incompatibilities, the core may consist of several layers as well. Thus, the tablet coat for obtaining sustained release may also consist of several layers, whereby the excipients mentioned above for tablets may be used.

Drinks of the active ingredients or active ingredient combinations according to the invention may additionally contain a sweetener, such as saccharin, cyclamate, glyciner or sugar, as well as an agent improving the taste, for example, a flavor, such as vanilla or orange extract. Besides they may comprise suspension auxiliaires or thickeners, such as sodium carboxymethylcellulose, wetting agents, such as condensation products of fatty alcohols with ethylene oxide, or protective substances, such as p-hydroxybenzoates.

Injectable solutions are produced in the conventional way, such as under addition of preservation agents, such as p-hydroxybenzoates, or stabilizers, such as "Komplexon" (the sodium salt of ethylene diaminetetraacetic acid), and filled into injection vials or ampoules.

Capsules containing the active ingredients or active ingredient combinations may be produced, for example, by admixing the active ingredients with inert carri-
ers, such as lactose or sorbitol, and filling same into gelatin capsules.

Suitable suppositories may be produced by mixing the active ingredients or active ingredient combinations envisaged for same with conventional carriers, such as neutral fats or polyoxyethylene-9-glycerol or its derivatives.

The compounds of the invention are suitable as well for combination with other pharmacodynamically active substances, such as, for example, coronary dilators, sympathicomimetics, cardiac glycosides or tranquilizers.

The following examples illustrate the invention without restricting same in any manner.

EXAMPLE 1
1-α-Naphthoxy-3-(3-ethylpentyl-4-amino-3)-2-propanol. HCl (according to process [α]) (I, R₁ = H, R₃ + R₄ = -CH=CH-CH=CH-, R₅ and R₆ = C₆H₅)

10 Grams (0.05 mol) of 1-α-naphthoxy-2,3-epoxypropane were dissolved in 80 ml of ethanol. 5.5 Grams (0.05 mol) of 3-ethyl-3-amino-pentylene-4 were added and the mixture was refluxed for two hours at boiling temperature. After having cooled off, the solvent was distilled off. The residue was dissolved in ether and acidified with alcoholic HCl. The crystallizable compound was isolated and recrystallized from a mixture of acetonitrile and ethanol.

Yield: 9.5 gm, m.p. 195° to 196°C.

EXAMPLE 2
1-m-Tolyloxy-3-(2-methylbutynyl-3-amino-2)-2-propanol. HCl (according to process [α]) (I, R₁ = 3-CH₃, R₂ and R₃ = H, R₄ and R₅ = CH₃)

8.2 Grams (0.05 mol) of 1-m-tolyloxy-2,3-epoxypropane were dissolved in 90 ml of ethanol, and after addition of 6.25 gm (0.075 mol) of 2-methyl-2-amino-butyne-3, the mixture was refluxed for two hours. After distilling off the solvent, the residue was recrystallized from ethyl acetate under addition of petroleum ether. The crystalline base was dissolved in acetonitrile; alcoholic HCl was added and crystallization was started under addition of ether. 6.5 Grams of colorless crystals were obtained, which are chromatographically pure. M.p. 139° to 141°C.

EXAMPLE 3
1-(2-Allylphenoxy)-3-(2-methylbutynyl-3-amino-2)-2-propanol.oxalate (according to process [α]) (I, R₁ = 2-allyl, R₂ and R₃ = H, R₄ and R₅ = CH₃)

9.5 Grams (0.05 mol) of 1-(2-allylphenoxy)-2,3-epoxypropane were dissolved in 60 ml of methanol. 8.3 gm (0.1 mol) of 2-methyl-2-amino-butyne-3 were added and the mixture was refluxed for three hours.

After having distilled off the solvent, the basic residue was dissolved in acetone and a solution of 6 gm of oxalic acid was added. The precipitating crystalline oxalate was recrystallized from acetone once more.

