

PATENT SPECIFICATION

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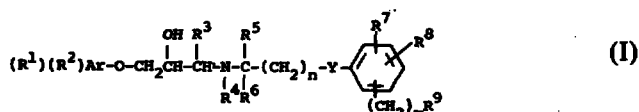


(54) AMINES

(71) We, AB HASSLE, a Swedish Body Corporate of Fack, S-431 20 Molndal 1, Sweden, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to amines having β -receptor blocking activity, useful in treating cardiovascular diseases, to methods for their preparation, to compositions containing them and to their use.

The compounds of the present invention are those of the general formula:



wherein

R^1 is $-CH_2CH=CH_2$, $-CH_2C=CH$, $-OCH_2CH=CH_2$, $-OCH_2C=CH$, alkoxyalkyl containing 1 to 7 carbons in the alkoxy residue and 1 to 7 carbons in the alkyl residue, alkoxyalkoxy containing 1 to 7 carbons in each of the alkoxy residues, alkoxy-carbonylaminoalkoxy containing 1 to 7 carbons in each of the alkoxy residues, $HOCH_2CH_2NHCOCH_2O-$, $CH_3OCH_2CH_2NHCOCH_2O-$ or $-CH=NOR$, wherein R is hydrogen or alkyl having 1 to 6 carbon atoms, R^2 is hydrogen, R^3 is hydrogen or C_1-C_7 alkyl, R^4 is hydrogen, C_1-C_7 alkanoyl or benzyl, R^5 and R^6 are each hydrogen or C_1-C_7 alkyl, R^7 and R^8 are each hydrogen, halogen, or C_1-C_7 alkyl, R^9 is hydrogen, alkoxy-carbonylaminoalkyl containing 1 to 7 carbons in the alkoxy residue and 1 to 7 carbons in the alkyl residue, C_1-C_7 alkanoyl, cyano, trifluoromethyl, $-CONR^{10}R^{11}$, $-CONHNR^{10}R^{11}$, wherein R^{10} and R^{11} are hydrogen, or wherein R^{10} and R^{11} together with the nitrogen atom to which they are bound form a heterocyclic ring, Y is $-O-$ or $-CH_2-$, n is 0 or an integer from 1 to 5, inclusive, m is 0, 1 or 2 and Ar is a phenyl ring, R^1 being in the 2 or 3 position on the phenyl ring, and therapeutically acceptable acid addition salts thereof.

In the compounds of the invention:—

R^5 and R^6 may be the same or may be different.

R^7 and R^8 may be the same or may be different.

Alkoxyalkyl R^1 has preferably up to 4 carbon atoms in each of the alkoxy and alkyl residues and each of them may be straight and/or branched. Alkoxyalkyl R^1 is thus e.g. methoxymethyl, methoxyethyl, ethoxyethyl, isopropoxyethyl, n-propoxymethyl, and t-butyloxymethyl.

Alkoxyalkoxy R^1 has preferably up to 4 carbon atoms in each, alkoxy residue and each of them may be straight or branched. Alkoxyalkoxy R^1 is thus e.g. methoxymethoxy, methoxyethoxy, ethoxyethoxy, isopropoxyethoxy, 2-ethoxy-1-methylethoxy, and t-butoxyethoxy.

Alkoxy-carbonylaminoalkoxy R^1 has preferably up to 4 carbon atoms in each alkoxy residue each of which is straight and/or branched. Alkoxy-carbonylaminoalkoxy R^1 is e.g. methoxycarbonylamino-methoxy, methoxycarbonylaminoethoxy,

ethoxycarbonylaminoethoxy, isopropoxycarbonylaminoethoxy or isopropoxy-carbonylaminoethoxy.

When R^1 is $-\text{CH}=\text{NOR}$, wherein R is hydrogen or alkyl with 1 to 6 carbon atoms, it may be isonitrosomethyl, methylisonitrosomethyl, ethylisonitrosomethyl, n-propylisonitrosomethyl or isopropylisonitrosomethyl.

Alkyl R^2 has preferably up to 4 carbon atoms, and is straight or branched and is e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl.

Alkanoyl R^4 has preferably up to 4 carbon atoms, and is straight or branched, and is e.g. formyl, acetyl, propionyl, butyryl, isopropionyl, or sec-butyryl.

Alkyl R^5 and alkyl R^6 have preferably up to 4 carbon atoms and are e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl and t-butyl.

Halogen R^7 is e.g. chloro, fluoro or bromo.

Alkyl R^7 and alkyl R^8 have preferably up to 4 carbon atoms and are e.g. methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl and t-butyl.

Alkanoyl R^9 has preferably up to 4 carbon atoms and is e.g. formyl, acetyl, propionyl, n-butyryl and t-butyryl.

Cyano R^9 is the group $\text{NC}-$.

When R^{10} and R^{11} , together with the nitrogen to which they are bonded, form a ring, that ring is preferably pyrrolidine, piperidine, piperazine or morpholine.

m is preferably 0 or 1.

n is preferably 1 or 2.

The new compounds have valuable pharmacological properties in that they block cardiac β -receptors, which is shown by the determination of the antagonism of tachycardia after an intravenous injection of $0.5 \mu\text{g/kg}$ of d/l-isoproterenol sulphate on an anaesthetized cat at an intravenous dose of 0.002 to 2 mg/kg . They also block the vascular β -receptors which is shown by the determination of the antagonism of vasodilation after an intravenous injection of $0.5 \mu\text{g/kg}$ of d/l-isoproterenol sulphate on an anaesthetized cat at an intravenous dose of 3 mg/kg or more. They are thus heart selective.

The new compounds can be used as cardioselective antagonists of adrenergic β -receptor stimulators, e.g. in the treatment of exogenously or endogenously caused arrhythmias and angina pectoris.

The compounds of the invention are also useful as intermediates for the preparation of other valuable pharmaceutical compounds.

Preferred classes of compounds of the invention are those in which:—

1. R^1 is $-\text{CH}_2\text{CH}=\text{CH}_2$ or $-\text{CH}_2\text{C}\equiv\text{CH}$, and R^9 is hydrogen, alkanoyl, cyano, trifluoromethyl, alkoxy-carbonylaminoalkyl, $-\text{CONR}^{10}\text{R}^{11}$, or $-\text{CONHNR}^{10}\text{R}^{11}$, especially those wherein R^1 is o- $\text{CH}_2\text{CH}=\text{CH}_2$, m- $\text{CH}_2\text{CH}=\text{CH}_2$, o- $\text{CH}_2\text{C}\equiv\text{CH}$, or m- $\text{CH}_2\text{C}\equiv\text{CH}$, R^3 is hydrogen or methyl, R^4 is hydrogen, formyl, acetyl or benzyl, R^5 and R^6 are each hydrogen, methyl or ethyl, R^7 and R^8 are each hydrogen, chloro, bromo, methyl or ethyl, R^9 is hydrogen, formyl, acetyl, cyano, trifluoromethyl, methoxycarbonylaminoethyl, ethoxycarbonylaminoethyl, carbamyl or morpholinylcarbonyl, and particularly those wherein R^1 is o- $\text{CH}_2\text{CH}=\text{CH}_2$ or o- $\text{CH}_2\text{C}\equiv\text{CH}$, R^3 is hydrogen, R^4 is hydrogen, R^5 and R^6 are each hydrogen or methyl, R^7 and R^8 are each hydrogen or methyl, R^9 is hydrogen, carbamyl, methoxycarbonylaminoethyl, or morpholinylcarbonyl, Y is $-\text{O}-$ and n is 1 or 2.

2. R^1 is $-\text{OCH}_2\text{CH}=\text{CH}_2$ or $-\text{OCH}_2\text{C}\equiv\text{CH}$, and R^9 is hydrogen, alkanoyl, cyano, trifluoromethyl, alkoxy-carbonylaminoalkyl, $-\text{CONR}^{10}\text{R}^{11}$, or $-\text{CONHNR}^{10}\text{R}^{11}$, especially those wherein R^1 is $-\text{OCH}_2\text{CH}=\text{CH}_2$ or $-\text{OCH}_2\text{C}\equiv\text{CH}$, R^3 is hydrogen or methyl, R^4 is hydrogen, formyl, acetyl or benzyl, R^5 and R^6 are each hydrogen, methyl or ethyl, R^7 and R^8 are each hydrogen, chloro, bromo, methyl or ethyl, R^9 is hydrogen, formyl, acetyl, cyano, trifluoromethyl, methoxycarbonylaminoethyl, ethoxycarbonylaminoethyl, carbamyl or morpholinylcarbonyl, and particularly those wherein R^1 is o- $\text{OCH}_2\text{CH}=\text{CH}_2$ or o- $\text{OCH}_2\text{C}\equiv\text{CH}$, R^3 is hydrogen, R^4 is hydrogen, R^5 and R^6 are each hydrogen or methyl, R^7 and R^8 are each hydrogen or methyl, R^9 is hydrogen, carbamyl, methoxycarbonylaminoethyl, or morpholinylcarbonyl, Y is $-\text{O}-$ and n is 1 or 2.

