

PATENT SPECIFICATION

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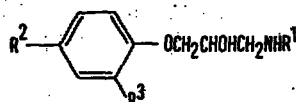


(54) NEW AMINES AND PROCESS FOR THEIR PREPARATION

(71) We, AKTIEBOLAGET 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 new amines, processes for their preparation and pharmaceutical compositions containing them.

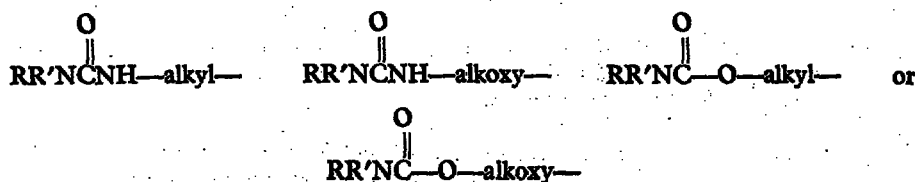
The compounds of the invention have the formula:



(I)

wherein R¹ is a C₁₋₄ alkyl or hydroxy-C₁₋₄ alkyl group, R² is a carbamoylamino-C₁₋₄ alkyl, mono- or di-C₁₋₄ alkylcarbamoylamino-C₁₋₄ alkyl, carbamoylamino-C₁₋₄ alkoxy, mono- or di-C₁₋₄ alkylcarbamoylamino-C₁₋₄ alkoxy, carbamoyloxy-C₁₋₄ alkyl, mono- or di-C₁₋₄ alkylcarbamoyloxy-C₁₋₄ alkyl, carbamoyloxy-C₁₋₄ alkoxy or mono- or di-C₁₋₄ alkylcarbamoyloxy-C₁₋₄ alkoxy group and R³ is a hydrogen or halogen atom or a C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, (C₁₋₄ alkoxy)methyl, C₁₋₄ alkoxy, C₂₋₄ alkenyloxy, C₂₋₄ alkynyloxy, C₁₋₄ alkylthio, C₂₋₄ alkenylthio, C₂₋₄ alkynylthio or C₁₋₄ acyl groups.

In other words, R² represents one of the following groups:



in which R and R', which may be the same or different, each represents a hydrogen atom or a C₁₋₄ alkyl group and the alkyl and alkoxy groups shown in the formulae have 1 to 4 carbon atoms.

In this specification, all alkyl groups have 1 to 4 carbon atoms unless otherwise specified.

If R¹ is alkyl, it may be a straight-chain group, but it is preferably branched especially at the α-carbon atom, examples of such groups being sec-butyl, tert-butyl or, especially, isopropyl. Similarly, if R¹ is hydroxyalkyl, the alkyl group may be a straight-chain group but it is preferably branched, especially at the α-carbon atom, examples of such groups being 1-hydroxy-propyl-2 or 1-hydroxy-2-methyl-propyl-2.

The alkyl and/or alkoxy portions of the various groups which R² may represent may be straight or branched, the preferred alkyl and alkoxy groups being isopropyl, n-propyl, ethyl, methyl, propoxy, ethoxy and methoxy.

If R³ is halogen, it may, for example be fluorine, bromine or chlorine (which is preferred). The preferred alkyl groups for R³ are iso- or n-propyl, straight or branched butyl, ethyl or, preferably, methyl. If R³ is alkenyl, it may for example, be vinyl, 2-methylvinyl, methallyl or, preferably, allyl; suitable alkynyl groups for R³ are 1-propynyl, 2-propynyl or ethynyl.

If R³ is alkoxy or alkoxymethyl, the alkyl part of the alkoxy group is preferably ethyl, iso- or n-propyl or, especially, methyl.

The preferred alkenyloxy groups for R³ are methallyloxy or, especially, allyloxy, and the preferred alkynyloxy group is 2-propynyloxy.

The preferred alkylthio groups for R³ are methylthio, ethylthio, n-propylthio, isopropylthio and butylthio, methylthio and ethylthio being preferred. Suitable alkenylthio groups are vinylthio, 2-methyl-vinylthio, methallylthio and especially allylthio, and suitable alkynylthio groups are ethynylthio, 1-propynylthio, and 2-propynylthio. Suitable acyl groups for R³ are formyl, acetyl, or propionyl.

The new compounds have valuable pharmacological properties. For example, they block cardiac β -receptors, as demonstrated by the determination of the antagonism of tachycardia after an intravenous injection of 0.5 μ g/kg of d/l-isoproterenol sulphate on an anaesthetized cat at an intravenous dose of 0.002 to 2 mg/kg, and by the determination of tachycardia after the addition of 0.005 μ g/ml of d/l-isoproterenol sulphate to an isolated guinea-pig heart *in vitro* at a concentration of 0.02 to 2 mg/ml; and they block the vascular β -receptors, as demonstrated by the determination of the antagonism of vasodilation after an intravenous injection of 0.5 μ g/kg of d/l-isoproterenol sulphate on an anaesthetized cat at an intravenous dose of 3 mg/kg or more.

The new compounds can be used as cardioselective antagonists of adrenergic β -receptor-stimulators, for example in the treatment of arrhythmias and angina pectoris. They may also be used as intermediates in the preparation of other useful compounds, especially pharmaceutically active compounds.

The preferred amines of the invention are those of the following classes:

(a) Compounds of formula (I) in which R¹ is as defined above, R² is a mono- or di-C₁₋₄ alkylcarbamoyloxy-C₁₋₄ alkyl group containing at most 10 carbon atoms and R³ is a hydrogen or halogen atom or a C₁₋₄ alkyl, C₂₋₄ alkenyl, (C₁₋₄ alkoxy)methyl, C₁₋₄ alkoxy or C₂ or 4 alkenyloxy group. Of these, the following are preferred:

(a') Compounds of formula (I) in which R¹ is a tert-butyl, isopropyl, 1-hydroxy-propyl-2 or 1-hydroxy-2-methyl-propyl-2 group, R² is a methyl carbamoyloxymethyl, methylcarbamoyloxyethyl, methylcarbamoyloxypropyl, dimethylcarbamoyloxypropyl or diethylcarbamoyloxyethyl group and R³ is a hydrogen, chlorine or bromine atom or a methyl, allyl, methoxymethyl, methoxy or allyloxy group,

and the following are especially preferred:

(a'') Compounds of formula (I) in which R¹ is a tert-butyl or isopropyl group, R² is a methylcarbamoyloxyethyl, methylcarbamoyloxypropyl or diethylcarbamoyloxyethyl group and R³ is as defined under (a').

(b) Compound of formula (I) in which R¹ and R³ are as defined under (a) and R² is a mono- or di-C₁₋₄ alkylcarbamoyloxy C₁₋₄ alkoxy group containing at most 10 carbon atoms. Of these the following are preferred:

(b') Compounds of formula (I) in which R¹ and R³ are as defined under (a') and R² is a methylcarbamoyloxyethoxy, dimethylcarbamoyloxyethoxy, ethylcarbamoyloxyethoxy, or diethylcarbamoyloxyethoxy group,

and the following are especially preferred:

(b'') Compounds of formula (I) in which R¹ and R³ are as defined under (a'') and R² is a methylcarbamoyloxyethoxy or dimethylcarbamoyloxyethoxy group.

(c) Compounds of formula (I) in which R¹ and R³ are as defined under (a) and R² is a mono- or di-C₁₋₄ alkylcarbamoylamino-C₁₋₄ alkyl group containing at most 10 carbon atoms. Of these, the following are preferred:

(c') Compounds of formula (I) in which R¹ and R³ are as defined under (a') and R² is a methylcarbamoylaminoethyl, methylcarbamoylaminoethyl, methylcarbamoylamino-n-propyl or dimethylcarbamoylaminoethyl group,

and the following are especially preferred:

(c'') Compounds of formula (I) in which R¹ and R³ are as defined under (a'') and R² is a dimethylcarbamoylaminoethyl or methylcarbamoylaminoethyl group.