Yield: 4.7 gm, m.p. 144° to 146°C.

EXAMPLE 4
1-(2-Cyanophenoxy)-3-(2-methylbutynyl-3-amino-2)-2-propanol. HCl (according to process [α]) (I, R₁ = 2-CN, R₂ and R₃ = H, R₄ and R₅ = CH₃)

17.5 Grams (0.1 mol) of 1-(2-cyanophenoxy)-2,3-epoxypropane were dissolved in 130 ml of ethanol. After addition of 16.6 gm (0.2 mol) of 2-methyl-2-amino-butyne-3, the mixture was refluxed for 2 hours. The solvent was distilled off. The remaining residue was acidified with HCl and shaken. After vacuum filtering, the insoluble particles, the filtrate was adjusted alkaline by NaOH. The precipitating base was dissolved in chloroform and the organic phase, after separation, was dried over Na₂SO₄. After filtration the chloroform was distilled off and the residue was recrystallized from ethyl acetate under addition of petroleum ether. The base was dissolved in acetonitrile and acidified with alcoholic HCl. The hydrochloride crystallized colorlessly.

Yield: 13.9 gm (uniform substance, in the thin-layer chromatogram). M.p. 169° to 171°C.

EXAMPLE 5
1-(2-Cyanophenoxy)-3-(1-ethynylcyclohexylamino)-2-propanol. HCl (according to process [α]) (I, R₁ = 2-CN, R₂ and R₃ = R₄ and R₅, together = -(CH₂)₄-)

9 Grams (0.05 mol) of 1-ethynylcyclohexylamine were dissolved together with 8.7 gm (0.05 mol) of 1-(2-cyanophenoxy)-2,3-epoxypropane in 100 ml of ethanol and refluxed for 2 hours. After having distilled off the solvent, the residue was dissolved in ethyl acetate and shaken with diluted HCl. The aqueous phase was separated and adjusted alkaline with NaOH. The precipitated base was extracted with ethyl acetate. The organic phase was washed, dried over MgSO₄, filtered and the solvent was distilled off. The remaining residue was recrystallized from ethyl acetate under addition of ligroin. The colorless crystalline base was dissolved in alcohol. Alcoholic HCl was added and the hydrochloride was brought to crystallization by dropping in ether.

After separation, the salt was recrystallized once more from ethanol under addition of ether.

Yield: 6.5 gm, m.p. 176° to 177°C.

Analogous to the Examples 1 to 5, the following compounds of formula I are produced in line with process (a), e.g. by reacting the correspondingly substituted 1-phenoxy-2,3-epoxypropane according to formula II with the corresponding amine according to formula III in ethanol.

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>R₅</th>
<th>°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-CN</td>
<td>H</td>
<td>H</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>170-171</td>
</tr>
<tr>
<td>3-CH₃</td>
<td>H</td>
<td>H</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>143-145</td>
</tr>
<tr>
<td>2-O-CH₂-CH=CH₂</td>
<td>H</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>112-113</td>
<td></td>
</tr>
<tr>
<td>2-CH₂-CH=CH₂</td>
<td>H</td>
<td>H</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>128-129</td>
</tr>
<tr>
<td>H</td>
<td>2,3-CH=CH-CH=CH-CH₃</td>
<td>H</td>
<td>C₆H₅</td>
<td>159-161</td>
<td></td>
</tr>
<tr>
<td>2-O-CH₂-CH=CH₂</td>
<td>H</td>
<td>CH₃</td>
<td>CH₃</td>
<td>100-103</td>
<td></td>
</tr>
<tr>
<td>R₁</td>
<td>R₂</td>
<td>R₃</td>
<td>R₄</td>
<td>R₅</td>
<td>M.P. of HCl-Salt in Case</td>
</tr>
<tr>
<td>---------</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>--------------------------</td>
</tr>
<tr>
<td>3-CH₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>159-160</td>
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<tr>
<td>2-CH₃-</td>
<td>CH=CH₂</td>
<td>H</td>
<td>H</td>
<td>H</td>
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<tr>
<td>2-Br</td>
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<td>H</td>
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<td>H</td>
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<td>CH₃</td>
<td>108-110 (Base)</td>
</tr>
<tr>
<td>2-OCH₃</td>
<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>CH₃</td>
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<tr>
<td>4-COOCH₃</td>
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<td>3.4--(CH₂)₃--</td>
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<td>CH₃</td>
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<td>4-Tert</td>
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<td>H</td>
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<td>4-NH-CO-</td>
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<td>H</td>
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<td>134-137 (dihydro-</td>
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<td></td>
<td>chloride)</td>
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<tr>
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<td>CH₃</td>
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</tr>
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<td>3-Br</td>
<td>4-NH₂ 5-Br</td>
<td>H</td>
<td>CH₃</td>
<td>CH₃</td>
<td>183-185 (dihydro-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>chloride)</td>
</tr>
<tr>
<td>2-C</td>
<td>C-CH₃</td>
<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>164-166</td>
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<td>H</td>
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<td>CH₃</td>
<td>136-137.5 (Base)</td>
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<td>H</td>
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<td>CH₃</td>
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</tr>
<tr>
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<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>CH₃</td>
<td>150-151</td>
</tr>
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</table>