3. R^1 is alkoxyalkyl, and R^9 is hydrogen, alkanoyl, cyano, trifluoromethyl, alkoxy-carbonylaminoalkyl, $-\text{CONR}^{10}\text{R}^{11}$, or $-\text{CONHNR}^{10}\text{R}^{11}$, especially those wherein R^1 is alkoxyalkyl, R^3 is hydrogen or methyl, R^4 is hydrogen, formyl, acetyl, or benzyl, R^5 and R^6 are each hydrogen, methyl or ethyl, R^7 and R^8 are each hydrogen, chloro, bromo, methyl or ethyl, R^9 is hydrogen, formyl, acetyl, cyano, trifluoromethyl, methoxycarbonylaminoethyl, ethoxycarbonylaminoethyl,

carbamyl, or morpholinylcarbonyl, and particularly those wherein R¹ is methoxymethyl, methoxyethyl or ethoxyethyl, R³ is hydrogen, R⁴ is hydrogen, R⁵ and R⁶ are each hydrogen or methyl, R⁷ and R⁸ are each hydrogen or methyl, R⁹ is hydrogen, carbamyl, methoxycarbonylaminoethyl, or morpholinylcarbonyl, Y is —O— and n is 1 or 2.

4. R¹ is alkoxyalkoxy, and R⁹ is hydrogen, alkanoyl, cyano, trifluoromethyl, alkoxy-carbonylaminoalkyl, —CONR¹⁰R¹¹, or —CONHNR¹⁰R¹¹, especially those wherein R¹ is alkoxyalkoxy, R³ is hydrogen or methyl, R⁴ is hydrogen, formyl, acetyl or benzyl, R⁵ and R⁶ are each hydrogen, methyl or ethyl, R⁷ and R⁸ are each hydrogen, chloro, bromo, methyl or ethyl, R⁹ is hydrogen, formyl, acetyl, cyano, trifluoromethyl, methoxycarbonylaminoethyl, ethoxycarbonylaminoethyl, carbamyl, or morpholinylcarbonyl, and particularly those wherein R¹ is methoxymethoxy, methoxyethoxy or ethoxyethoxy, R³ is hydrogen, R⁴ is hydrogen, R⁵ and R⁶ are each hydrogen or methyl, R⁷ and R⁸ are each hydrogen or methyl, R⁹ is hydrogen, carbamyl, methoxycarbonylaminoethyl, or morpholinylcarbonyl, Y is —O— and n is 1 or 2.

5. R¹ is alkoxy-carbonylaminoalkoxy, HOCH₂CH₂NHCOCH₂O— or CH₂OCH₂NHCOCH₂O—, and R⁹ is hydrogen, alkanoyl, cyano, trifluoromethyl, alkoxy-carbonylaminoalkyl, —CONR¹⁰R¹¹ or —CONHNR¹⁰R¹¹, especially those wherein R¹ is alkoxy-carbonylaminoalkoxy, HOCH₂CH₂NHCOCH₂O— or CH₂OCH₂CH₂NHCOCH₂O—, R³ is hydrogen or methyl, R⁴ is hydrogen, formyl, acetyl or benzyl, R⁵ and R⁶ are each hydrogen, methyl or ethyl, R⁷ and R⁸ are each hydrogen, chloro, bromo, methyl or ethyl, R⁹ is hydrogen, formyl, acetyl, cyano, trifluoromethyl, methoxycarbonylaminoethyl, ethoxycarbonylaminoethyl, carbamyl, or morpholinylcarbonyl, and particularly those wherein R¹ is methoxy-carbonylamino-methoxy, methoxycarbonylaminoethoxy, ethoxycarbonylaminoethoxy, ethoxycarbonylamino-methoxy, HOCH₂CH₂NHCOCH₂O— or CH₂OCH₂CH₂NHCOCH₂O—, R³ is hydrogen, R⁴ is hydrogen, R⁵ and R⁶ are each hydrogen, hydroxy or methyl, R⁷ and R⁸ are each hydrogen, or methyl, R⁹ is hydrogen, carbamyl, methoxycarbonylaminoethyl, or morpholinylcarbonyl, Y is —O— and n is 1 or 2.

6. R¹ is —CH=NOR, and R⁹ is hydrogen, alkanoyl, cyano, trifluoromethyl, alkoxy-carbonylaminoalkyl, —CONR¹⁰R¹¹, or —CONHNR¹⁰R¹¹, especially those wherein R¹ is —CH=NOR, R³ is hydrogen or methyl, R⁴ is hydrogen, formyl, acetyl, or benzyl, R⁵ and R⁶ are each hydrogen, methyl or ethyl, R⁷ and R⁸ are each hydrogen, chloro, bromo, methyl or ethyl, R⁹ is hydrogen, formyl, acetyl, cyano, trifluoromethyl, methoxycarbonyl, aminoethyl, ethoxycarbonylaminoethyl, carbamyl, or morpholinylcarbonyl, and particularly those wherein R¹ is isonitroso-methyl, methylisonitrosomethyl, ethylisonitrosomethyl, propylisonitrosomethyl or t-butylisonitrosomethyl, R³ is hydrogen, R⁴ is hydrogen, R⁵ and R⁶ are each hydrogen or methyl, R⁷ and R⁸ are each hydrogen, or methyl, R⁹ is hydrogen, carbamyl, methoxycarbonylaminoethyl, or morpholinylcarbonyl, Y is —O— and n is 1 or 2.

Specific compounds of the invention include the following:

- 1) 1 - [2 - (4 - carbamylphenoxy)ethylamino] - 3 - (2 - allylphenoxy)propanol - 2.
- 2) 1 - [2 - (4 - carbamylphenoxy)ethylamino] - 3 - (2 - methoxyethylphenoxy)propanol - 2.
- 3) 1 - [1 - methyl - 2 - (4 - carbamylphenoxy)ethylamino] - 3 - (2 - allylphenoxy)propanol - 2.
- 4) 1 - [1 - methyl - 2 - (2 - methylphenoxy) - ethylamino] - 3 - (2 - allylphenoxy)propanol - 2.
- 5) 1 - [1 - methyl - 2 - (4 - methylphenoxy)ethylamino] - 3 - (2 - allylphenoxy)propanol - 2.
- 6) 1 - [2 - (4 - morpholinylcarbonylphenoxy)ethylamino] - 3 - (2 - allylphenoxy)propanol - 2.
- 7) 1 - [1 - methyl - 2 - (4 - carbamylphenoxy)ethylamino] - 3 - (2 - methylisonitrosomethylphenoxy)propanol - 2.
- 8) 1 - [2 - (4 - carbamylphenoxy)ethylamino] - 3 - (3 - allylphenoxy)propanol - 2.

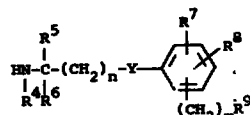
The new compounds can be obtained in accordance with methods known *per se*. Thus a compound of formula II



II

wherein

Ar, R¹, R² and R³ have the meanings given above, X¹ is a hydroxy group and Z is halogeno or another reactive group formed by esterification of a hydroxy group with a strong organic or with an inorganic acid, or X¹ and Z together form an epoxy group, is reacted with an amine of the formula (III)



III

wherein

R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, Y, m and n have the same meanings as given above. The esterified hydroxy group is particularly a hydroxy group esterified with a hydrohalogen acid, such as hydrochloric acid, hydrobromic acid, or hydroiodic acid, or sulphuric acid or a strong organic sulphonic acid, particularly a strong aromatic sulphonic acid, e.g. benzenesulphonic acid, 4-bromobenzenesulphonic acid or 4-toluenesulphonic acid. Thus, Z is preferably chloro, bromo or iodo.

This reaction is carried out conventionally, preferably in the presence of a basic condensing agent and/or with an excess of amine. Suitable basic condensing agents are e.g. alkali metal hydroxides such as sodium or potassium hydroxide, alkali metal carbonates such as potassium carbonate and alkali metal alcoholates such as sodium methylate, potassium ethylate and potassium tert.butylate.

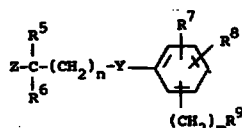
Alternatively a compound of formula IV



(IV)

wherein

Ar, R¹, R², R³ and R⁴ have the same meanings as given above, can be reacted with a compound of the formula V

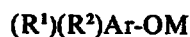


(V)

wherein

R⁵, R⁶, R⁷, R⁸, R⁹, Y, m, n and Z have the same meanings as given above. This reaction is carried out conventionally, preferably in the presence of a basic condensing agent and/or an excess of amine. Suitable basic condensing agents are e.g. alkali metal alcoholates, preferably sodium or potassium alcoholate, or alkali metal carbonates such as sodium or potassium carbonate.

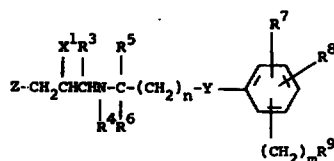
Alternatively, a compound of formula VI



(VI)

wherein

Ar, R¹ and R² have the same meanings as given above and M is hydrogen or an alkali metal can be reacted with compound of formula VII



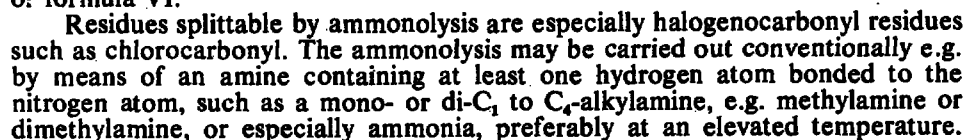
(VII)

wherein

R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, m, n, Y, Z and X¹ have the same meanings as given above.

This reaction is carried out conventionally. In those cases where reactive esters are used as starting material, the compound of formula VI may suitably be

Other compounds having hydrolyzable residues are of formula VIII, when R⁴ is hydrogen



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Instead of ammonia one may use an agent which releases ammonia such as hexamethylenetetramine.