(d) Compounds of formula (I) in which R^1 and R^3 are as defined under (a) and R^2 is a carbamoylamino- C_{1-4} alkyl group. Of these, the following are preferred:

(d') Compounds of formula (I) in which R^1 and R^3 are as defined under (a') and R^2 is a carbamoylaminomethyl, carbamoylaminoethyl, carbamoylamino-n-propyl or carbamoylamino-n-butyl group,

and the following are especially preferred:

(d'') Compounds of formula (I) in which R^1 and R^3 are as defined under (a'') and R^2 is a carbamoylaminoethyl or carbamoylamino-n-propyl group.

(e) Compounds of formula (I) in which R^1 and R^3 are as defined under (a) and R^2 is a carbamoyloxy- C_{1-4} alkyl group. Of these, the following are preferred:

(e') Compounds of formula (I) in which R^1 and R^3 are as defined under (a') and R^2 is a carbamoyloxymethyl, carbamoyloxyethyl or carbamoyloxy-n-propyl group,

and the following are especially preferred:

(e'') Compounds of formula (I) in which R^1 and R^3 are as defined under (a'') and R^2 is a carbamoyloxyethyl group.

(f) Compounds of formula (I) in which R^1 and R^3 are as defined under (a) and R^2 is a carbamoyloxy- C_{1-4} alkoxy group. Of these the following are preferred:

(f') Compounds of formula (I) in which R^1 and R^3 are as defined under (a') and R^2 is a carbamoyloxymethoxy, carbamoyloxyethoxy or carbamoyloxy-n-propoxy group,

and the following are especially preferred:

(f'') Compounds of formula (I) in which R^1 and R^3 are as defined under (a'') and R^2 is a carbamoyloxyethoxy group.

(g) Compounds of formula (I) in which R^1 and R^3 are as defined under (a) and R^2 is a carbamoylamino- C_{1-4} alkoxy group. Of these, the following are preferred:

(g') Compounds of formula (I) in which R^1 and R^3 are as defined under (a') and R^2 is a carbamoylaminomethoxy, carbamoylaminoethoxy or carbamoylamino-n-propoxy group,

and the following are especially preferred:

(g'') Compounds of formula (I) in which R^1 and R^3 are as defined under (a'') and R^2 is a carbamoylaminoethoxy group.

The following compounds are especially preferred:

- 1) 1-[4-(2-methylcarbamoyloxyethoxy)-phenoxy]-2-hydroxy-3-isopropylamino-propane,
- 2) 1-[2-chloro-4-(2-dimethylcarbamoyloxyethoxy)-phenoxy]-2-hydroxy-3-isopropylamino-propane,
- 3) 1-[4-(2-carbamoyloxyethoxy)-phenoxy]-2-hydroxy-3-isopropylamino-propane,
- 4) 1-[4-(3-methylcarbamoyloxypropyl)-phenoxy]-2-hydroxy-3-isopropylamino-propane,
- 5) 1-[4-(2-carbamoylaminoethyl)-phenoxy]-2-hydroxy-3-isopropylamino-propane,
- 6) 1-[4-(2-dimethylcarbamoylaminoethyl)-phenoxy]-2-hydroxy-3-isopropylamino propane,
- 7) 1-[2-chloro-4-(2-carbamoylaminoethyl)-phenoxy]-2-hydroxy-3-isopropylamino-propane,
- 8) 1-[4-(3-carbamoylaminoethyl)-phenoxy]-2-hydroxy-3-isopropylamino-propane,

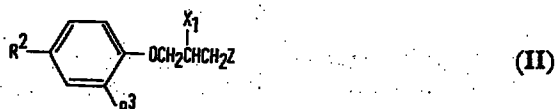
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- 9) 1-[4-(2-methylcarbamoylaminoethyl)-phenoxy]-2-hydroxy-3-isopropylamino-propane,
 - 10) 1-[4-(2-carbamoyloxyethyl)-phenoxy]-2-hydroxy-3-isopropylamino-propane,
 - 11) 1-[2-chloro-4-(2-methylcarbamoyloxyethyl)-phenoxy]-2-hydroxy-3-isopropylamino-propane,
 - 12) 1-[4-(2-methylcarbamoyloxyethyl)-phenoxy]-2-hydroxy-3-isopropylamino-propane,
 - 13) 1-[4-(2-dimethylcarbamoyloxyethyl)-phenoxy]-2-hydroxy-3-isopropyl-amino-propane,

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These compounds block the cardiac β -receptors, as demonstrated 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 0.03 to 1 mg/kg; the vascular β -receptors, as demonstrated by the determination of the antagonism of the vasodilation at an intravenous injection of 0.5 $\mu\text{g/kg}$ of d/l-isoproterenol sulphate to the anaesthetized cat at an intravenous dose from 3 mg/kg or more; and the cardiac β -receptors as demonstrated by the determination of the antagonism of tachycardia after an addition of 0.005 $\mu\text{g/ml}$ of d/l-isoproterenol sulphate to an isolated guinea-pig heart *in vitro* at a concentration of 0.03 to 1 $\mu\text{g/ml}$.

The new compounds may be obtained by methods known *per se*. For example, a compound of formula II



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wherein R^2 and R^3 have the meanings given above, X_1 is a hydroxy group and Z is a reactive, esterified hydroxy group, or X_1 and Z together form an epoxy group, may be reacted with an amine of the formula $\text{NH}_2\text{—}R^1$, wherein R^1 has the same meaning as given above.

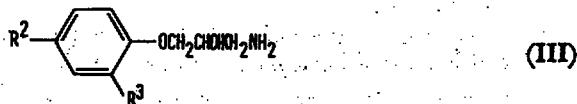
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The reactive, esterified hydroxy group is preferably a hydroxy group esterified with a strong, inorganic or organic acid, preferably a hydrohalic acid, such as hydrochloric acid, hydrobromic acid, or hydroiodic acid, sulphuric acid or a strong organic sulphonic acid such as a strong aromatic sulphonic acid, for example, benzenesulphonic acid, 4-bromobenzenesulphonic acid or 4-toluenesulphonic acid. Z is preferably chloro, bromo or iodo.

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This reaction is carried out in a conventional manner, preferably in the presence of a basic condensating agent and/or an excess of an amine. Suitable basic condensating agents are, for example, 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.

Furthermore, a compound of formula III



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wherein R^2 and R^3 have the same meanings as given above, may be reacted with a compound of the formula $Z\text{—}R^1$, wherein R^1 and Z have the same meanings as given above.

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This reaction may be carried out in a conventional manner, preferably in the presence of a basic condensating agent and/or an excess of an amine. Suitable basic condensating agents are, for example, alkaline alcoholates, preferably sodium or potassium alcoholate, or alkaline carbonates as sodium or potassium carbonate.

Furthermore, a compound of formula IV



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wherein R^2 and R^3 have the same meanings as given above may be reacted with a compound of formula V



wherein Z, X and R¹ have the same meanings as given above.

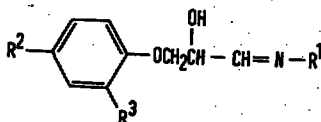
This reaction is carried out in a conventional manner; if a reactive ester is used as starting material, the compound of formula IV is suitably used in the form of a metal phenolate such as an alkali metal phenolate, preferably sodium phenolate, or the reaction is performed in the presence of an acid binding agent, preferably a condensating agent, which can form a salt of the compound of formula IV as an alkali metal alcoholate.

Another suitable process involves the hydrolysis of a compound of formula I above, wherein R¹, R² and R³ have the same meanings as above and in which the nitrogen atom of the amino group and/or the hydroxy group has attached thereto a residue, capable of being removed by hydrolysis. This residue is an arylsulphonyl group such as a toluenesulphonyl or bromobenzenesulphonyl group, a benzoyl group, a cyano group, a silyl group such as a trimethylsilyl group an alkylidene group, a benzylidene group, a phosphorylidene group such as a triphenylphosphorylidene group or a substituted methylene group. The substituent on the methylene residue may be any organic residue which does not interfere with the hydrolysis, for example, an aliphatic or aromatic residue such as alkyl or aryl, e.g. phenyl or pyridyl.