**EXAMPLE 6**

1-(2-Allyloxyphenoxy)-3-(2-methylbutyne)-3-amino-2-propanol. HCl (according to process [b]) (I, R₁ = 2-OCH₂CH=CH₂, R₂ and R₃ = H, R₄ and R₅ = CH₃)

2.4 Grams (0.025 mol) of tetrahydropryan were dropped slowly into 6.42 gm (0.025 mol) of 1-(2-allyloxyphenoxy)-3-bromo-2-propanol and a catalytic quantity of p-toluenesulfonic acid at 20° to 25°C. Then the mixture was heated for 30 minutes to 40°C, dissolved in 40 ml of benzene, and 5 gm (0.06 mol) of 2-methyl-2-amine-butyne-3 were added to it. The mixture was refluxed for 2 hours; then the solvent was distilled off and the residue was heated for 15 minutes with diluted hydrochloric acid to 80°C. After cooling off, it was extracted from ether and the aqueous phase was adjusted alkaline with NaOH and the precipitating basic portions were taken up in ether. The organic phase was dried with MgSO₄ and after filtering the ether was distilled off. The residue was dissolved in little ethanol. Etheric HCl was added and the crystalline hydrochloride recrystallized twice. M.p. 99° to 102°C.

**EXAMPLE 7**

1-(4-Nitrophenoxy)-3-(2-methylbutynyl-3-amino-2)-2-propanol. HCl (according to process [c]) (I, R₁ = 4-NO₂, R₂ and R₃ = H, R₄ and R₅ = CH₃)

2.7 Grams (approximately 0.008 mol) of 1-(4-nitrophenoxy)-3-(N-acetyl-2-methylbutynyl)-3-amino-2)-2-propanol were refluxed in 25 ml of ethanol with 1 gm of KOH for 2 hours. After having distilled off the solvent, a viscous residue remained, which was treated with diluted HCl. After shaking out with chloroform, the aqueous phase was adjusted alkaline with NaOH and the precipitating amine was taken up in chloroform. After drying over NaSO₄, the solvent was distilled off and the residue was recrystallized from ethyl acetate under addition of petroleum ether.