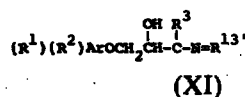
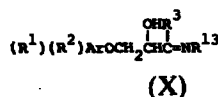
Residues splittable by reduction are e.g. α -arylalkyl such as benzyl or α -aralkoxycarbonyl such as benzyloxycarbonyl, which may be split off conventionally by means of hydrogenolysis, especially by catalytically activated hydrogen, such as hydrogen in the presence of hydrogenating catalysts, e.g. Raney-nickel. Other residues splittable by hydrogenolysis are 2-halogenoalkoxycarbonyl such as 2,2,2-trichloroethoxycarbonyl or 2-iodoethoxy- or 2,2,2-tribromoethoxycarbonyl, which may be split off conventionally, suitably by means of a metallic reduction (so called nascent hydrogen). Nascent hydrogen may be obtained by reacting metal or metal alloys, such as amalgam with compounds which give hydrogen together with acetic acid being preferred. 2-halogenoalkoxycarbonyl residues may also be hydrogenated using chromium or chromium (II) compounds such as chromium (II) chloride or chromium (II) acetate.

Another residue splittable by reduction is arylsulphonyl such as toluenesulphonyl, which may be split off conventionally by reduction using nascent hydrogen, e.g. by means of an alkali metal, such as lithium or sodium in liquid ammonia. This residue may be split off from a nitrogen atom. Care has to be taken to avoid other reducible groups being reduced.

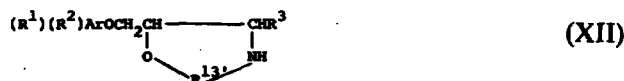
Residues splittable by means of pyrolysis, especially residues splittable from the nitrogen atom, are substituted or unsubstituted carbamoyl groups. Suitable substituents are e.g. C_1 — C_4 alkyl or aryl- C_1 to C_4 -alkyl such as methyl or benzyl or aryl, such as phenyl. The pyrolysis is carried out conventionally taking care not to influence other thermally susceptible groups.

Residues splittable by means of fermentation, especially residue splittable from the nitrogen atom are substituted, or unsubstituted carbamoyl groups. Suitable substituents, are e.g. C_1 — C_4 alkyl or aryl- C_1 to C_4 -alkyl, such as methyl or benzyl, or aryl such as phenyl. The fermentation is carried out conventionally e.g. by means of the enzyme urease or soy bean extract, at about 20°C or a slightly elevated temperature.

In a further method, a Schiff's base of formula X or XI when R^4 , R^5 and R^6 are hydrogen.

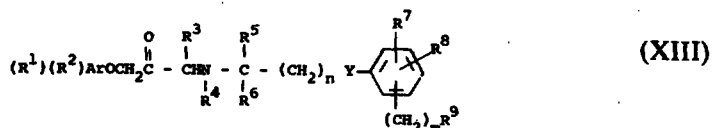


or a cyclic tautomer of formula XI having formula XII



can be reduced, wherein Ar, R^1 , R^2 , R^3 and R^{13} have the same meaning as given above and $R^{13'}H$ is the same as R^{13} . This reduction is carried out conventionally, e.g. using a di-light metal hydride, such as sodium-borohydride, lithium aluminium hydride, using a hydride such as Borane with formic acid, or by means of catalytic hydrogenation such as with hydrogen in the presence of Raney-nickel, care being taken not to reduce other reducible groups.

In a further method, the oxo group in the compound of formula XIII

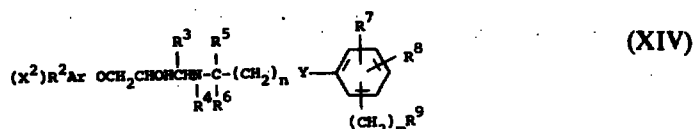


wherein

Ar, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , m, n and Y have the same meanings as given above, can be reduced to a hydroxy group. This reduction is carried out conventionally, especially using a di-light metal hydride, as mentioned above, or according to the "Meerwein-Ponndorf-Verley" method, or a modification thereof, suitably using an alkanol as a reaction component and a solvent, e.g. isopropanol,

and using a metal alkanolate such as a metal isopropanolate, e.g. aluminium isopropanolate.

In a further method, a compound of formula XIV



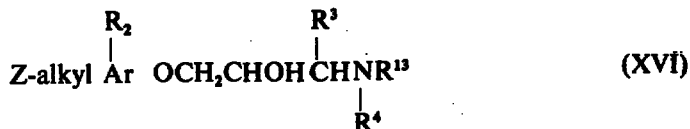
wherein

Ar, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, m, n, and Y have the same meanings as given above, and wherein X² is a residue which is able to be transformed to a residue R¹ is used as reactant.

When R¹ is alkoxyalkyl, X² can be Z¹-alkyl and compound XIV can be reacted with a compound alkyl-Z², when one of Z¹ and Z² is a hydroxy group and the other is Z having the meaning given above. Thus, one can react either a compound of formula XV



with a compound alkyl-Z, or a compound of formula XVI



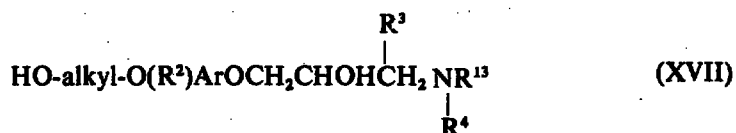
with a compound alkyl-OH, whereby R², R³, R⁴, R¹³ and Z have the same meanings as given above. The reaction is carried out conventionally e.g. in the same way as the reaction of a compound of formula II with an amine



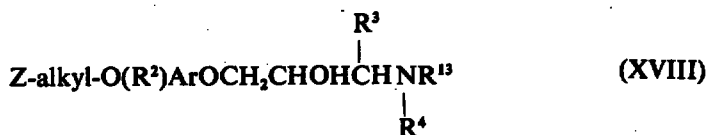
When R¹ is alkoxyalkoxy, X² can be Z¹-alkyl-O- or a hydroxy group.

A compound XIV when X² is Z¹-alkyl-O- can be reacted with a compound alkyl-Z², where one of Z¹ and Z² is hydroxy and the other is Z having the same meaning as given above.

Thus, one can react a compound of formula XVII



with a compound alkyl-Z or a compound of formula XVIII



with a compound alkyl-OH, whereby R², R³, R⁴, R¹³ and Z have the same meanings as given above. The reaction is carried out conventionally e.g. in the same way as the reaction of a compound of formula II with an amine

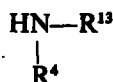


A compound of formula XIV in which X² is a hydroxy group can be reacted conventionally with a compound alkoxyalkyl-Z, where Z has the same meaning as above.

Thus, one can react a compound of formula XIX



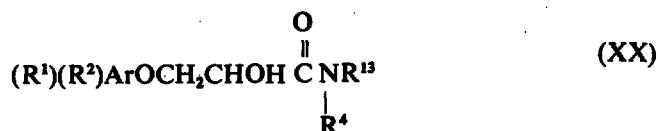
with a compound alkoxyalkyl-Z, wherein R², R³, R⁴, R¹³ and Z have the same meanings as given above. The reaction is carried out conventionally, e.g. in the same way as the reaction of a compound of formula II with an amine



In an alternative method, a derivative of a formula I compound where R³, R⁵ and R⁶ are each hydrogen and which carries an oxo group at a carbon atom bound to a nitrogen atom may be reduced at the oxo group. The residue R¹ is preferably not one of the residues containing a carbonyl group.



Said compounds are e.g. of the formula XX



wherein

R¹, R², R⁴ and R¹³ have the meaning given above, when R³ is hydrogen.

The reduction can be carried out according to the above described manner using complex methyl hydrides, e.g. lithium aluminium hydride or di-isobutyl aluminium hydride. Suitably the reaction takes place in an inert solvent such as an ether, e.g. diethylether or tetrahydrofuran.

It is also possible to start from unsaturated reactants and to hydrogenate catalytically C—C double bonds or C—C triple bonds to C—C single bonds by means of hydrogen in the presence of a hydrogenation catalyst, e.g. platinum, palladium or nickel, such as Raney-nickel taking care not to reduce other reducible groups.

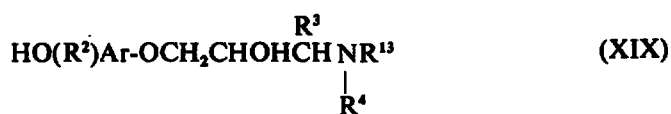
In compounds containing a C—C triple bond, this may be transformed into a C—C double bond and, if desired, stereospecifically into C—C-cis or C—C-trans double bond. The hydrogenation of a C—C triple bond to a C—C double bond may, for example, be carried out using 1 mole of hydrogen in the presence of a less active hydrogenation catalyst such as iron or palladium, e.g. Raney-iron or palladium with bariumsulphate, preferably at an elevated temperature. The hydrogenation to a C—C-cis double bond may take place e.g. between 1 mole of hydrogen and a deactivated catalyst, such as palladium on active carbon and in the presence of quinoline, palladium on calcium carbonate in the presence of lead salts or Raney-nickel.

The hydrogenation to a C—C-trans double bond may take place by means of sodium in liquid ammonia, using to avoid affecting other reducible groups, short reaction times and no excess of the reducing agent. Optionally, an ammonium halogenide, such as ammonium chloride, can be added as a catalyst.

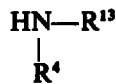
5 In the reduction mentioned above, care must be taken that no further reducible groups are reduced. In the reduction using Raney-nickel and hydrogen one has to consider especially any halogen atom bonded to the aromatic ring, so that it is not replaced by hydrogen. Furthermore, in all reductions, especially catalytic hydrogenations, one has to consider any thioether group present. Preferably sulphur resistant catalysts are used. The volume of hydrogen to be absorbed for the desired hydrogenation is calculated and when the calculated amount is absorbed, the hydrogenation is terminated.