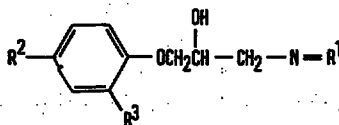
The hydrolysis may be carried out in a conventional manner for example, in the presence of an acidic hydrolysing agent such as a dilute mineral acid, for example, sulphuric acid or a hydrohalic acid, or in the presence of a basic hydrolysing agent such as an alkali metal hydroxide, for example, sodium hydroxide. Aryl sulphonyl residues and cyano groups are suitably removed by means of an acidic reagent such as a hydrohalic acid, suitably hydrobromic acid. The preferred acid is dilute hydrobromic acid, or a mixture of hydrobromic acid with acetic acid. Cyano groups are preferably split off by means of hydrobromic acid at an elevated temperature, for example in boiling hydrobromic acid, according to the "bromocyano method" (v. Braun).

An arylsulphonyl group such as a toluenesulphonyl group, may also be removed by reduction using nascent hydrogen generated for example, by means of an alkali metal, such as lithium or sodium in liquid ammonia. In this case the arylsulphonyl group is preferably attached to the nitrogen atom of the amino group and care has to be taken that other groups in the molecule are not influenced by the reduction.

Another suitable process comprises reducing a Schiff's base of formula VII or VIII

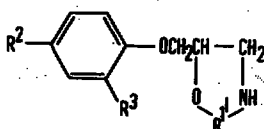


(VII)



(VIII)

or a cyclic tautomer corresponding to formula VIII, said tautomer having the formula IX

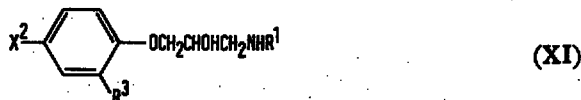


(IX)

wherein R¹, R² and R³ have the same meaning as given above and R¹H is the same as R¹ and where the compounds of formula VIII and IX may exist together.

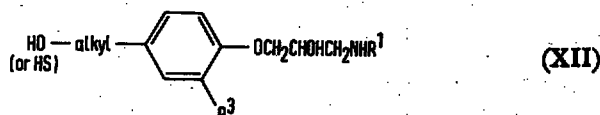
This reduction can be carried out in a conventional manner using, for example, a di-lightmetalhydride, such as sodiumboronhydride, lithiumaluminiumhydride, a hydride such as Boran with formic acid, or by means of a catalytic hydrogenation, with for example, hydrogen in the presence of Raney-nickel. Care must be taken to ensure that other groups are not affected by the reduction.

Another type of process for the preparation of the compounds of the invention involves the conversion of the group X^2 in a compound of formula XI.

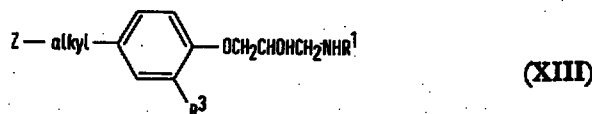


wherein R^1 and R^3 have the same meanings as given above by methods known *per se* (i.e. methods heretofore used or described in the literature) into a group as defined for R^2 . X^2 is a hydroxyalkyl-, esterified hydroxyalkyl-, hydroxyalkoxy-, esterified hydroxyalkoxy-, hydroxy-, aminoalkyl-, aminoalkoxy-, alkanoylaminoalkyl-, alkanoylaminoalkoxy-, alkanoyloxyalkyl-, alkanoyloxyalkoxy-, aminothiocarbamylaminoalkyl-, aminothiocarbamoylaminoalkoxy-, alkylaminothiocarbamoylaminoalkyl-, alkylaminothiocarbamylaminoalkoxy-, imino(halo)carbaminalkyl-, imino(halo)carbaminalkoxy-, imino-carbiminoalkyl-, or iminocarbiminoalkoxy- group.

For example, compounds in which R^2 is a carbamoylaminoalkyl, alkylcarbamoyl-alkyl, carbamoyloxyalkyl or alkylcarbamoyloxyalkyl group can be prepared by reacting either a compound of formula XII



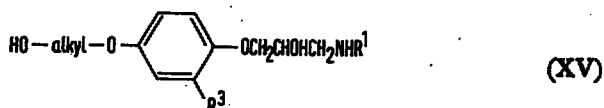
with a compound of formula carbamyl- Z^2 or alkylcarbamoyl- Z^2 or a compound of formula XIII



with carbamoylamine or a dialkylcarbamoylamine wherein R^1 and R^3 have the same meanings as given above, Z is a reactive esterified hydroxy group and Z^2 is a hydroxy or mercapto group. The reaction may be carried out in a conventional manner, for example under the same conditions as the reaction of a compound of formula II with an amine NH_2R^1 .

If R^2 is a carbamoylaminoalkoxy, alkylcarbamoylaminoalkoxy, carbamoyloxyalkoxy, or alkylcarbamoyloxyalkoxy residue, X^2 may be, for example, a residue $Z^1\text{---alkyl---O---}$ where Z^1 is a hydroxy or mercapto group, or a reactive esterified hydroxy group, or a hydroxy group.

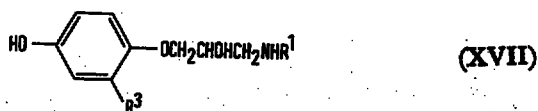
For example, a compound of formula XV



may be reacted with a compound of formula carbamyl- Z^2 or alkylcarbamoyl- Z^2 , or a compound of formula XVI



may be reacted with carbamoylamine or a dialkylcarbamoylamine or a dialkylcarbamic acid, or a compound of formula XVII



may be reacted with a compound of formula carbamoylaminoalkyl- Z , alkylcarbamoyl-aminoalkyl- Z , carbamoyloxyalkyl- Z , or alkylcarbamoyloxyalkyl- Z , wherein R^1 , R^3 and Z have the same meanings as given above.

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If R^2 is a carbamoylaminoalkyl or carbamoylaminoalkoxy group, X^2 may be, for example, a group of formula H_2N -alkyl or H_2N -alkoxy. For example, a compound of the formula XVIII



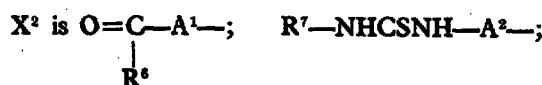
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can be reacted with a cyanate or carbamoylchloride. Furthermore, if R^2 is an alkyl-carbamoylaminoalkyl or alkylcarbamoylaminoalkoxy group a compound of the formula XVIII can be reacted with a compound of formula alkylcarbamoyl-Z, wherein R^1 , R^3 and Z have the meanings given above.

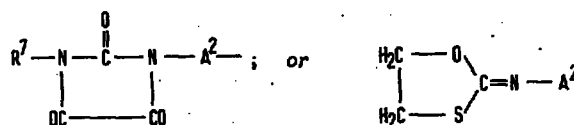
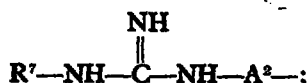
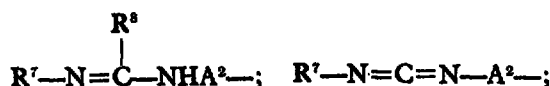
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Other compounds of the formula XI, which can be used are those wherein

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wherein A^1 is $-NH$ -alkyl-, $-NH$ -alkoxy-, $-O$ -alkyl- or $-O$ -alkoxy, A^2 is $-alkyl$ or $-alkoxy$ -, R^6 is alkoxy having 1 to 4 carbon atoms, for example, substituted phenoxy, alkylthio having 1 to 4 carbon atoms, for example, substituted phenylthio, hydrazino, halogen, or together with NH forms a further C-N-bond, R^7 is hydrogen or alkyl and R^8 is halogen, a O-acyl group, S-acyl group or a S-alkyl group.