Yield: 1.5 gm, m.p. 125° to 127°C (base). Mixed melting point with substance obtained according to process (a): 126° to 127°C.
EXAMPLE 8
1-(2-Cyanophenox)-3-(2-methylbutynyl-3-amino-2)-2-propanol. HCl (according to process [d]) (I, R₁ = 2-CN, R₂ = H, R₃ = R₄ and R₅ = CH₃)

2.84 Grams (0.01 mol) of 3-(2-methylbutynyl-3-yl-2)-5-(2-cyanophenoxymethyl)-oxazolidine-2-one were refluxed in 20 ml of ethanol, after addition of 3 gm of KOH in 6 ml of water, for three hours. After having distilled off the solvent, the residue was treated with water and extracted with chloroform. Then the chloroform solution was shaken with diluted HCl and the separated aqueous phase was adjusted alkaline with NaOH. The precipitating base was taken up in chloroform. The organic phase was washed with water and dried over Na₂SO₄. After filtration, CHCl₃ was distilled off and the residue was recrystallized from ethyl acetate under addition of petroleum ether.

Yield: 1.3 gm, m.p. 84° to 86°C (base). Mixed melting point with identical substance: 83° to 85°C.

EXAMPLE 9
1-(4-Aminophenoxy)-3-(2-methylbutynyl-3-amino-2)-2-propanol. HCl (according to process [e]) (I, R₁ = 4-NH₂, R₂ and R₃ = H, R₄ and R₅ = CH₃)

A mixture of 8.1 gm of tin-II chloride in 20 ml of conc. HCl was heated to 60°C and 2.62 gm (0.01 mol) of 1-(4-nitrophenoxy)-3-(2-methylbutynyl-3-amino-2)-2-propanol were added in portions, so that the temperature did not exceed 65°C. After the addition had been finished, the mixture was stirred for 30 minutes and after cooling off it was adjusted alkaline with NaOH. The precipitating basic portions were shaken with chloroform. The chloroform solution was washed with water and dried over Na₂SO₄. After distilling off the CHCl₃, a solid residue remained, which was recrystallized from ethyl acetate under addition of petroleum ether.

Yield: 1.4 gm, m.p. 122° to 123°C (base).

According to process (e), the compound 1-(4-hydroxyphenoxy)-3-(2-methylbutynyl-3-amino-2)-2-propanol was made by heating the compound 1-(4-difluorobenzoyloxyphenoxy)-3-(2-methylbutynyl-3-amino-2)-2-propanol (m.p. of hydrochloride: 126°C) in the presence of concentrated aqueous HCl. M.p. of the end product (base) is 136° to 137.5°C.

EXAMPLE 10
1-(2-Cyano-4-chlorophenoxy)-3-(2-methylbutynyl-3-amino-2)-2-propanol. HCl (according to process [f]) (I, R₁ = 2-CN, R₂ = 4-Cl, R₃ = H, R₄ and R₅ = CH₃)

3.87 Grams (0.015 mol) of 1-(2-cyano-phenoxo)-3-(2-methylbutynyl-3-amino-2)-2-propanol were admixed with 25 ml of conc. HCl and heated to 45°C. While cooling 1.7 gm (0.015 mol) of 30% H₂O₂ were dropped in in such a way that the temperature did not rise above 65°C. After the batch had been stirred for a further 30 minutes, the crystal mass was vacuumed off and washed with water. The hydrochloride was recrystallized from ethanol.

Yield: 1.95 gm, m.p. 176° to 177°C.

EXAMPLE 11
1-(2-Cyanophenox)-3-(2-methylbutynyl-3-amino-2)-2-propanol. HCl (according to process [g]) (I, R₁ = 2-CN, R₂ = H, R₃ and R₅ = CH₃)

0.697 Gram (0.002 mol) of 1-(3-bromophenoxy)-3-(2-methylbutynyl-3-amino-2)-2-propanol hydrochloride were admixed with 0.376 gm (0.0042 mol) of Cu(N)CN and 0.4 gm of dimethylformamide and heated for 2 hours to 190°C. After cooling, the mixture was treated with water and adjusted alkaline with NaOH. The basic portions were taken up in CHCl₃ and washed with water. The chloroform was distilled off and the residue was purified through a silica gel column. The pure base thus obtained was dissolved in acetonitrile and acidified with alcoholic HCl. The hydrochloride crystallized colorlessly. M.p. 168° to 171°C.