10 Compounds of formula I in which R¹ is alkoxycarbonylaminoalkoxy can be prepared by reacting a compound XIV in which X² is a hydroxy group with an alkoxycarbonylaminoalkyl-Z compound.

Thus, one can react a compound of formula XIX

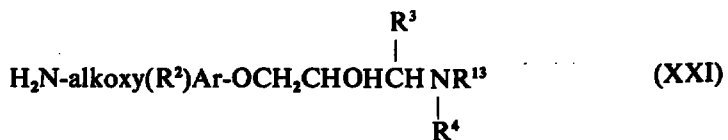


15 with alkoxycarbonylamino-Z where R², R³, R⁴, R¹³ and Z have the meanings given above. The reaction is carried out conventionally, e.g. in the same way as has been mentioned for the reaction of a compound of formula II with an amine

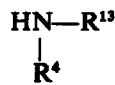


20 A compound I in which R¹ is alkoxycarbonylaminoalkoxy can also be obtained by reacting a compound XIV in which X² is H₂N-alkoxy with an alkoxycarbonylchloride.

Thus one can react a compound of the formula XXI

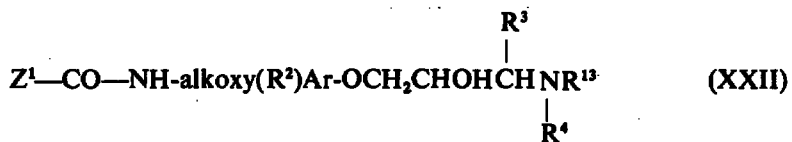


25 with an alkoxycarbonylchloride, whereby R², R³, R⁴, and R¹³ have the meanings given above. The reaction is carried out conventionally e.g. as has been mentioned for the reaction of a compound of formula II with an amine



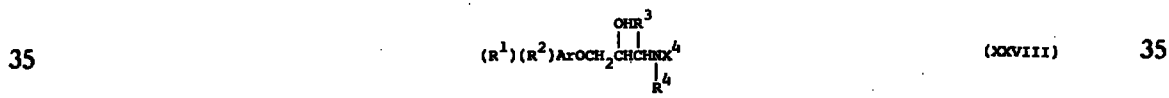
30 A compound I in which R¹ is alkoxycarbonylaminoalkoxy can also be obtained by reacting a compound XIV in which X² is Z¹-CO-NH-alkoxy with a compound alkyl-Z², where Z¹ and Z² have the meanings given above.

Thus one can react a compound of formula XXII



with a compound alkyl-Z², whereby R², R³, R⁴, R¹³, Z¹ and Z² have the meanings given above.

In an alternative method, the reactant can be a compound of formula XXVIII



(16)

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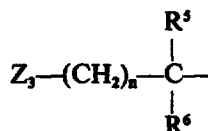
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wherein

Ar, R¹, R², R³ and R⁴ have the same meanings as given above and wherein X⁴ is a residue transformable to a residue R¹³.

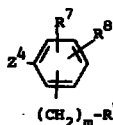
When R¹³ is e.g. (substituted)-phenoxyalkyl, X⁴ can be

5



5

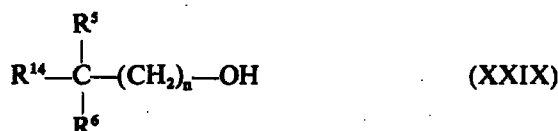
A compound XXVIII having X⁴ Z³-alkyl can be reacted conventionally with a compound



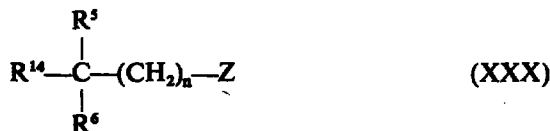
10

where one of Z³ and Z⁴ is hydroxy group and the other is Z as defined above. Thus, one can react either a compound of formula XXIX

10



with a compound (substituted)-phenyl-Z, or a compound of formula XXX



15

with a compound (substituted)phenyl-OH, where R⁵, R⁶ and n have the same meanings as given above and R¹⁴ is

15



wherein

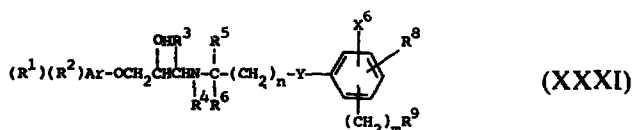
Ar, R¹, R², R³ and R⁴ have the same meanings as given above. The reaction is carried out conventionally e.g. as in the reaction of a compound of formula II with an amine of formula

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20



In an alternative method, the reactant can be a compound of the formula XXXI:



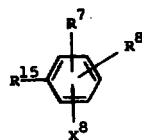
25

wherein

Ar, R¹, R², R³, R⁴, R⁵, R⁶, R⁸, R⁹, Y, n and m have the meanings as above, and X⁶ is a residue transformable to R⁷.

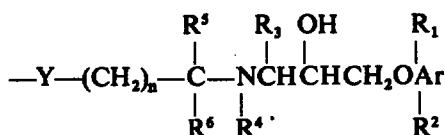
25

In an alternative method, the reactant can be a compound of the formula XXXVII:



(XXXVII)

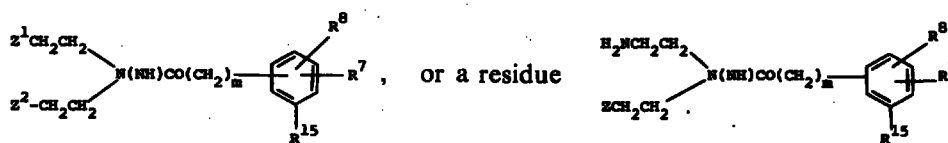
wherein R^{15} is



wherein

$R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, Y$ and n have the above meaning, and X^8 is a residue transformable to $-(CH_2)_m R^9$, m and R^9 having the above meanings.

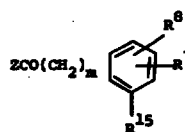
A residue X^8 able to be transformed into $-(CH_2)_m R^9$ is e.g. a residue X^8 transformable into a $-(CH_2)_m CONR^{10}R^{11}$, or a $-(CH_2)_m CONHNR^{10}R^{11}$, when R^{10} and R^{11} together with adjacent nitrogen form a morpholinyl or piperazinyl group, such as a residue



wherein

$R^7, R^8, R^9, R^{15}, m, Z, Z^1$ and Z^2 have the above meanings. These residues are each reacted conventionally to bring about ring closure e.g. as in the reaction between a compound of formula II with a compound of formula III.

Another residue X^8 transformable into $-(CH_2)_m R^9$ is e.g. a residue transformable into a $-(CH_2)_m CONR^{10}R^{11}$, or a $-(CH_2)_m CONHNR^{10}R^{11}$, such as a residue



which is reacted conventionally with a compound



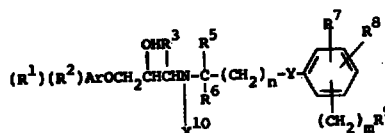
or a compound



The reaction is carried out in the same way as the reaction between a compound of formula II and a compound of formula III.

Another residue X^8 transformable into $(CH_2)_m R^9$ is e.g. a residue transformable into an alkoxycarbonylaminoalkyl- $(CH_2)_m$ residue. These reactions and residues are the same as those described above for the cases when X^2 is a residue transformable into an alkoxycarbonylaminoalkyl residue R^1 .

In an alternative method, the reactant is a compound of the formula XL:



(XL)

wherein

Ar, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, Y, m and n have the above meanings, and X¹⁰ is a residue transformable to hydrogen, e.g. benzyl or alkanoyl which can be hydrolyzed to leave R⁴ = H.

The above mentioned reactions may be carried out simultaneously or after each other in any sequence.

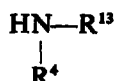
The above mentioned reactions are carried out in a manner known *per se* in the presence or absence of any necessary or desired diluting, condensing and/or catalytic agents at room or elevated temperature, optionally being carried out in closed vessel.

In a still further method of preparing the compounds, one may react an aldehyde of the formula XXXVIII:



wherein

R¹ and R² have the same meanings as given above, with an amine of the formula:



wherein

R⁴ and R¹³ have the same meanings as given above, in the presence of a suitable reducing agent, such as one of the above mentioned. This gives a compound of formula X as an intermediate, which then is reduced as described above.

Further, one may, in a manner known *per se*, react an amine of the formula III with an aldehyde or a ketone of the formula O = R¹³, wherein R¹³ has the meaning given above, in the presence of a suitable reducing agent, such as one of the above mentioned. This gives a compound of formula XI or XII as an intermediate, which then is reduced as described above.

Further, one may, in a manner known *per se*, react a phenol of formula V above with an acetidinol of the formula XXXIX:



wherein

R¹³ has the meaning given above, to form a compound of formula I.

This reaction is carried out conventionally, e.g. under alkaline conditions, in a suitable solvent, such as benzylalcohol by boiling the reaction mixture for some hours. Thereby the phenol is primarily converted to its metal phenolate e.g. alkali-metal phenolate before it is added to the acetidinol of formula XXXIX.

It is obvious from the above described methods for preparing the compounds of the invention that the different substituents can be added by analogous processes. Thus the addition of —OCH₂CH=CH₂ and —OCH₂C≡CH groups as R¹ can be done by conventional etherification.

Depending on the process conditions and the starting material, the end product is obtained either in free base form or in the form of its acid addition salt, and, in this specification and claims, references to the compounds includes the free base forms and the acid addition salts unless the context requires otherwise.