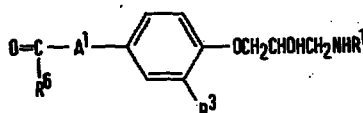
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Thus a compound of the formula

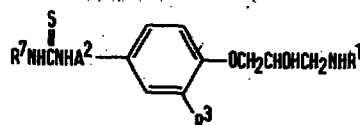
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i)



can be reacted with NH_2R^7 ;

ii)

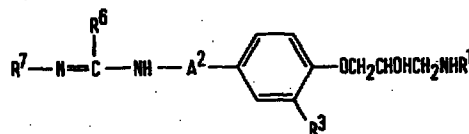


or an isothiocarbamido salt thereof, can be treated so that the sulphur or the thioether group is replaced by oxygen;

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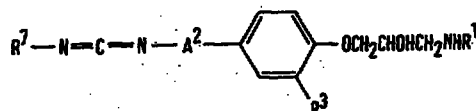
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iii)

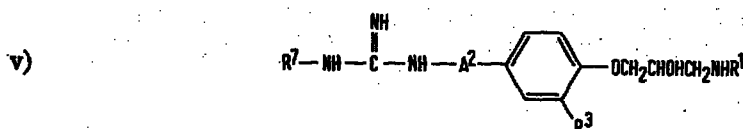


can be hydrolysed;

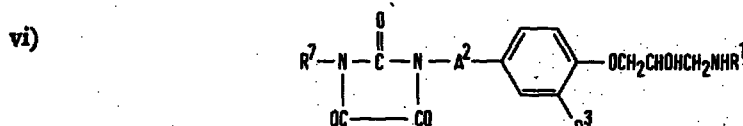
iv)



can be treated in such a way that water is added.

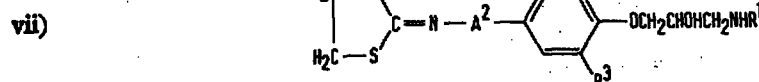


can be hydrolysed;



can be saponified or

or



can be reacted with NH_2R^1 .

In the processes for preparing the compounds of the invention substituents may be introduced, removed or transformed by conventional techniques.

For example, it is possible 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 to ensure that other reducible groups are not reduced.

In compounds obtained containing a C—C triple bond, this may further be transformed into a C—C double bond and, if desired, be hydrogenated stereospecifically into a 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 calciumcarbonate 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, the reaction time being kept short and no excess of the reducing agent being used. A catalyst such as an ammonium halide, for example ammonium chloride, may be added.

In the reduction mentioned above, one has to ensure that no further reducible groups are reduced. In the reduction using Raney-nickel and hydrogen one has to consider especially any halogen atoms bonded to aromatic rings. Furthermore, in all reductions, especially catalytic hydrogenations, one has to consider any thioether groups present. Preferably sulphur-resistant catalysts are used and, in practice, the volume of hydrogen to be absorbed is calculated and when the calculated amount has been absorbed, the reduction is discontinued.

The above mentioned reactions may be carried out simultaneously or in any desired sequence, in a manner known *per se*, for example in the presence or absence of diluting, condensing and/or catalytic agents at a low, room or an elevated temperature, and, if desired, in a closed vessel.

Depending on the process conditions and the starting material the end product is obtained either in free form or in the form of its acid addition salt; such salts are included in the scope of the invention. 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 be transformed into free compounds in a manner known *per se* using e.g. basic agents as alkali or ion exchanger. On the other hand, the free bases obtained may be converted to salts with organic or inorganic acids. In the preparation of acid addition salts, the preferred acids are those which form suitable therapeutically acceptable salts. Such acids are, for example, hydrohalic acids, sulphuric acid, phosphoric acid, nitric acid, perchloric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxy or sulphonic acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxy-maleic or pyruvic acid, phenylacetic, benzoic, *p*-aminobenzoic, anthranilic, *p*-hydroxybenzoic, salicylic or *p*-aminosalicylic acid, embonic acid, methanesulphonic, ethanesulphonic, hydroxyethanesulphonic, ethylenesulphonic acids, halogenbenzenesulphonic, toluene-

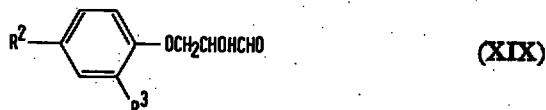
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sulphonic, naphthylsulphonic acids or sulphanilic acid, methionine, tryptophane, lysine or arginine.

5 These or other salts of the new compounds, such as picrates, may serve as purifying agents for the free bases. The free bases may be transformed into salts, these are separated and the bases are then set free from the salts again.

Other processes which may be used for preparing compounds of the invention are as follows:

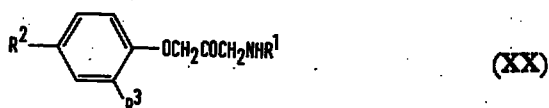
a) Reaction of a compound of formula



10 wherein R^2 and R^3 have the same meaning as given above, with an amine of the formula H_2N-R^1 , wherein R^1 has the same meaning as given above, in the presence of a suitable reducing agent, such as one of those mentioned above. A compound of formula VII is obtained as an intermediate, which then is reduced as described above.

15 b) Reaction, in a manner known *per se*, of an amine of the formula III with an aldehyde or a ketone of the formula $O=R^1$, wherein R^1 has the above meaning, in the presence of a suitable reducing agent such as one of those mentioned above. A compound of formula VIII or IX is obtained as an intermediate, which can then be reduced as described above.

c) Hydrogenation of a compound of the formula XX



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

25 The isomer mixtures (racemate mixtures) obtained may, depending on the physical-chemical differences of the components, be separated into the stereoisomeric (diastereomeric) pure racemates, e.g. by means of chromatography and/or fractionated crystallisation.

30 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 reaction with an optically active acid to form salts of the compounds and separating the salts thus obtained, e.g. by means of their different solubility. Suitable optically active acids are, for example, the L- and D-forms of tartaric acid, di-*o*-tolyltartaric acid, maleic acid, mandelic acid, camphorsulphonic acid or quinic acid. Preferably the more active of the two antipodes is isolated.

35 The starting materials may be obtained according to processes known *per se*.

40 In clinical use the compounds of the invention are generally administered orally, rectally or by injection in the form of a pharmaceutical preparation, which contains an active component of the invention either as free base or as pharmaceutically acceptable, non-toxic acid addition salt, such as a hydrochloride, lactate, acetate or sulphamate in combination with a pharmaceutically acceptable carrier. The carrier may be a solid, semisolid or liquid diluent or a capsule. These pharmaceutical preparations are a further aspect of the invention. 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.

45 In the preparation of pharmaceutical preparations containing a compound of the present invention in the form of dosage units for oral administration, the compound may for example be mixed with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, starch, such as potato starch, corn starch amylopectin, a cellulose derivative or gelatine, and with an antifriction agent such as magnesium stearate, calcium stearate or a polyethyleneglycol wax, and pressed into tablets. If coated tablets are wanted, the above prepared core may be coated with a concentrated solution of sugar, which solution may contain, for example, 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 readily between tablets with different active compounds or with different amounts of the active compound present.

17-18

In the preparation of soft gelatine capsules (pearl-shaped, closed capsules), which consist of gelatine, and, for example, glycerine or in the preparation of similar closed capsules the active compound may be 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, starch (e.g. potato starch, corn starch or amylopectin), a cellulose derivative or gelatine.

Dosage units for rectal administration may be prepared in the form of suppositories, which contain the active substance in admixture 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.

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

Solutions for 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 about 0.5% by weight to about 0.10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may suitably be available in different dosage unit ampoules.

The preparation of tablets for peroral use may be carried out in accordance with the following method:

The solid substances included are ground or sieved to a certain particle size. The binding agent is homogenized and suspended in a certain amount of solvent. The therapeutic compound and necessary auxiliary agents are mixed thoroughly with the binding agent solution and are moistened so that the solution is uniformly divided in the mass without overmoistening any parts. The amount of solvent is usually adapted so that the resulting mass has the consistency 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 is carried out for 10 hours and has to be standardized carefully as the degree of moisture of the granulate is of utmost importance. 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.

Disintegrating, lubricants or antiadhesive agents are added if desired, and the composition is passed to the tableting step.

The cleaned tablet punching machine is provided with a certain set of punches and dies, whereupon the suitable adjustment for the weight of the tablets and the degree of compression is tested out. The weight of the tablet 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 latter two properties the choice of compression pressure (0.5 to 5 ton) is something of a compromise. When the right adjustment is set, the preparation of tablets is started, which is carried out with 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 pulver and are then stored in closed packages until they are delivered.

Many tablets, especially these which are rough or bitter, are coated with a layer of sugar or some other suitable coating.

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

The daily dose of the active substance varies depending 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 per day at intravenous administration.

The following Examples illustrate the invention. Temperatures are in degrees Centigrade.

