

PATENT SPECIFICATION

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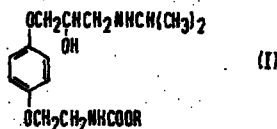


(54) 3-[4-(2-ALKOXY CARBONYLAMINO ETHYL)-PHENOXY]-1-ISOPROPYLAMINO-PROPAN-2-OLS, METHODS FOR THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM

(71) AKTIEBOLAGET HASSLE, a Swedish Body Corporate of Fack, S-431 20 Molndall, 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 having valuable pharmacological properties, to processes for their preparation and to compositions containing them.

The amines of the present invention are compounds of formula I



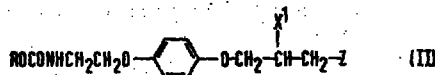
wherein

R is methyl or ethyl.

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

The compounds of formula I can be used as cardioselective antagonists of adrenergic β -receptor-stimulators e.g. in the treatment of arrhythmias and angina pectoris. They are also valuable intermediates for the preparation of other useful compounds, especially pharmaceutically active compounds.

The compounds of formula I can be obtained by methods known *per se*. In method a, a compound of formula II

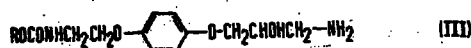


wherein

R is as defined above, X¹ is a hydroxy group, Z is a reactive, esterified hydroxy group, or X¹ and Z together form an epoxy group, is reacted with isopropylamine. The reactive, esterified hydroxy group can be a hydroxy group esterified with a strong, inorganic or organic acid, preferably a hydrohalogen acid, such as hydrochloric acid, hydrobromic acid, or hydroiodic acid; or sulphuric acid or a strong organic sulphonic acid, such as a strong aromatic sulphonic acid, e.g. benzene-sulphonic acid, 4-bromobenzenesulphonic acid or 4-toluenesulphonic acid. Thus, Z is preferably chloro, bromo or iodo. This reaction is carried out conventionally. When a reactive ester is used as a starting material, the

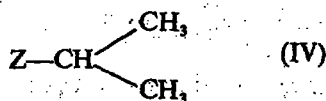
preparation takes place preferably in the presence of a basic condensing agent and/or with an excess of an amine. Suitable basic condensing agents are e.g. alkali metal hydroxides such as sodium or potassium hydroxide, alkali metal carbonates such as potassium carbonate and alkali metal alcoholates such as sodium methylate, potassium ethylate and potassium *tert.*-butylate.

In method b), a compound of formula III



wherein

R is as defined above, is reacted with a compound of formula IV



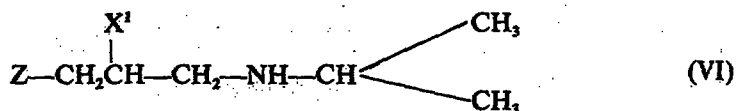
where Z is a reactive esterified hydroxy group. This reaction is carried out conventionally, preferably in the presence of a basic condensing agent and/or an excess of an amine. Suitable basic condensing agents are e.g. alkali metal alcoholates, preferably sodium or potassium alcoholates, or alkali metal carbonates such as sodium or potassium carbonate.

In method c), a compound of formula V



wherein

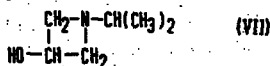
R is as defined above, is reacted with a compound of formula VI



wherein

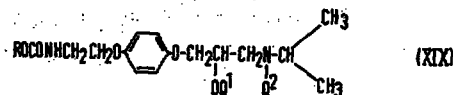
X' and Z are as defined above. This reaction is carried out conventionally. In those cases where a reactive ester is used as starting material, the compound of formula V may suitably be used in the form of its metal phenolate such as an alkali metal phenolate, preferably sodium phenolate, or the reaction can be carried out in the presence of an acid binding agent, preferably a condensing agent which can form a salt of the compound of formula V, such as an alkali metal alcoholate.