Thus, for example, basic, neutral or mixed salts may be obtained as well as hemiamino, sesqui- or polyhydrates. The acid addition salts of the new compounds may, in a manner known *per se*, be transformed into free base compounds using e.g. basic agents such as alkali or ion exchanger. On the other hand, the free bases obtained may form salts with organic or inorganic acids. In the preparation of acid addition salts, preferably such acids are used which form therapeutically acceptable salts. Such acids are e.g. hydrohalogen acids, sulphuric acid, phosphoric acid, nitric acid, perchloric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxy or sulphonc acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic or pyruvic acid, phenylacetic, benzoic, p-aminobenzoic, anthranilic p-hydroxybenzoic, salicylic or p-amino-salicylic acid, embonic acid (i.e. pamoic acid), methanesulphonic, ethane-

sulphonic, hydroxyethanesulphonic, ethylenesulphonic, halogenbenzene-sulphonic, toluenesulphonic, naphthylsulphonic acids or sulphanilic acid: methionine, tryptophane, lysine or arginine.

5 These or other salts of the new compounds such as e.g. picrates, may be used to purify free bases obtained by synthesis. The free bases are transformed into salts, these are isolated and the bases are then set free from the salts. 5

The new compounds may, depending on the choice of starting material and process, be present as optical antipodes or racemate, or, if they contain at least one asymmetric carbon atom, be present as an isomer mixture (racemate mixture).

10 The isomer mixtures (racemate mixtures) obtained may, depending on physical-chemical differences of the components, be separated into stereo-isomeric (diastereomeric) forms e.g. by means of chromatography and/or fractional crystallisation. 10

15 The racemates obtained can be separated according to known methods, e.g. by means of recrystallisation from an optically active solvent, by means of micro-organisms, or by a reaction with topically active acids forming salts of the compound and separating the salts thus obtained, e.g. by means of their different solubility in the diastereomers. The individual antipodes can then be recovered by treating the salt with a suitable reagent. Suitable optically active acids are e.g. the L- and D-forms of tartaric acid, di-o-tolytartaric acid, malic acid, mandelic acid, 20 camphorsulphonic acid or china acid, i.e. 1,3,4,5-tetrahydrocyclohexane carboxylic acid. Preferably the more active part of two antipodes is isolated. 20

25 In clinical use, the compounds of the invention are administered normally orally, rectally or by injection in the form of a pharmaceutical preparation, which contains an active component either as free base or as pharmaceutically acceptable non-toxic acid addition salts, e.g. the hydrochloric, lactate, acetate or sulphamate in combination with a pharmaceutically acceptable carrier. Such compositions form a further aspect of the present invention. The carrier may be a solid, semi-solid or liquid diluent or a capsule. Usually, the amount of active compound is 0.1 to 95% by weight of the preparation, suitably 0.5 to 20% by weight in preparations for injection and 2 to 50% by weight in preparations for oral administration. 25

30 In the preparation of pharmaceutical preparations containing a compound of the present invention in the form of dosage units for oral administration, the compound selected may be mixed with a solid, pulverulent carrier, e.g. with lactose, saccharose, sorbitol, mannitol, a starch, e.g. potato starch, corn starch or amylopectin, a cellulose derivative or gelatine, as well as with an antifriction agent such as magnesium stearate, calcium stearate, or polyethyleneglycol waxes and pressed into tablets. If coated tablets are required, the above prepared core may be coated with a concentrated solution of sugar, which solution may also contain e.g. gum arabic gelatine, talc or titanium dioxide. Furthermore, the tablets may be coated with a lacquer dissolved in an easily volatile organic solvent or mixture of solvents. To this coating, a dye may be added in order to distinguish easily between tablets with different active compounds or with different amounts of the active compound present. 30

35 In the preparation of soft gelatine capsules (pearl-shaped, closed capsules), which consist of gelatine and e.g. glycerine, or in the preparation of similar closed capsules, the active compound is mixed with a vegetable oil. Hard gelatine capsules may contain granules of the active compound in combination with a solid, pulverulent carrier such as lactose, saccharose, sorbitol, mannitol, a starch, e.g. potato starch, corn starch or amylopectine), a cellulose derivative or gelatine. 35

40 Dosage units for rectal administration may be prepared in the form of suppositories, which contain the active substance in a mixture with a neutral fat base, or they may be prepared in the form of gelatine-rectal capsules which contain the active substance in a mixture with a vegetable oil or paraffin oil. 40

45 Liquid preparations for oral administration may be in the form of syrups or suspensions, e.g. solutions containing from 0.2% by weight to 20% by weight of the active substance described, the residue consisting of sugar and a mixture of ethanol, water, glycerol and propylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl-cellulose as a thickening agent. 45

50 Solutions of parenteral administration by injection may be prepared as an aqueous solution of a water soluble pharmaceutically acceptable salt of the active compound, preferably in a concentration from 0.5% by weight to 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may suitably be prepared in different dosage unit ampoules. 50

20

The preparation of tablets for peroral use can be carried out by the following method:

The solid substances included are ground or sieved to a selected particle size. A binding agent is homogenized and suspended in a selected amount of solvent. The active compound and necessary auxiliary agents are mixed continuously with the binding agent solution and are moistened so that the solution is uniformly divided in the mass without over-moistening any parts. The amount of solvent is usually selected so that the mass attains a consistency reminiscent of wet snow. The moistening of the pulverulent mixture with the binding agent solution causes the particles to gather together slightly to form aggregates and the real granulating process is carried out in such a way that the mass is pressed through a sieve in the form of a net of stainless steel having a mesh size of about 1 mm. The mass is then placed in thin layers on a tray to be dried in a drying cabinet. This drying takes place over 10 hours and has to be standardized carefully as the liquid content of the granulate is of utmost importance for the following process and for the feature of the tablets. Drying in a fluid bed may possibly be used. In this case the mass is not put on a tray but is poured into a container having a net bottom.

After the drying step, the granules are sieved so that the desired particle size is obtained. Under certain circumstances, powder has to be removed.

To the so-called final mixture, disintegrating, antifriction agents and anti-adhesive agents are added. After this mixing, the mass should have the right composition for tableting.

A cleaned tablet punching machine is provided with a selected set of punches and dies, and is adjusted for the weight of the tablets and the degree of compression selected. The weight of the tablets is decisive for the size of the dose in each tablet and is calculated starting from the amount of therapeutic agent in the granules. The degree of compression affects the size of the tablet, its strength and its ability to disintegrate in water. Especially as regards the two latter properties, the choice of compression pressure (0.5 to 5 ton) is very important. When the right adjustment is set, the preparation of tablets commences, e.g. a rate of 20,000 to 200,000 tablets per hour. The pressing of the tablets requires different times and depends on the size of the batch.

The tablets are freed from adhering powder and are then stored in closed packages until they are used.

Many tablets, especially those which are rough or bitter, are coated with a coating, e.g. of sugar.

The tablets are usually packed by machines having an electronic counting device into glass or plastic gallipots, or boxes, tubes or specific dosage adapted packages.

The daily dose of the active substance varies and is dependent on the type of administration, but as a general rule it is 100 to 400 mg/day of active substance at peroral administration and 5 to 20 mg/day at intravenous administration.

The following Examples illustrate the invention. Temperatures are given in degrees C.

EXAMPLE 1.

1.9 g of 1,2-epoxy-3-(2-allylphenoxy)propane and 1.8 g of 4-(2-aminoethoxy)benzamide were refluxed in 25 ml of isopropanol for 1.5 hours. The reaction mixture was evaporated *in vacuo*, whereupon the residue was dissolved in acetone and the hydrochloride of 1-[2-(4-carbamylphenoxy)-ethylamino]-3-(2-allylphenoxy)propanol-2 was precipitated by introducing either containing HCl. Mp. 211°C. The structure was verified with NMR.

EXAMPLE 2.

2.1 g of 1,2-epoxy-3-[4-(2-methoxyethyl)phenoxy]propane and 1.8 g of 4-(2-aminoethoxy)benzamide were reacted with each other in accordance with Example 1. The melting point of 1-[2-(4-carbamylphenoxy)-ethylamino]-3-(2-methoxyethylphenoxy)propanol-2 hydrochloride was 105°C. The structure was verified with NMR.

EXAMPLE 3.

1.9 g of 1,2-epoxy-3-(2-allylphenoxy)propane and 2.5 g of 4-(2-aminopropoxy)benzamide were reacted in accordance with Example 1. The hydrochloride of 1-[1-methyl-2-(4-carbamylphenoxy)-ethylamino]-3-(2-allylphenoxy)propanol-2 melted at 94°C. The structure was verified using NMR.

(21)

EXAMPLE 4.

3.8 g of 1,2-epoxy-3-(2-allylphenoxy)propane and 3.3 g of 1-(2-methylphenoxy)-2-propylamine were reacted in accordance with Example 1. The hydrochloride of 1-[1-methyl-2-(2-methylphenoxy)-ethylamino]-3-(2-allylphenoxy)-propanol-2 melted at 142°C. The structure was verified using NMR.

EXAMPLE 5.

3.8 g of 1,2-epoxy-3-(2-allylphenoxy)propane and 3.3 g of 1-(4-methylphenoxy)-2-propylamine were reacted in accordance with Example 1. The hydrochloride of 1-[1-methyl-2-(4-methylphenoxy)-ethylamino]-3-(2-allylphenoxy)-propanol-2 melted at 146°C. The structure was verified with NMR.

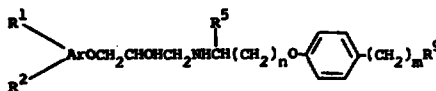
EXAMPLE 6.