Example 1

1,2-Epoxy-3-[4-(2-methylcarbamoyloxyethoxy)-phenoxy]-propane (13.1 g is

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(19)

mixed with 100 ml of isopropanol and 13 ml of isopropylamine. The mixture is then heated on a boiling water-bath for 3 hours under reflux. The reaction mixture is then evaporated to dryness and the residue is dissolved in ether and the hydrochloride precipitated by the addition of gaseous HCl in ether at pH 4. After recrystallisation from acetonitrile the hydrochloride of 1-isopropylamino-3-[4-(2-methylcarbamoyloxyethoxy)-phenoxy]-propanol-2 is obtained. Melting point 124°C. mol. weight: found 365, calcul. 362.5.

In accordance with the method of Example 1 the following compounds are obtained as hydrochlorides.

Example 2

1 - Isopropylamino - 3 - [2 - chloro - 4 - (2 - dimethylcarbamoyloxyethoxy)-phenoxy]-propanol-2. Melting point 115°C. Mol. weight: found 415, calculated 411.

Example 3

1-Isopropylamino-3-[4-(2-carbamoyloxyethoxy)-phenoxy]-propanol-2. Melting point 146°C. Mol. weight: found 356, calculated 348.5.

Example 4

1-Isopropylamino-3-[4-(3-methylcarbamoyloxypropyl)-phenoxy]-propanol-2. Melting point 127.5°C. Mol. weight: found 361, calculated 360.5.

Example 5

1-Isopropylamino-3-[4-(2-methylcarbamoyloxyethyl)-phenoxy]-propanol-2. Melting point 50°C. Mol. weight: found 349.5, calculated 346.5.

Example 6

1 - Isopropylamino - 3 - [2 - chloro - 4 - (2 - methylcarbamoyloxyethyl) - phenoxy] - propanol - 2, was repeated from 2 - chloro - 4 - (2 - methylcarbamoyloxyethyl) - phenylglycidylether. M.p. 138°C.

Example 7

1-Isopropylamino-3-[4-(2-dimethylcarbamoyloxyethyl)-phenoxy]-propanol-2 was prepared from 4-(2-dimethylcarbamoyloxyethyl)-phenyl-glycidylether. M.p. 115°C.

Example 8

1-Isopropylamino-3-[4-(2-carbamoyloxyethyl)-phenoxy]-propanol-2 was prepared from 4-(2-carbamoyloxyethyl)-phenylglycidylether. M.p. 108°C.

Example 9

13 g of 2-chloro-4-(2-dimethylcarbamoyloxyethoxy)-phenol were added to 200 ml of epichlorohydrine and 0.5 ml of piperidine and the resulting mixture was heated on a boiling waterbath for 10 hours. The excess of epichlorohydrin was then evaporated and the residue was dissolved in chloroform and was shaken first with 2N HCl and then with H₂O. After evaporation the residue was dissolved in 50 ml of isopropanol and to the mixture 50 ml of isopropylamine was added and the resulting mixture was refluxed for 10 hours. The solvents were evaporated and to the residue 2N NaOH was added and the mixture was extracted with ether. The ether phase was evaporated, and the residue was transformed into its hydrochloride as described in Example 1. In this way the hydrochloride of 1-isopropylamino-3-[2-chloro-4-(2-dimethylcarbamoyloxyethoxy)-phenoxy]-propanol-2 was obtained. M.p. 115°C. Mol. weight: found 412, calculated 411.

Example 10

4-(2-Methylcarbamoyloxyethyl)-phenylglycidylether (10 g) in 100 ml of ethanol was saturated with gaseous ammonia and the mixture was heated in an autoclave on a boiling water bath for 4 hours. The mixture was evaporated and the residue was dissolved in ethylacetate and gaseous HCl was introduced into the solution. The hydrochloride precipitated, and it was filtered off and dissolved in 60 ml of ethanol. To the ethanol solution 20 ml of isopropyl iodide and 15 mg of K₂CO₃ were added. The mixture was heated in an autoclave at 120°C for 10 hours, after which it was evaporated and the residue was dissolved in 100 ml of 2N HCl and 100 ml of ether. The aqueous phase was separated off and was made alkaline with 2N NaOH and was extracted with ethyl acetate. The ethyl acetate phase was dried over K₂CO₃, and the chloride was precipitated with gaseous HCl. In this way the hydrochloride 1-isopropyl-

amino-3-[4-(2-methylcarbamoyloxyethyl)-phenoxy]-propanol-2 was obtained. M.p. 51°C. Mol. weight: found 350, calculated 346.5.

Example 11

2.4 g of Na were dissolved in 100 ml of ethanol and 19.5 g of 4-(2-methylcarbamoyloxyethyl)-phenol and 15.2 g of 1-isopropylamino-3-chloropropanol-2 were added. The mixture was heated in an autoclave on a boiling water bath for 15 hours, after which it was filtered and the filtrate was evaporated to dryness. The residue was made acidic with 2N HCl and was extracted with ether, after which it was made alkaline with NaOH and extracted with ether again. After drying of the ether phase over K₂CO₃, the hydrochloride was precipitated with gaseous HCl. In this way the hydrochloride of 1-isopropylamino-3-[4-(2-methylcarbamoyloxyethyl)-phenoxy]-propanol-2 was obtained. M.p. 50°C. Mol. weight: found 345, calculated 346.5.

Example 12

In accordance with the foregoing Example, N-benzyl-1-isopropylamino-3-[4-(2-methylcarbamoyloxyethyl)-phenoxy]-propanol-2 hydrochloride was prepared from 4-(2-methylcarbamoyloxyethyl)-phenol and N-benzyl-1-isopropylamino-3-chloropropanol-2. 10 g of the compound thus obtained were dissolved in 100 ml of ethanol, were mixed with 0.5 g of Pd/C and were hydrogenated until the calculated amount of H₂ had been absorbed. After filtration the reaction mixture was evaporated to dryness and the residue was recrystallized from acetonitrile. The compound obtained, 1-isopropylamino-3-[4-(2-methylcarbamoyloxyethyl)-phenoxy]-propanol-2 hydrochloride, melted at 52°C. Mol. weight: found 348, calculated 346.5.

Example 13

10 g of 1-Amino-3-[4-(2-methylcarbamoyloxyethyl)-phenoxy]-propanol-2 (obtained by a method of the type described in Example 10) were dissolved in 80 ml of methanol and 20 ml of acetone. The solution was cooled on an icebath and 10 g of sodium borohydride were gradually added. The temperature was then allowed to rise to ambient temperature and after 1 hour, 200 ml of water was added and the resulting mixture was extracted with ether. The ether phase was dried over K₂CO₃ and the substance was transformed into its hydrochloride. The hydrochloride of 1-isopropylamino-3-[4-(2-methylcarbamoyloxyethyl)-phenoxy]-propanol-2 obtained was recrystallized from acetonitrile. M.p. 51°C. Mol. weight: found 348, calculated 346.5.

Example 14 (Method F)

1-Isopropylamino-3-[4-(2-aminoethyl)-phenoxy]-propanol-2. HCl (13 g) and potassium isocyanate (3.2 g) were dissolved in 50 ml of H₂O and the pH was adjusted to 5. The reaction mixture was heated under reflux over night. The reaction mixture was then made alkaline by means of NaOH, and an oil separated off. This oil was chromatographed on a silica acid column using ethanol as eluting agent. After evaporation the substance was dissolved in acetonitrile and mixed with a solution of m-hydroxybenzoic acid in ethanol. In this way the m-hydroxybenzoate of 1-isopropylamino-3-[4-(2-carbamoylaminoethyl)-phenoxy]-propanol-2 was obtained, which after recrystallisation from isopropanol had a melting point at 138°C. Mol. weight: found 439.0, calculated 433.0.

Example 15

1-Isopropylamino-3-[4-(2-aminoethyl)-phenoxy]-propanol-2 (7.3 g) was dissolved in 150 ml of methylenechloride and mixed with dimethylcarbamoylchloride (1.65 g). The mixture was allowed to stand for 2 hours at room temperature, after which it was heated under reflux for 1 hour and then was filtered. The filtrate was evaporated, and the resulting oil was chromatographed on silica gel using ethanol as eluting agent. When the ethanol had been evaporated a crystalline residue was obtained which was dissolved in ethanol-nitromethane and was mixed with a solution of gaseous HCl in ethylacetate to pH 5. The hydrochloride of 1-isopropylamino-3-[4-(2-dimethylcarbamoylaminoethyl)-phenoxy]-propanol-2 was obtained in crystalline form; after recrystallisation from acetonitrile-nitromethane, the melting point was 152°C. Mol. weight: found 366.0, calculated 359.9.