In method d), a compound of formula V is reacted with a compound of formula VII

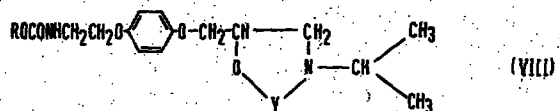


In method e), a compound of formula I is prepared by a process which comprises

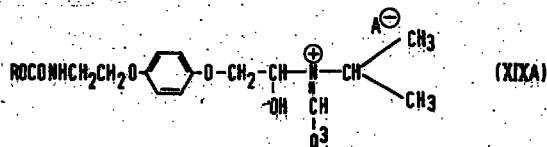
(i) solvolysis of a compound of the general formula



where R is as defined above and Q¹ and Q², which may be the same or different, each is hydrogen (with the proviso that both Q¹ and Q² do not represent hydrogen), or an acyl, cyano or silyl group; or of a compound of general formula



where R is as defined above and Y is a carbonyl or thiocarbonyl residue; or a compound of the general formula



where R is as defined above, $=CH-Q^3$ is an alkylidene, benzylidene or phosphorylidene group and A is an anion;

or (ii) reduction of a compound of general formula XIX where R is as defined above and Q^1 and Q^2 , which may be the same or different, each is hydrogen, (with the proviso that both Q^1 and Q^2 do not represent hydrogen), or an α -aryl-alkyl, α -alkoxycarbonyl, 2-halogenoalkoxycarbonyl or an arylsulphonyl group;

or (iii) pyrolysis or fermentation of a compound of general formula XIX where R is as defined above and Q^1 and Q^2 , which may be the same or different, each is hydrogen (with the proviso that both Q^1 and Q^2 do not represent hydrogen) or a carbamoyl, alkylcarbamoyl, aralkylcarbamoyl or arylcarbamoyl group.

Residues splittable by solvolysis are preferably residues splittable by hydrolysis or ammonolysis.

Residues splittable by hydrolysis are acyl, e.g. oxycarbonyl residues, such as alkoxycarbonyl, e.g. *tert*-butoxycarbonyl, or ethoxycarbonyl, aralkoxycarbonyl such as phenylalkoxycarbonyl residues, e.g. carbobenzyloxy halogenocarbonyl e.g. chlorocarbonyl, arylsulphonyl such as toluenesulphonyl, or bromobenzenesulphonyl or alkanoyl such as formyl, acetyl or trifluoroacetyl, or a benzoyl residue; or a cyano group or a silyl residue, such as trimethylsilyl.

Of the above mentioned hydrolysable residues, preferably the oxycarbonyl or alkanoyl or benzoyl residue is used.

In reagents of formula XIXA, when a phosphorylidene group is used, it can be a triphenylphosphorylidene group.

The hydrolysis may be carried out conventionally, suitably in a basic or preferably in acid medium e.g. in the presence of an acidic agent such as dilute mineral acids, such as sulphuric acid or a hydrohalic acid, or in the presence of basic agents such as alkali metal hydroxides, such as sodium hydroxide. Oxycarbonyl or aryl sulphonyl residues and cyano groups may suitably be split off by means of acidic agents such as a hydrohalic acid, suitably hydrobromic acid. Preferably the splitting takes place using dilute hydrobromic acid, possibly in a mixture with acetic acid. Cyano groups are preferably split off by means of hydrobromic acid at an elevated temperature, e.g. in boiling hydrobromic acid, according to the "bromocyano method" (v. Braun). A *tert*-butoxycarbonyl residue may be split off under anhydrous conditions by treatment with a suitable acid, such as trifluoroacetic acid. Acidic agents are preferably used for hydrolysis of compounds of formula VIII.

Residues removable by ammonolysis are halogenocarbonyl residues, such as a chlorocarbonyl residue. The ammonolysis may be carried out conventionally e.g. by using an amine containing at least one hydrogen atom bound to nitrogen such as a mono- or dialkylamine e.g. methylamine or dimethylamine, or especially ammonia, preferably at an elevated temperature. Instead of ammonia, one may use an agent which liberates ammonia such as hexamethylene tetraamine.

Residues removable by reduction are α -arylalkyl residues such as benzyl or an α -aralkoxycarbonyl residue such as benzyloxycarbonyl which can be removed conventionally by hydrogenolysis, especially using catalytically activated hydrogen, such as hydrogen in the presence of hydrogenating catalysts, e.g. Raney-nickel. Other residues removable by hydrogenolysis are 2-halogenalkoxycarbonyl residues such as 2,2,2-trichloroethoxycarbonyl, 2-iodoethoxycarbonyl or 2,2,2-tribromoethoxycarbonyl, which may be removed conventionally by a metallic reduction (so called nascent hydrogen). Nascent hydrogen may be produced by the use of a metal or metal alloy, such as amalgams on compounds which give hydrogen such as carboxy acids, alcohols or water; zinc or zinc alloy together with acetic acid is preferred. Hydrogenolysis of 2-halogenalkoxycarbonyl residues may also be carried out using chromium (II) compounds such as chromium (II) chloride or chromium (II) acetate.