1.8 g of 1-amino-3-(2-methylisopropylphenoxy)-propanol-2 and 1.55 g of 4-methylcarbonylmethoxybenzamide were dissolved in 25 ml of methanol and cooled to 0°C. 1.8 g of NaBH₄ were then added during 1/2 hour. 50 ml of water were added and the product was extracted with ethylacetate. The ethyl acetate phase is evaporated *in vacuo* and the substance, 1-[1-methyl-2-(4-carbamylphenoxy)ethylamino]-3-(2-methylisopropylphenoxy)-propanol-2, is washed with ether and ethyl acetate. Mp. 106°C. (HCl).

EXAMPLE 7.

1-[2-(4-carbamylphenoxy)-ethylamino]-3-(3-allylphenoxy)-propanol-2 was prepared in accordance with Example 1 starting from 1,2-epoxy-3-(3-allylphenoxy)-propane and 4-aminoethoxybenzamide. Mp. 228°C as hydrochloride.

The following compounds have further been prepared by analogous methods



Example	Ar	R ¹	R ²	R ³	n	m	R ⁴	Mp. °C
8	Phenyl	2-CH ₂ =CH-CH ₂ -O-	H	H	1	0	4-NH ₂ CO-	136-7 (HCl)
9	"	2-CH ₂ =C-CH ₂ O-	H	H	1	0	4-NH ₂ CO-	215 (HCl)
10	"	2-HOCH ₂ CH ₂ NHCOCH ₂ O-	H	H	1	0	4-NH ₂ CO-	66 (p-OH-benzoate)
11	"	2-CH ₂ =CH-CH ₂ O-	H	H	2	0	4-NH ₂ CO-	200 (HCl)
12	"	2-CH ₂ =CH-CH ₂ O	H	H	4	0	4-NH ₂ CO-	oil (HCl)

EXAMPLE 13.

A syrup containing 2% (weight per volume of active substance was prepared from the following ingredients:

5	1-[2-(4-carbamylphenoxy)-ethylaminol]-3-(2-allylphenoxy)-propanol-2 HCl	2.0 g	5
	Saccharine	0.6 g	
	Sugar	1 30.0 g	
	Glycerine	5.0 g	
10	Flavouring	agent 0.1 g	10
	Ethanol	96% 10.0 ml	
	Distilled water	ad 100.0 ml	

Sugar, saccharine and the active compound were dissolved in 60 g of warm water. After cooling, glycerine and a solution of flavouring agents dissolved in ethanol were added. To the mixture, water was then added to make up 100 ml.

The above given active substance may be replaced with other pharmaceutically acceptable acid addition salts.

EXAMPLE 14.

20	Active compound of formula I (250 g) was mixed with lactose (175.8 g), potato starch (169.7 g) and colloidal silicic acid (32 g). The mixture was moistened with a 10% solution of gelatine and was granulated through a 12-mesh sieve. After drying, potato starch (160 g), talc (50 g) and magnesium stearate (5 g) were admixed and	20
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the mixture thus obtained was pressed into tablets (10,000) each of which contain 25 mg of active substance. The tablets are provided with a breaking score to give dose other than 25 mg when broken.

EXAMPLE 15.

Granules were prepared from 1-[2-(4-carbamylphenoxy)-ethylamino]-3-(2-(2-methoxyethyl)phenoxy)propanol-2-hydrochloride (250 g), lactose (175.9 g) and an alcoholic solution of polyvinylpyrrolidone (25 g). After drying step the granules were mixed with talc (25 g), potato starch (40 g) and magnesium stearate (2.50 g) and was pressed into 10,000 biconvex tablets. These tablets are first coated with a 10% alcoholic solution of shellac and then with an aqueous solution containing saccharose (45%), gum arabic (5%), gelatine (4%) and dyestuff (0.2%). Talc and powder sugar were used for powdering after the first five coatings. The coating was then coated with a 66% sugar syrup and polished with a 10% carnauba wax solution in carbon tetrachloride.

EXAMPLE 16.

Active compound of formula I (1 g), sodium chloride (0.8 g) and ascorbic acid (0.1 g) were dissolved in sufficient amount of distilled water to give 100 ml of solution. This solution, which contains 10 mg of active substance on each ml. was used in filling ampoules, which were sterilized by heating at 120°C for 20 minutes.

Biological Effects.

The β -receptor blocking agents of the present invention were tested to demonstrate their biological properties. All compounds were tested in anaesthetized cats (males and females weighing 2.5—3.5 kg) pretreated with reserpine (5 mg/kg body weight administered intramuscularly) about 16 hours before the experiments. The animals were pretreated with reserpine in order to eliminate the endogenous sympathetic control of heart rate and vascular smooth muscle tone. The cats were anaesthetized with pentobarbital (30 mg/kg body weight administered i.p.) and artificially ventilated with room air. A bilateral vagotomy was performed in the neck. Blood pressure was obtained from a cannulated carotid artery and heart rate was registered from a cardi tachometer, triggered by the electrocardiogram (ECG). Intrinsic beta-mimetic activity on the heart was seen as increased heart rate after drug administration. The test compounds were given intravenously in logarithmically increasing doses. The values obtained were plotted on dose-response curves, from which affinity values (ED_{50}) were estimated. At the end of each experiment high doses of isoprenaline were given in order to obtain the maximal heart rate response.

The compounds were also tested on conscious dogs. Beagle dogs were trained to be lying quietly and to be lifted to an erect position by placing their forelegs on a table for 2 minutes. Arterial blood pressure was registered via a blood pressure transducer attached to the dog at the heart level. Heart rate was triggered from the ECG. All dogs were pretreated with methylscopolamine to avoid vagal influences. Recordings were taken before and 15 and 75 minutes after administration of the test compound, first in supine position for 2 minutes and then in the erect position for 2 minutes. The test compounds were given in increasing doses with 2 hour intervals.

Table 1 below shows affinity values and intrinsic β -mimetic activity in reserpinized cats and effects on blood pressure in conscious dogs of compounds of the present invention. Corresponding values for propranolol, (1-isopropylamino-3-(1-naphthoxy)propanol-2), practolol, (4-(2-hydroxy-3-isopropylaminopropoxy)-acetanilide), metaprolol, (1-isopropylamino-3-[4-(2-methoxyethyl)phenoxy]propanol-2-), tolamolol, (4-[2-(2-hydroxy-3-o-tolyloxypropylamino)ethoxy]benzamide) and AH 5158 (5-[1-hydroxy-2-[1-(methyl-3-phenylpropyl)-amino-ethyl]salicylamide), are shown for comparison.

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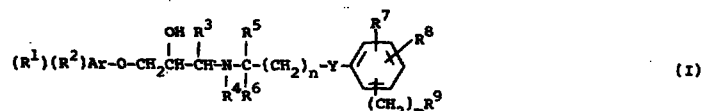
TABLE I

Compound	Reserpinized cat		Intrinsic activity beats/min	Conscious dog ΔBP. in mm Hg after 1.5 mg/kg i.v.	
	Block of isoprene ED ₅₀ mg/kg			Supine	Erect
Propanolol	0.1	0.1	0	+5	0
Practolol	0.3	35	+15		
Metoprolol	0.2	4.7	0	-5	-3
Tolamolol	0.1	1.5	+9	-23	-32
AH 5158	0.2	0.6	+21	-38	-67
Ex 1	0.3	1.8	0	-28	-45
Ex 2	1.1	8.5	0		
Ex 3	0.05	0.2	+15	-43	-42
Ex 4	0.5	0.5	+24		
Ex 8	0.1	1.5	+ 8	-23	-46
Ex 9	0.04	0.3	+13		
Ex 10	0.03	>8.5	+11		

The experiments demonstrate that the compounds tested are potent β-receptor antagonists with or without intrinsic β-mimetic activity. The compounds also decrease blood pressure in conscious dogs significantly more than propranolol, practolol and metoprolol and the same extent as tolamolol. The orthostatic effects of the new compounds, are not as pronounced as that of AH 5158, i.e. the blood pressure does not decrease markedly from supine to erect position.

WHAT WE CLAIM IS:—

1. An amine of the general formula I



wherein

R¹ is —CH₂CH=CH₂, —CH₂C≡CH, —OCH₂CH=CH₂, —OCH₂C≡CH, alkoxyalkyl containing 1 to 7 carbons in the alkoxy residue and 1 to 7 carbons in the alkyl residue, alkoxyalkoxy containing 1 to 7 carbons in each of the alkoxy residues, alkoxycarbonyl-aminoalkoxy containing 1 to 7 carbons in each of the alkoxy residues, HOCH₂CH₂NHCOCH₂O—, CH₃OCH₂CH₂NHCOCH₂O— or —CH=NOR, wherein R is hydrogen or alkyl having 1 to 6 carbon atoms, R² is hydrogen, R³ is hydrogen or C₁—C₇ alkyl, R⁴ is hydrogen, C₁—C₇ alkanoyl or benzyl, R⁵ and R⁶ are each hydrogen or C₁—C₇ alkyl, R⁷ and R⁸ are each hydrogen, halogen, or C₁—C₇ alkyl, R⁹ is hydrogen, alkoxycarbonylaminoalkyl containing 1 to 7 carbons in the alkoxy residue and 1 to 7 carbons in the alkyl residue, C₁—C₇ alkanoyl, cyano, trifluoromethyl, —CONR¹⁰R¹¹, —CONHNR¹⁰R¹¹, wherein R¹⁰ and R¹¹ are hydrogen, or wherein R¹⁰ and R¹¹ together with the nitrogen atom to which they are bound form a heterocyclic ring, Y is —O— or —CH₂—, n is 0 or an integer from 1 to 5, inclusive, m is 0, 1 or 2 and Ar is a phenyl ring, R¹ being in the 2

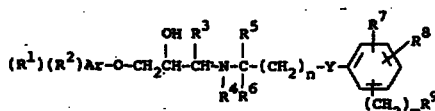
TABLE 1

Compound	Reserpinized cat		Intrinsic activity beats/min	Conscious dog ΔBP. in mm Hg after 1.5 mg/kg i.v.	
	Block of isoprene ED ₅₀ mg/kg			Supine	Erect
Propanolol	0.1	0.1	0	+5	0
Practolol	0.3	35	+15		
Metoprolol	0.2	4.7	0	-5	-3
Tolamolol	0.1	1.5	+9	-23	-32
AH 5158	0.2	0.6	+21	-38	-67
Ex 1	0.3	1.8	0	-28	-45
Ex 2	1.1	8.5	0		
Ex 3	0.05	0.2	+15	-43	-42
Ex 4	0.5	0.5	+24		
Ex 8	0.1	1.5	+8	-23	-46
Ex 9	0.04	0.3	+13		
Ex 10	0.03	>8.5	+11		

The experiments demonstrate that the compounds tested are potent β-receptor antagonists with or without intrinsic β-mimetic activity. The compounds also decrease blood pressure in conscious dogs significantly more than propranolol, practolol and metoprolol and the same extent as tolamolol. The orthostatic effects of the new compounds, are not as pronounced as that of AH 5158, i.e. the blood pressure does not decrease markedly from supine to erect position.