The following compounds were obtained according to the method described in Example 14.

Example 16

1 - Isopropylamino - 3 - [2 - chloro - 4 - (2 - carbamoylaminoethyl) - phenoxy] - propanol - 2 was prepared from 1-isopropylamino-3-[2-chloro-4-(2-aminoethyl)-phenoxy]-propanol-2. M.p. 117°C.

Example 17

1 - Isopropylamino - 3 - [4 - (3 - carbamoylaminoethyl) - phenoxy] - propanol-2 was prepared from 1-isopropylamino-3-[4-(3-aminopropyl)-phenoxy]-propanol-2. M.p. 110°C.

Example 18

1 - Isopropylamino - 3 - [4 - (2 - methylcarbamoylaminoethyl) - phenoxy] - propanol - 2 was prepared from 1-isopropylamino-3-[4-(2-aminoethyl)-phenoxy]-propanol-2. M.p. 118°C.

Example 19

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

1-Isopropylamino-3-[4-(2-methylcarbamoyloxyethoxy)-phenoxy]-propanol-2 . HCl	2.0 g
Saccharine	0.6 g
Sugar	30.0 g
Glycerine	5.0 g
Flavouring agent	0.1 g
Ethanol 96%	10.0 ml
Distilled water	ad 100.0 ml

Sugar, saccharine and the ether salt 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 100 ml.

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

Example 20

1 - Isopropylamino - 3 - [2' - chloro - 4' - (2 - dimethylcarbamoyloxyethoxy)-phenoxy] - propanol - 2 - hydrochloride (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 added and the mixture thus obtained was pressed into tablets (10,000), each of which contained 25 mg of substance and were provided with a breaking score to give doses smaller than 25 mg when broken.

Example 21

Granules were prepared from 1-isopropylamino-3-[4-(2-carbamoyloxyethoxy)-phenoxy]-propanol-2-hydrochloride (250 g), lactose (175.9 g) and an alcoholic solution of polyvinylpyrrolidone (25 g). After the drying step the granules were mixed with talc (25 g), potato starch (40 g) and magnesium stearate (2.50 g) and pressed into 10,000 biconvex tablets. These tablets were primarily coated with a 10% alcoholic solution of shellac and then with an aqueous solution containing saccharose (45%), gum arabicum (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 22

1 - Isopropylamino - 3 - [4 - (2 - dimethylcarbamoylaminoethyl) - phenoxy]-propanol-2-hydrochloride (1 g), sodiumchloride (0.8 g) and ascorbic acid (0.1 g) were dissolved in an amount of distilled water sufficient to give 100 ml of solution. This solution, which contained 10 mg of active substance per ml, was used in filling ampoules, which were sterilized by heating at 120°C for 20 minutes.

Pharmacological evaluation

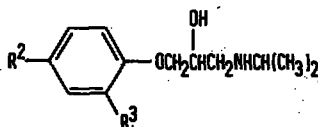
The compounds prepared in Examples 1-18 were evaluated for intrinsic activity and blocking effect on heart rate and for peripheral vasodilator response to isoprenaline in the cat. Alprenolol was used as a reference substance.

Cats weighing about 1.8 kg were anaesthetized with 30 mg/kg pentobarbital sodium i.p. The cats had been pretreated with reserpine, 5 mg/kg i.m. about 18 hours before the experiment. Bilateral vagotomy was performed before the start of the experiment.

The heart rate was recorded on an Offner cardi tachometer triggered by the EKG-complex. Mean intraarterial blood pressure was recorded from a carotide artery. The peripheral resistance was measured in one of the legs of the cat in the following way: The femoral artery was opened in the inguinal region and the leg was perfused by blood delivered through a sigma motor pump at constant rate. The flow resistance (the pressure) was recorded via a strain gauge transducer connected to the catheter distally to the pump. The paw was excluded from the circulation by a tight ligature around the ankle. Intravenously injected isoprenaline increased the heart rate and reduced the perfusion pressure. An isoprenaline dose giving 70—80% of the maximal chronotropic response was determined. This dose (usually 0.1 $\mu\text{g/kg}$) was then repeated with 20 minute intervals. Ten minutes before each isoprenaline injection, the tested substances were administered intravenously for two minutes, starting with a dose of 0.01 mg/kg and increasing each subsequent dose fourfold. The intrinsic effects of the test substances were determined. The dose producing 50% blockade of the isoprenaline responses were evaluated from the plotted log dose per cent blockade diagrams.

TABLE

Intrinsic stimulating activity on heart rate in cats, beta-blocking activity on heart rate and peripheral vascular resistance in cat;



Compound

Reserpinized cat.

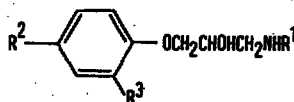
R^2	R^3	Intrinsic activity % of isoprenaline heart rate response	β -blockage Heart rate ED_{50} mg/kg	β -blockage Peripheral vascular resistance ED_{50} mg/kg
o-allyl (alprenolol)		20	0.1	0.05
$\text{CH}_3\text{NHCO}-\text{OC}_2\text{H}_5\text{O}-$	H	25	0.5	>8.5
$(\text{CH}_3)_2\text{NCO}-\text{O}-\text{C}_2\text{H}_5\text{O}-$	Cl	5	0.1	1.7
$\text{H}_2\text{NCO}-\text{O}-\text{C}_2\text{H}_5\text{O}-$	H	40	0.4	8
$\text{CH}_3\text{NHCO}-\text{O}-\text{C}_2\text{H}_4-$	H	0	0.4	2.4
$\text{CH}_3\text{NHCO}-\text{O}-\text{C}_2\text{H}_4-$	Cl	0	0.3	1.8
$\text{H}_2\text{NCONHC}_2\text{H}_4-$	H	0	0.4	14
$\text{H}_2\text{NCONHC}_2\text{H}_4-$	Cl	0	0.4	2.6

As is evident from the Table the seven test substances were 1—5 times less active than alprenolol as regards blockage of the β -receptors of the heart. However, the peripheral vascular β -blocking activity for the seven test substances was 34—280 times lower than the activity of alprenolol.

The results demonstrate that the seven test substances developed a relatively stronger blockade of the β -receptors of the heart than of the receptors in smooth muscles. Due to their cardioselectivity the test substances may be expected to give therapeutic effects in heart diseases without developing complications due to β -blockage in bronchi and blood vessels.

WHAT WE CLAIM IS:—

1. A compound of the formula



wherein R^1 is a C_{1-4} alkyl or hydroxy- C_{1-4} alkyl group, R^2 is a carbamoylamino- C_{1-4} alkyl, mono- or di- C_{1-4} alkylcarbamoylamino- C_{1-4} alkyl, carbamoylamino- C_{1-4} alkoxy, mono- or di- C_{1-4} alkylcarbamoylamino- C_{1-4} alkoxy, carbamoyloxy- C_{1-4} alkyl, mono- or di- C_{1-4} alkylcarbamoyloxy- C_{1-4} alkyl, carbamoyloxy- C_{1-4} alkoxy or mono- or di- C_{1-4} alkylcarbamoyloxy- C_{1-4} alkoxy group and R^3 is a hydrogen or halogen atom or a

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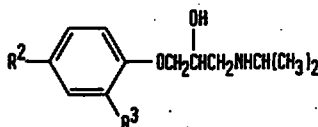
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The heart rate was recorded on an Offner cardiometer triggered by the EKG-complex. Mean intraarterial blood pressure was recorded from a carotide artery. The peripheral resistance was measured in one of the legs of the cat in the following way: The femoral artery was opened in the inguinal region and the leg was perfused by blood delivered through a sigma motor pump at constant rate. The flow resistance (the pressure) was recorded via a strain gauge transducer connected to the catheter distally to the pump. The paw was excluded from the circulation by a tight ligature around the ankle. Intravenously injected isoprenaline increased the heart rate and reduced the perfusion pressure. An isoprenaline dose giving 70—80% of the maximal chronotropic response was determined. This dose (usually 0.1 μ g/kg) was then repeated with 20 minute intervals. Ten minutes before each isoprenaline injection, the tested substances were administered intravenously for two minutes, starting with a dose of 0.01 mg/kg and increasing each subsequent dose fourfold. The intrinsic effects of the test substances were determined. The dose producing 50% blockade of the isoprenaline responses were evaluated from the plotted log dose per cent blockade diagrams.