The residue removable by reduction may also be an arylsulphonyl group such

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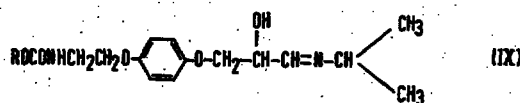
as toluenesulphonyl which may be removed conventionally by reduction using nascent hydrogen, e.g. by means of an alkali metal, such as lithium or sodium in liquid ammonia. In carrying out the reduction care should be taken that other reducible groups are not affected.

Residues removable by pyrolysis, especially residues removable from the nitrogen atom, are carbamoyl groups unsubstituted or substituted e.g. by alkyl such as methyl or aralkyl such as benzyl or aryl, such as phenyl, the pyrolysis is carried out conventionally, care being taken to avoid affecting any other thermally susceptible groups.

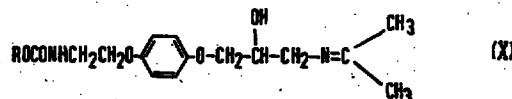
Residues removable by fermentation, especially residues removable from the nitrogen atom are the carbamoyl groups mentioned above. The fermentation is carried out conventionally e.g. using the enzyme urease or soya bean extract at about 20°C or a slightly elevated temperature.

In method f), a Schiff's base of formula IX or X

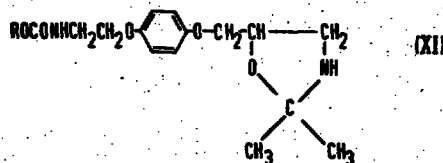
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or a cyclic tautomer of Schiff base X having formula XI



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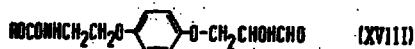
in which R is as defined above, can be reduced. Both compounds of formula X and XI can be present in the material being reduced. The reduction can be carried out conventionally e.g. using a di-light metal hydride, such as sodium borohydride, lithium aluminium hydride, with a hydride such as borane, with formic acid, or by means of catalytic hydrogenation, e.g. with hydrogen in the presence of Raney-nickel. In the reduction care should be taken so that other groups in the molecule are not reduced.

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The compound of formula IX can be obtained by reacting an aldehyde of formula

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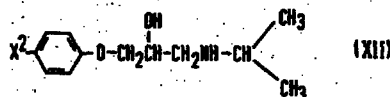
with isopropylamine.

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A compound of formula X or XI can be obtained by reacting an amine of the formula III with acetone.

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In method g), the group X², which is one of the groups indicated in formulae XIII to XVI below, is converted in a compound of formula XII



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into a group ROCONHCH₂CH₂O—.

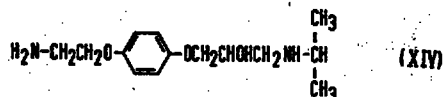
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In method g), a compound of formula XIII

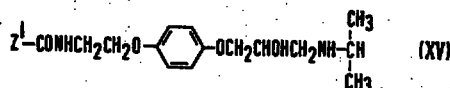


can be reacted with a compound ROCONH₂, wherein R and Z are as defined above.

Alternatively a compound of formula XIV

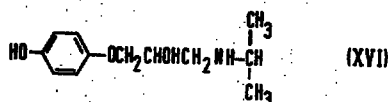


can be reacted with a compound ROCOCl , wherein R is as defined above.
Alternatively, a compound of formula XV



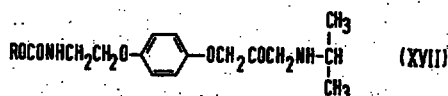
can be reacted with a compound $\text{R}-\text{Z}^2$, wherein R is as defined above, one of Z^1 and Z^2 is Z as defined above and the other is OH.

Alternatively a compound of formula XVI



can be reacted with a compound $\text{ROCONHCH}_2\text{CH}_2-\text{Z}$, wherein R and Z are as defined above. All the reactions with a compound of formula XII can be carried out conventionally e.g. as in the reaction according to method a) of a compound of formula II with isopropylamine.

In method h), an amine of formula XVII



can be hydrogenated.