WHAT WE CLAIM IS:—

1. An amine of the general formula I



wherein

R¹ is —CH₂CH=CH₂, —CH₂C≡CH, —OCH₂CH=CH₂, —OCH₂C≡CH, alkoxyalkyl containing 1 to 7 carbons in the alkoxy residue and 1 to 7 carbons in the alkyl residue, alkoxyalkoxy containing 1 to 7 carbons in each of the alkoxy residues, alkoxycarbonyl-aminoalkoxy containing 1 to 7 carbons in each of the alkoxy residues, HOCH₂CH₂NHCOCH₂O—, CH₂OCH₂CH₂NHCOCH₂O— or —CH=NOR, wherein R is hydrogen or alkyl having 1 to 6 carbon atoms, R² is hydrogen, R³ is hydrogen or C₁—C₇ alkyl, R⁴ is hydrogen, C₁—C₇ alkanoyl or benzyl, R⁵ and R⁶ are each hydrogen or C₁—C₇ alkyl, R⁷ and R⁸ are each hydrogen, halogen, or C₁—C₇ alkyl, R⁹ is hydrogen, alkoxycarbonylaminoalkyl containing 1 to 7 carbons in the alkoxy residue and 1 to 7 carbons in the alkyl residue, C₁—C₇ alkanoyl, cyano, trifluoromethyl, —CONR¹⁰R¹¹, —CONHNR¹⁰R¹¹, wherein R¹⁰ and R¹¹ are hydrogen, or wherein R¹⁰ and R¹¹ together with the nitrogen atom to which they are bound form a heterocyclic ring, Y is —O— or —CH₂—, n is 0 or an integer from 1 to 5, inclusive, m is 0, 1 or 2 and Ar is a phenyl ring, R¹ being in the 2



* C L H S *

or 3 position on the phenyl ring, and therapeutically acceptable acid addition salts thereof.

2. An amine according to claim 1, wherein R^{10} and R^{11} together with the nitrogen atom to which they are attached form a pyrrolidine, piperidine, piperazine or morpholine ring.

3. An amine according to claim 1 or 2, wherein R^1 is $-\text{CH}_2\text{CH}=\text{CH}_2$ or $-\text{CH}_2\text{C}\equiv\text{CH}$, R^9 is hydrogen, alkanoyl, cyano, trifluoromethyl, alkoxycarbonylaminoalkyl, $-\text{CONR}^{10}\text{R}^{11}$, or $-\text{CONHNR}^{10}\text{R}^{11}$, wherein R^{10} and R^{11} are as claimed in claim 1.

4. An amine according to claim 1 or 2, wherein R^1 is $-\text{OCH}_2\text{CH}=\text{CH}_2$ or $-\text{OCH}_2\text{C}\equiv\text{CH}$, R^9 is hydrogen, alkanoyl, cyano, trifluoromethyl, alkoxycarbonylaminoalkyl, $-\text{CONR}^{10}\text{R}^{11}$ or $-\text{CONHNR}^{10}\text{R}^{11}$, wherein R^{10} and R^{11} are as defined in claim 1.

5. An amine according to claim 4, wherein R^1 is in the ortho position on the phenyl ring.

6. An amine according to claim 1 or 2, wherein R^1 is alkoxyalkyl, R^9 is hydrogen, alkanoyl, cyano, trifluoromethyl, alkoxycarbonylaminoalkyl, $-\text{CONR}^{10}\text{R}^{11}$, or $-\text{CONHNR}^{10}\text{R}^{11}$ wherein R^{10} and R^{11} are as defined in claim 1.

7. An amine according to claim 6, wherein R^1 is methoxymethyl, methoxyethyl or ethoxyethyl.

8. An amine according to claim 1 or 2, wherein R^1 is alkoxyalkoxy, R^9 is hydrogen, alkanoyl, cyano, trifluoromethyl, alkoxycarbonylaminoalkyl, $-\text{CONR}^{10}\text{R}^{11}$, or $-\text{CONHNR}^{10}\text{R}^{11}$ wherein R^{10} and R^{11} are as defined in claim 1.

9. An amine according to claim 8, wherein R^1 is methoxymethoxy, methoxyethoxy, or ethoxyethoxy.

10. An amine according to claim 1 or 2, wherein R^1 is alkoxycarbonylaminoalkoxy, $\text{HOCH}_2\text{CH}_2\text{NHCOCH}_2\text{O}-$ or $\text{CH}_3\text{OCH}_2\text{CH}_2\text{NHCOCH}_2\text{O}-$, R^9 is hydrogen, cyano, trifluoromethyl, alkoxycarbonylaminoalkyl, $-\text{CONR}^{10}\text{R}^{11}$ or $-\text{CONHNR}^{10}\text{R}^{11}$, wherein R^{10} and R^{11} are as defined in claim 1.

11. An amine according to claim 10, wherein R^1 is methoxycarbonylamino-methoxy, methoxycarbonylaminoethoxy, ethoxycarbonylaminoethoxy, ethoxycarbonylamino-methoxy, $\text{HOCH}_2\text{CH}_2\text{NHCOCH}_2\text{O}-$ or $\text{CH}_3\text{OCH}_2\text{CH}_2\text{NHCOCH}_2\text{O}-$.

12. An amine according to claim 1 or 2, wherein R^1 is $-\text{CH}=\text{NOR}$, wherein R is as defined in claim 1, R^9 is hydrogen, alkanoyl, cyano, trifluoromethyl, alkoxycarbonylaminoalkyl, $-\text{CONR}^{10}\text{R}^{11}$ or $-\text{CONHNR}^{10}\text{R}^{11}$, wherein R^{10} and R^{11} are as defined in claim 1, with the proviso that when Y is $-\text{CH}_2-$, n is 1 to 5.

13. An amine according to claim 12, wherein R^1 is isonitrosomethyl, methylisonitrosomethyl, ethylisonitrosomethyl, propylisonitrosomethyl, or t-butylisonitrosomethyl.

14. An amine according to any one of the preceding claims, wherein R^3 is hydrogen or methyl, R^4 is hydrogen, formyl, acetyl, or benzyl, R^5 and R^6 are each hydrogen, methyl or ethyl, R^7 and R^8 are each hydrogen, chloro, bromo, methyl or ethyl, R^9 is hydrogen, formyl, acetyl, cyano, trifluoromethyl, methoxycarbonylaminoethyl, ethoxycarbonylaminoethyl, carbamyl, or morpholinylcarbonyl.

15. An amine according to claim 14, wherein R^3 is hydrogen, R^4 is hydrogen, R^5 and R^6 are each hydrogen or methyl, R^7 and R^8 are each hydrogen, or methyl, R^9 is hydrogen, carbamyl, methoxycarbonylaminoethyl, or morpholinylcarbonyl, Y is $-\text{O}-$ and n is 1 or 2.

16. 1-[2-(4-carbamylphenoxy)ethylamino]-3-(2-allylphenoxy)propanol-2.

17. 1-[2-(4-carbamylphenoxy)ethylamino]-3-[2-(2-methoxyethyl)-phenoxy]propanol-2.

18. 1-[1-methyl-2-(4-carbamylphenoxy)ethylamino]-3-(2-allylphenoxy)propanol-2.

19. 1-[1-methyl-2-(2-methylphenoxy)ethylamino]-3-(2-allylphenoxy)propanol-2.

20. 1-[1-methyl-2-(4-methylphenoxy)ethylamino]-3-(2-allylphenoxy)propanol-2.

21. 1-[2-(4-morpholinylcarbonylphenoxy)ethylamino]-3-(2-allylphenoxy)propanol-2.

22. 1-[1-methyl-2-(4-carbamylphenoxy)ethylamino]-3-(2-methylisonitrosomethylphenoxy)propanol-2.

23. 1-[2-(4-carbamylphenoxy)ethylamino]-3-(3-allylphenoxy)propanol-2.



24. An amine according to any one of the preceding claims, in the form of the free base.

25. An amine according to any one of claims 1 to 23, in the form of a therapeutically acceptable salt.

26. An amine according to any one of the preceding claims, in the form of a mixture of isomers.

27. An amine according to any one of claims 1 to 25, in the form of an individual isomer.

28. An amine according to any one of claims 1 to 26, in the form of a racemic mixture.

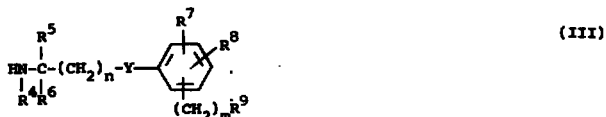
29. An amine according to claim 27, in the form of an optically active isomer.