TABLE

Intrinsic stimulating activity on heart rate in cats, beta-blocking activity on heart rate and peripheral vascular resistance in cat;



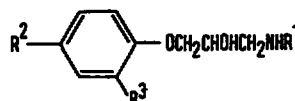
Compound	R ²	R ³	Intrinsic activity % of isoprenaline heart rate response	Reserpinized cat.	
				β -blockage Heart rate ED ₅₀ ,mg/kg	β -blockage Peripheral vascular resistance ED ₅₀ ,mg/kg
o-allyl (alprenolol)		H	20	0.1	0.05
CH ₃ NHCO—OC ₂ H ₅ O—		H	25	0.5	>8.5
(CH ₃) ₂ NCO—O—C ₂ H ₅ O—		Cl	5	0.1	1.7
H ₂ NCO—O—C ₂ H ₅ O—		H	40	0.4	8
CH ₃ NHCO—O—C ₂ H ₄ —		H	0	0.4	2.4
CH ₃ NHCO—O—C ₂ H ₄ —		Cl	0	0.3	1.8
H ₂ NCONHC ₂ H ₄ —		H	0	0.4	14
H ₂ NCONHC ₂ H ₄ —		Cl	0	0.4	2.6

As is evident from the Table the seven test substances were 1—5 times less active than alprenolol as regards blockage of the β -receptors of the heart. However, the peripheral vascular β -blocking activity for the seven test substances was 34—280 times lower than the activity of alprenolol.

The results demonstrate that the seven test substances developed a relatively stronger blockade of the β -receptors of the heart than of the receptors in smooth muscles. Due to their cardioselectivity the test substances may be expected to give therapeutic effects in heart diseases without developing complications due to β -blockage in bronchi and blood vessels.

WHAT WE CLAIM IS:—

1. A compound of the formula



wherein R¹ is a C₁₋₄ alkyl or hydroxy-C₁₋₄ alkyl group, R² is a carbamoylamino-C₁₋₄ alkyl, mono- or di-C₁₋₄ alkylcarbamoylamino-C₁₋₄ alkyl, carbamoylamino-C₁₋₄ alkoxy, mono- or di-C₁₋₄ alkylcarbamoylamino-C₁₋₄ alkoxy, carbamoyloxy-C₁₋₄ alkyl, mono- or di-C₁₋₄ alkylcarbamoyloxy-C₁₋₄ alkyl, carbamoyloxy-C₁₋₄ alkoxy or mono- or di-C₁₋₄ alkylcarbamoyloxy-C₁₋₄ alkoxy group and R³ is a hydrogen or halogen atom or a



C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, (C₁₋₄ alkoxy)methyl, C₁₋₄ alkoxy, C₂₋₄ alkenyloxy, C₂₋₄ alkynyloxy, C₁₋₄ alkylthio, C₂₋₄ alkenylthio, C₂₋₄ alkynylthio or C₁₋₄ acyl group.

2. A compound according to claim 1 wherein R¹ is a tert butyl, isopropyl, 1-hydroxy-propyl-2 or 1-hydroxy-2-methyl-propyl-2 group.

3. A compound according to claim 2 wherein R¹ is a tert butyl or isopropyl group.

4. A compound according to any one of the preceding claims wherein R² is a hydrogen or halogen atom or a C₁₋₄ alkyl, C₂₋₄ alkenyl, (C₁₋₄ alkoxy)methyl, C₁₋₄ alkoxy or C_{3 or 4} alkenyloxy group.

5. A compound according to claim 4 wherein R² is a hydrogen, chlorine or bromine atom or an allyl, methyl, methoxymethyl, methoxy or allyloxy group.

6. A compound according to claim 1, wherein R² is a mono- or di-C₁₋₄ alkyl-carbamoyloxy-C₁₋₄ alkyl group containing at most 10 carbon atoms, R¹ is as defined in claim 1 and R³ is as defined in claim 4.

7. A compound according to claim 6 wherein R² is a methylcarbamoyloxymethyl, methylcarbamoyloxyethyl, methylcarbamoyloxypropyl, dimethylcarbamoyloxypropyl or diethylcarbamoyloxyethyl group, R¹ is as defined in claim 2 and R³ is as defined in claim 5.

8. A compound according to claim 7 wherein R² is a methylcarbamoyloxyethyl, methylcarbamoyloxypropyl or diethylcarbamoyloxyethyl group, R¹ is as defined in claim 3 and R³ is as defined in claim 5.

9. A compound according to claim 1 wherein R² is a mono or di-C₁₋₄ alkyl-carbamoyloxy-C₁₋₄ alkoxy group containing at most 10 carbon atoms, R¹ is as defined in claim 1 and R³ is as defined in claim 4.

10. A compound according to claim 9 wherein R² is a methylcarbamoylethoxy, dimethylcarbamoyloxyethoxy, ethylcarbamoyloxyethoxy or diethylcarbamoyloxyethoxy group, R¹ is as defined in claim 2 and R³ is as defined in claim 5.

11. A compound according to claim 10 wherein R² is a methylcarbamoyloxyethoxy or dimethylcarbamoyloxyethoxy group, R¹ is as defined in claim 3 and R³ is as defined in claim 5.

12. A compound according to claim 1 wherein R² is a mono- or di-C₁₋₄ alkyl-carbamoylamino-C₁₋₄ alkyl group containing at most 10 carbon atoms, R¹ is as defined in claim 1 and R³ is as defined in claim 4.

13. A compound according to claim 12 wherein R² is a methylcarbamoylamino-methyl, methylcarbamoylaminoethyl, methylcarbamoylamino-n-propyl or dimethylcarbamoylaminoethyl group, R¹ is as defined in claim 2 and R³ is as defined in claim 5.

14. A compound according to claim 13 wherein R² is a dimethylcarbamoylaminoethyl or methylcarbamoylaminoethyl group, R¹ is as defined in claim 3 and R³ is as defined in claim 5.

15. A compound according to claim 1 wherein R² is a carbamoylamino-C₁₋₄ alkyl group, R¹ is as defined in claim 1 and R³ is as defined in claim 4.

16. A compound according to claim 15 wherein R² is a carbamoylaminomethyl, carbamoylaminoethyl, carbamoylamino-n-propyl or carbamoylamino-n-butyl group, R¹ is as defined in claim 2 and R³ is as defined in claim 5.

17. A compound according to claim 16 wherein R² is a carbamoylaminoethyl or carbamoylamino-n-propyl group, R¹ is as defined in claim 3 and R³ is as defined in claim 5.

18. A compound according to claim 1 wherein R² is a carbamoyloxy-C₁₋₄ alkyl group, R¹ is as defined in claim 1 and R³ is as defined in claim 4.

19. A compound according to claim 18 wherein R² is a carbamoyloxymethyl, carbamoyloxyethyl or carbamoyloxy-n-propyl group, R¹ is as defined in claim 2 and R³ is as defined in claim 5.

20. A compound according to claim 19 wherein R² is a carbamoyloxyethyl group, R¹ is as defined in claim 3 and R³ is as defined in claim 5.

21. A compound according to claim 1 wherein R² is a carbamoyloxy-C₁₋₄ alkoxy group, R¹ is as defined in claim 1 and R³ is as defined in claim 4.

22. A compound according to claim 21 wherein R² is a carbamoyloxymethoxy, carbamoyloxyethoxy or carbamoyloxy-n-propoxy group, R¹ is as defined in claim 2 and R³ is as defined in claim 5.

23. A compound according to claim 22 wherein R² is a carbamoyloxyethoxy group, R¹ is as defined in claim 3 and R³ is as defined in claim 5.