EXAMPLE 12
1-(4-Hydroxy carbonylphenoxy)-3-(2-methylbutynyl-3-amino-2)-2-propanol. HCl (according to process [e]) (I, R₁ = R = COOH, R₂ and R₃ = H, R₄ and R₅ = CH₃)

5 Grams of 1-(4-ethoxy carbonylphenoxy)-3-(2-methylbutynyl-3-amino-2)-2-propanol hydrochloride were refluxed in 30 ml of conc. HCl for two hours. After cooling, the crystalline mass that originated by hydrolysis was vacuum filtered and recrystallized twice from ethanol under addition of ether.

Yield: 3.1 gm, m.p. 159° to 162°C.

EXAMPLE 13
1-(3,5-Dibromo-4-aminophenoxo)-3-(2-methylbutynyl-3-amino-2)-2-propanol. 2 HCl (according to process [f]) (I, R₁ = 4-NH₂, R₂ = 3-Br, R₃ = 5-Br, R₄ and R₅ = CH₃)

4.96 Grams (0.02 mol) of 1-(4-aminophenoxy)-3-(2-methylbutynyl-3-amino-2)-2-propanol were added into a mixture of 30 ml of HBr (65%) and 10 ml of water and heated to 45°C. While stirring and cooling, 4.54 gm (0.04 mol) of H₂O₂, 30%, were dropped into the mixture in such a way that the temperature did not rise over 65°C. After it had been kept at approximately 65°C for a further 30 minutes, the crystalline substance was vacuum filtered after cooling. It was then recrystallized from ethanol under addition of ether. Then the hydrochloride was dissolved in water. NaOH was added. The base was extracted with CHCl₃ and, after evaporation of the solvent, recrystallized from ethyl acetate under addition of petroleum ether. The chromatographically pure base was dissolved in ethanol; alcoholic HCl was added and the dihydrochloride was brought to crystallization under addition of ether.

Yield: 3.8 gm, m.p. 183° to 185°C.

EXAMPLES OF FORMULATIONS

1. Tablets

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-(2-cyanophenoxo)-3-(2-methylbutynyl-3-amino-2)-2-propanol . HCl</td>
<td>40.0 mg</td>
</tr>
<tr>
<td>Corn starch</td>
<td>164.0 mg</td>
</tr>
<tr>
<td>Sec. calcium phosphate</td>
<td>240.0 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.0 mg</td>
</tr>
<tr>
<td></td>
<td>445.0 mg</td>
</tr>
</tbody>
</table>
PRODUCTION

The individual components were admixed well and the mixture was granulated in the usual way. The granulate was pressed into tablets of 445 mg by weight, of which each contains 40 mg of active ingredient.

Instead of the active ingredients mentioned in this example, the substances 1-(2-cyanophenoxo)-3-(1-ethynlyclohexylamino)-2-propanol. HCl and 1-(2-cyano-4-chlorophenoxo)-3-(2-methylbutynyl-3-amino-2)-2-propanol may be used in the same quantity.

2. Gelatin Capsules
The content of the capsules was composed as follows:

1-(2-ethynlyphenoxy)-3-(2-methylbutynyl-3-amino-2)-2-propanol . HCl
Corn starch

[Table]

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-(2-ethynlyphenoxy)-3-(2-methylbutynyl-3-amino-2)-2-propanol . HCl</td>
<td>25.0 mg</td>
</tr>
<tr>
<td>Corn starch</td>
<td>175.0 mg</td>
</tr>
<tr>
<td>Total</td>
<td>200.0 mg</td>
</tr>
</tbody>
</table>

PRODUCTION

The active ingredients of the content of capsule were mixed well and 200 mg portions of the mixture were filled into gelatin capsules of suitable size. Each capsule contains 25 mg of the active ingredient.