30. A process for the preparation of an amine as defined in claim 1, which comprises reacting a compound of formula II



wherein

Ar, R¹, R² and R³ are as defined in claim 1, and X¹ is a hydroxy group and Z is a halogen or other reactive group formed by esterification of a hydroxy group with a strong organic or with an inorganic acid, or X¹ and Z together form an epoxy group, with an amine of formula III



wherein

R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, Y, n and m are as defined in claim 1.

31. A process for the preparation of an amine as defined in claim 1, which comprises reacting a compound of formula IV



wherein

Ar, R¹, R², R³ and R⁴ are as defined in claim 1 with a compound of formula V



wherein

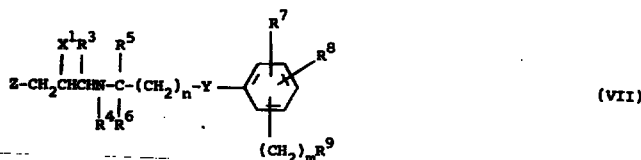
R⁵, R⁶, R⁷, R⁸, R⁹, Y, n and m are as defined in claim 1, and Z is as defined in claim 30.

32. A process for the preparation of an amine as defined in claim 1, which comprises reacting a compound of formula VI



wherein

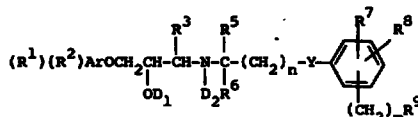
Ar, R¹ and R² are as defined in claim 1, and M is hydrogen or an alkali metal, with a compound of formula VII



wherein

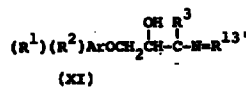
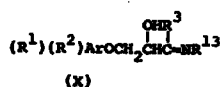
X^1 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , Y , n and m are as defined in claim 1 and Z is as defined in claim 30.

33. A process for the preparation of an amine as defined in claim 1, wherein the labile group(s) D_1 and D_2 is split off from a compound of the formula:

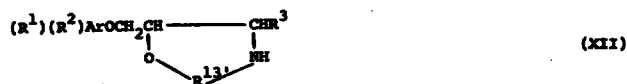


where D_1 is hydrogen or a labile group and D_2 is R^4 or a labile group, D_1 and D_2 not both being hydrogen and D_2 being alkanoyl or benzyl only when D_1 is a labile group.

34. A process for the preparation of an amine as defined in claim 1, which comprises reducing a Schiff's base of formula X or XI:



or a cyclic tautomer, corresponding to formula XI, of formula XII:



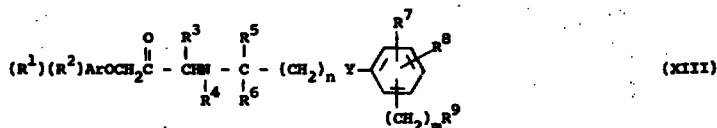
wherein Ar , R^1 , R^2 and R^3 are as defined in claim 1, and R^{13} is the group of formula IX:



wherein

R^3 , R^6 , R^7 , R^8 , R^9 , Y , n and m are as defined in claim 1, and R^{13} H is the same as $R^{13'}$.

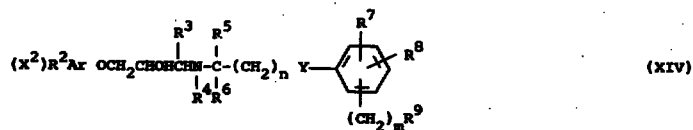
35. A process for the preparation of an amine as defined in claim 1, which comprises hydrogenating a compound of formula XIII:



wherein

Ar , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , Y , n and m are as defined in claim 1.

36. A process for the preparation of an amine as defined in claim 1 in which R^1 is alkoxycarbonylaminoalkoxy, which comprises reacting a compound of formula XIV:



wherein

Ar , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , Y , n and m are as defined in claim 1 and X^2 is (a) hydroxy or (b) aminoalkoxy or (c) Z^1 -carbonylaminoalkoxy, with, respectively, (a) an alkoxycarbonylamino- Z compound or (b) an alkoxycarbonyl chloride or (c)



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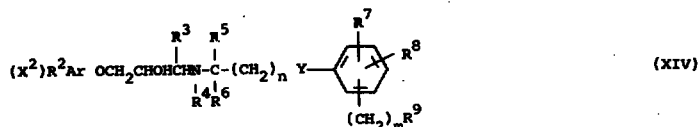
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an alkyl-Z² compound, wherein one of Z¹ and Z² is OH and the other is Z, and Z is as defined in claim 30.

37. A process for the preparation of an amine as defined in claim 1 in which R¹ is alkoxyalkyl or alkoxyalkoxy which comprises reacting a compound of formula XIV:



wherein

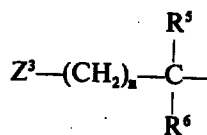
Ar, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, Y, n and M are as defined in claim 1 and X² is Z¹-alkyl- or Z¹-alkyl-O- and when X² is Z¹-alkyl- reacting with alkyl-Z² to give a compound I where R¹ is alkoxyalkyl and when X² is Z¹-alkyl-O-, reacting with alkyl-Z² to give a compound I where R¹ is alkoxyalkoxy, Z¹ and Z² being as defined in claim 36.

38. A process for the preparation of an amine as defined in claim 1 in which Y is O which comprises reacting a compound of formula XXVIII:

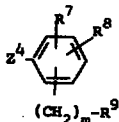


wherein

Ar, R¹, R², R³ and R⁴ are as defined in claim 1, and wherein X⁴ is

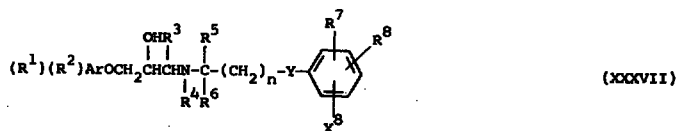


with a compound



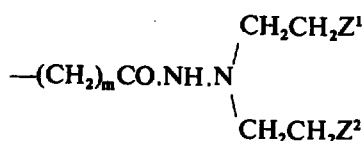
where one of Z³ and Z⁴ is OH and the other is Z as defined in claim 30.

39. A process for the preparation of an amine as defined in claim 1, which comprises reacting a compound of formula XXXVII

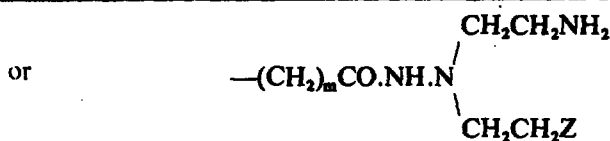


wherein

Ar, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, Y and n are as defined in claim 1, and X⁸ is a group



29



where m is as defined in claim 1 and Z^1 , Z^2 and Z are as defined in claim 36 and 30 and the compound is subjected to ring closure or X^8 is a residue $\text{---}(\text{CH}_2)_m\text{COZ}$ and the compound is reacted with $\text{R}^{10}\text{R}^{11}\text{NH}$ or $\text{R}^{10}\text{R}^{11}\text{N.NH}_2$, wherein m , R^{10} and R^{11} are as defined in claim 1 and Z is as defined in claim 30.

40. A process for the preparation of an amine as defined in claim 1, which comprises reacting a compound of formula V:



wherein

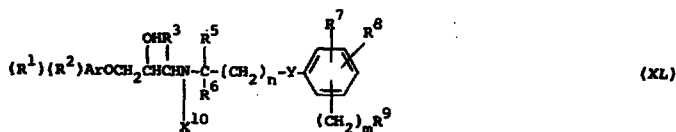
Ar , R^1 and R^2 are as defined in claim 1 and M is hydrogen, with a compound of formula XXXIX:



wherein

R^3 is as defined in claim 1, and R^{13} is as defined in claim 34.

41. A process for the preparation of an amine as defined in claim 1 in which $\text{R}^4=\text{H}$, which comprises hydrolyzing a compound of formula XL:



wherein

Ar , R^1 , R^2 , R^3 , R^5 , R^6 , R^7 , R^8 , R^9 , Y , m and n are as defined in claim 1 and X^{10} is benzyl or alkanoyl.

42. A process according to any one of claims 30 to 41, wherein an amine according to any one of claims 16 to 23, is prepared.

43. A process according to any one of claims 30 to 42, wherein the amine is prepared in the form of the free base.

44. A process according to any one of claims 30 to 42, wherein the amine is prepared in the form of a therapeutically acceptable salt.

45. A process according to any one of claims 30 to 44, wherein the amine is prepared in the form of a mixture of isomers.

46. A process according to any one of claims 30 to 45, wherein an individual isomer is isolated.

47. A process according to any one of claims 30 to 45, wherein the amine is prepared as a racemic mixture.

48. A process according to any one of claims 30 to 47, wherein an optically active isomer is isolated.

49. A process according to any one of claims 30 to 41, substantially as hereinbefore described with reference to any one of Examples 1 to 12.

50. An amine obtained by a process according to any one of claims 30 to 49.

51. A pharmaceutical preparation comprising an amine according to any one of claims 1 to 29 or 50 together with a pharmaceutically acceptable carrier or diluent.

52. A preparation according to claim 51, substantially as hereinbefore described with reference to any one of Examples 13 to 16.

53. A method of treating cardiovascular diseases in mammals excluding man which comprises administering to the mammal an amine according to any one of claims 1 to 29 or 50 or a preparation according to claim 51 or 52.



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