24. A compound according to claim 1 wherein R² is a carbamoylamino-C₁₋₄ alkoxy group, R¹ is as defined in claim 1 and R³ is as defined in claim 4.



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25. A compound according to claim 24 wherein R² is a carbamoylaminoethoxy, carbamoylaminoethoxy or carbamoylamino-n-propoxy group, R¹ is as defined in claim 2 and R³ is as defined in claim 5.

26. A compound according to claim 25 wherein R² is a carbamoylaminoethoxy group, R¹ is as defined in claim 3 and R³ is as defined in claim 5.

27. A compound according to any one of claims 1 to 26 in the form of a dextro-rotating optical isomer.

28. A compound according to any one of claims 1 to 26 in the form of a laevo-rotating optical isomer.

29. A compound according to any one of claims 1 to 28 in free form.

30. A compound according to any one of claims 1 to 28 in the form of a salt.

31. A compound according to any one of claims 1 to 28 in the form of a therapeutically acceptable salt.

32. 1-[4-(2-methylcarbamoyloxyethoxy)-phenoxy]-2-hydroxy-3-isopropylaminopropane.

33. 1-[2-chloro-4-(2-dimethylcarbamoyloxyethoxy)-phenoxy]-2-hydroxy-3-isopropylaminopropane.

34. 1-[4-(2-carbamoyloxyethoxy)-phenoxy]-2-hydroxy-3-isopropylaminopropane.

35. 1-[4-(2-carbamoyloxyethyl)-phenoxy]-2-hydroxy-3-isopropylaminopropane.

36. 1-[2-chloro-4-(2-methylcarbamoyloxyethyl)-phenoxy]-2-hydroxy-3-isopropylaminopropane.

37. 1-[4-(2-methylcarbamoyloxyethyl)-phenoxy]-2-hydroxy-3-isopropylaminopropane.

38. 1-[4-(2-dimethylcarbamoyloxyethyl)-phenoxy]-2-hydroxy-3-isopropylaminopropane.

39. 1-[4-(3-methylcarbamoyloxypropyl)-phenoxy]-2-hydroxy-3-isopropylaminopropane.

40. 1-[4-(2-carbamoylaminoethyl)-phenoxy]-2-hydroxy-3-isopropylaminopropane.

41. 1-[4-(2-dimethylcarbamoylaminoethyl)-phenoxy]-2-hydroxy-3-isopropylaminopropane.

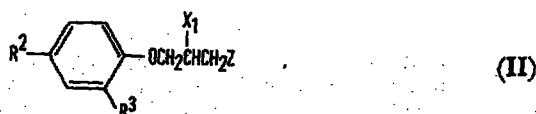
42. 1-[2-chloro-4-(2-carbamoylaminoethyl)-phenoxy]-2-hydroxy-3-isopropylaminopropane.

43. 1-[4-(3-carbamoylaminoethyl)-phenoxy]-2-hydroxy-3-isopropylaminopropane.

44. 1-[4-(2-methylcarbamoylaminoethyl)-phenoxy]-2-hydroxy-3-isopropylaminopropane.

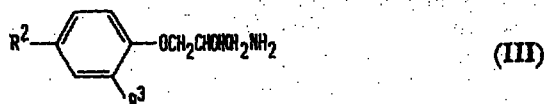
45. Each and every compound according to claim 1 hereinbefore specifically mentioned.

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



wherein R² and R³ are as defined in claim 1, X¹ is a hydroxy group and Z is a reactive, esterified hydroxy group or X¹ and Z together form an epoxy group, with an amine of the formula NH₂-R¹ wherein R¹ is as defined in claim 1.

47. A process for preparing an amine as defined in claim 1, which process comprises reacting a compound of the formula III



wherein R² and R³ are as defined in claim 1, with a compound of the formula Z-R¹, wherein Z is as defined in claim 46 and R¹ is as defined in claim 1.

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



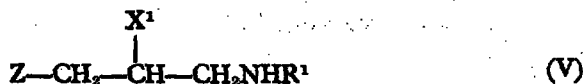


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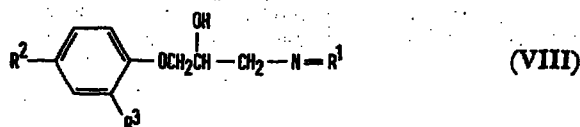
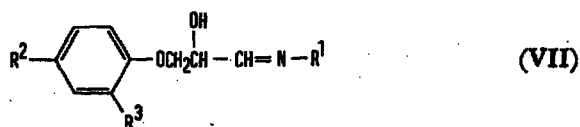
wherein R^2 and R^3 are as defined in claim 1, with a compound of the formula V



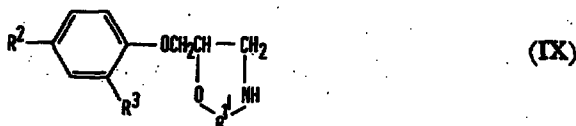
wherein Z and X^1 are as defined in claim 46 and R^1 is as defined in claim 1.

49. A process for preparing an amine as defined in claim 1 which process comprises hydrolysing a derivative of a compound as defined in claim 1, which derivative has an arylsulphonyl, benzoyl, cyano, silyl, alkylidene, benzylidene, phosphorylidene or substituted methylene substituent at the nitrogen atom of the amino group and/or at the hydroxy group, or reducing such a derivative having an arylsulphonyl substituent at the nitrogen atom or hydroxy group.

50. A process for preparing an amine as defined in claim 1, which process comprises reducing a Schiff's base of the formula VII or VIII

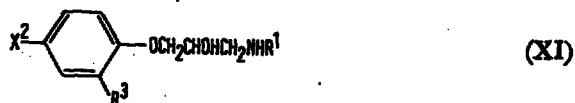


wherein R^1 , R^2 and R^3 are as defined in claim 1, or a cyclic tautomer corresponding to the compound of formula VIII, said tautomer having the formula



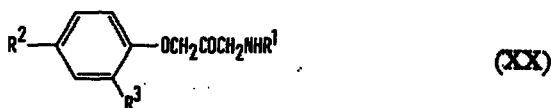
wherein R^1H is the same as R^1 and where the compounds VIII and IX may be present simultaneously.

51. A process for preparing an amine as defined in claim 1, which process comprises converting the group X^2 in a compound of the formula XI



wherein X^2 is a hydroxyalkyl-, esterified hydroxyalkyl-, hydroxyalkoxy-, esterified hydroxyalkoxy-, hydroxy-, aminoalkyl-, aminoalkoxy-, alkanoylaminoalkyl-, alkanoylaminoalkoxy-, alkanoyloxyalkyl-, alkanoyloxyalkoxy-, aminothiocarbamoylaminoalkyl-, aminothiocarbamylaminoalkoxy-, alkylaminothiocarbamylaminoalkyl-, alkylaminothiocarbamylaminoalkoxy-, imino(halo)carbaminoalkyl-, imino(halo)carbaminoalkoxy-, iminocarbiminoalkyl-, or iminocarbiminoalkoxy- group into a group as defined for R^2 in claim 1, using a method known *per se* for effecting such a conversion.

52. A process for preparing an amine as defined in claim 1, which process comprises hydrogenating a compound of the formula XX



wherein R^1 , R^2 and R^3 are as defined in claim 1

53. A process according to any one of claims 46 to 52 wherein R^1 , R^2 and R^3 are as defined in any one of claims 2 to 26.

54. A process according to any one of claims 46 to 53 wherein the amine is prepared in its dextro-rotating form.

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55. A process according to any one of claims 46 to 53 wherein the amine is prepared in its laevo-rotating form.
56. A process according to any one of claims 46 to 55 wherein the amine is prepared in the form of the free base.
57. A process according to any one of claims 46 to 55 wherein the amine is prepared in the form of a salt.
58. A process according to claim 57 wherein the amine is prepared in the form of a therapeutically acceptable salt.
59. A process according to any one of claims 46 to 58 substantially as hereinbefore described.
60. A compound according to claim 1 or a salt thereof obtained by a process as claimed in any one of claims 46 to 59.
61. A pharmaceutical preparation containing a compound or salt as claimed in any one of claims 1 to 45 and 60 together with a therapeutically acceptable carrier.
62. A preparation according to claim 61 substantially as hereinbefore described.

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