3. Injection Solution
The solution was produced of the following ingredients:

1-(2-cyano-5-methylphenoxy)-3-(2-methylbutynyl-3-amino-2)-2-propanol . HCl
Sodium salt of EDTA (ethylene-diaminetetraacetic acid)
Distilled water

[Table]

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-(2-cyano-5-methylphenoxy)-3-(2-methylbutynyl-3-amino-2)-2-propanol . HCl</td>
<td>2.5 parts</td>
</tr>
<tr>
<td>Sodium salt of EDTA (ethylene-diaminetetraacetic acid)</td>
<td>0.2 parts</td>
</tr>
<tr>
<td>Distilled water</td>
<td>ad</td>
</tr>
<tr>
<td>Total</td>
<td>100.0 parts</td>
</tr>
</tbody>
</table>

PRODUCTION

The active ingredient and EDTA-salt were dissolved in sufficient water and filled with water to the desired volume. The solution was filtered free from suspended particles and filled into ampoules under aseptic conditions. Finally, the ampoules were sterilized and sealed. Each ampoule contains 25 mg of active ingredient.

Instead of the active ingredient mentioned in this example, 1-(2-hydroxymethylphenoxy)-3-(2-methylbutynyl-3-amino-2)-2-propanol. HCl or 1-(2-allylphenoxy)-3-(2-methylbutynyl-3-amino-2)-2-propanol. HCl in the same quantity may be used as well.

4. Coated Tablets with Sustained Release Core:

1-(2-cyanophenoxo)-3-(2-methylbutynyl-3-amino-2)-2-propanol . HCl
Carboxymethyl cellulose (CMC)
Stearic acid
Cellulose acetate/phthalate (CAP)

[Table]

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-(2-cyanophenoxo)-3-(2-methylbutynyl-3-amino-2)-2-propanol . HCl</td>
<td>25.0 gm</td>
</tr>
<tr>
<td>Carboxymethyl cellulose (CMC)</td>
<td>295.0 gm</td>
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<tr>
<td>Stearic acid</td>
<td>20.0 gm</td>
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<tr>
<td>Cellulose acetate/phthalate (CAP)</td>
<td>40.0 gm</td>
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<tr>
<td>Total</td>
<td>380.0 gm</td>
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</tbody>
</table>

PRODUCTION

Active ingredient, CMC and stearic acid were mixed well and the mixture was granulated in the usual way, using a solution of the CAP in 200 ml of a mixture of ethanol/ethyl acetate. Then the granulate was pressed to 380 mg cores, coated in the conventional way with a sugary 5% solution of polyvinylpyrrolidone in water. Each coated tablet contains 25 mg of active ingredient.
3,925,446

18

R₂ is hydrogen, chlorine or —NH—CO—NHR, where R is alkyl of 1 to 3 carbon atoms, and R₄ and R₅ are methyl, or a physiologically compatible acid addition salt thereof.

5. A compound of claim 3, which is of the formula

4. A compound of claim 3, wherein

R₂ is hydrogen, chlorine or —NH—CO—NHR, where R is alkyl of 1 to 3 carbon atoms, and R₄ and R₅ are methyl, ethyl or together pentamethylene, or a physiologically compatible acid addition salt thereof.

6. A compound of claim 1, wherein R₁ is 2-cyano, R₂ is hydrogen and R₄ and R₅ are methyl.
UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,925,446 Dated December 9, 1975

Inventor(s) Herbert Köppe, et al

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Col. 1, Line 53 "1 to 4 carbon atoms" should read -- 2 to 4 carbon atoms --

Col. 1, Line 59 "\" should be deleted

Col. 8, Line 40 "mans" should read -- means --

Col. 9, Line 4 "actove" should read -- active --

Col. 10, Line 22 "wass" should read -- was --

Col. 10, Line 32 "R_3=R_4" should read -- R_3=H, R_4 --

Col. 11, Line 43 "2-C C-CH_3" should read -- 2-C=CC-CH_3 --

Signed and Sealed this first Day of June 1976

[SEAL]

Attest:

RUTH C. MASON
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents and Trademarks