Depending on the precise process conditions and the starting material selected, the end product is obtained either in the free base form or in the form of an acid addition salt. Thus, for example, basic, neutral or mixed salts may be obtained as well as hemiamino salts, or sesqui- or polyhydrates. The acid addition salts of the compounds of formula I may be converted in a manner known *per se*, into the free base using e.g. basic agents such as an alkali or an ion exchanger in basic form. The free bases obtained can be converted into salts with organic or inorganic acids. In the preparation of acid addition salts, it is preferred to use such acids which form therapeutically acceptable salts. Such acids are e.g. hydrohalic 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, pyruvic, phenylacetic, benzoic, *p*-aminobenzoic, anthranilic, *p*-hydroxybenzoic, salicylic, *p*-aminosalicylic, emboic, methanesulphonic, ethanesulphonic, hydroxyethanesulphonic, ethylenesulphonic, halogenobenzenesulphonic, toluenesulphonic, naphthylsulphonic or sulphanilic acid; methionine, tryptophane, lysine or arginine.

The above mentioned salts or other salts such as picrates, may be used to purify the free bases obtained by synthesis where the free base is transformed into a salt, which is separated from the reaction product and the base then liberated from the salt.

The new compounds may, depending on the choice of starting materials and process, be prepared as optical antipodes or as a racemate.

The racemates obtained can be separated according to known methods, e.g. by recrystallisation from an optically active solvent, by means of a microorganism, or by reaction with an optically active acid forming salt of the compound and separating the salts thus obtained, from one another, e.g. by means of their different solubility in a solvent. Suitable optically active acids to use in this way are e.g. the L- and D-forms of tartaric acid, di-*o*-tolyltartaric acid, malic acid, mandelic acid, camphor sulphonc acid or china acid (1,3,4,5-tetrahydroxy-cyclohexanecarboxylic acid). Preferably, the more active of the two isomers is isolated.

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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 the active component of formula I either as a free base or as a pharmaceutically acceptable, acid addition salt thereof, such as the hydrochloride, lactate, acetate or sulphamate in combination with a pharmaceutically acceptable carrier. 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.

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, such as lactose, saccharose, sorbitol, mannitol, starch (such as potato starch, corn starch, or amylopectin), a cellulose derivative or gelatine, together with an antifriction agent such as magnesium stearate, calcium stearate, or a polyethyleneglycol wax 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 contain e.g. gum arabicum, gelatine, talc or titanium dioxide. Furthermore, the tablets may be coated with a lacquer dissolved in a readily 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.

In the preparation of soft capsules (pearl-shaped, closed capsules), which consist of e.g. gelatine and e.g. glycerine, 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, starch (such as potato starch, corn starch or amylopectin), cellulose derivatives or gelatine.

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.

Liquid preparations for oral administration may be present in the form of syrups or suspensions, e.g. solutions containing from 0.2% to 20% by weight of the active substance 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 carboxymethylcellulose as a thickening agent.

Solutions for parenteral administration 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% to 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 pharmaceutical tablets for peroral use can be carried out in accordance with the following method:

The solid substances to be included are ground or sieved to a selected particle size. The binding agent is homogenized and suspended in a selected amount of solvent. The active compound and necessary auxiliary agents are mixed with the binding agent solution with continuous and constant mixing and are moistened so that the solution is uniform throughout the mass. The amount of solvent is usually selected so that the 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 as aggregates and the mass can be pressed through a sieve in the form 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 can take 10 hours and has to be standardized carefully as the water content of the granulate is of utmost importance for the following process. Drying in a fluid bed may also 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.

To the sieved mixture, disintegrating, antifriction and antiadhesive agents are added to give the right composition for the tableting step.

A clean tablet punching machine is used having suitable adjustment for the weight of the tablets and the degree of compression. The weight of the tablet is

decisive for the size of the dose in each tablet and is calculated 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. As regards the two latter properties, the choice of compression pressure (0.5 to 5 ton) is most important. When the right adjustment is found, the preparation of tablets is started and can be carried out at 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 required.

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

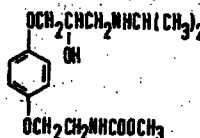
The tablets are usually packed by machines having an electronic counting device. The different types of packages may consist of glass or plastic gallipots, or boxes, tubes or specific dosage adapted packages.

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

The following Examples 1 and 3 to 12 illustrate the invention. Temperature is given in degrees centigrade.

EXAMPLE 1.

4.1 g of 1,2-epoxy-3-[4'-(2-methoxycarbonylaminoethoxy)-phenoxy]-propane were mixed with 4.1 ml isopropylamine and 2.5 ml of isopropanol. The mixture was refluxed for 3 hours and evaporated to dryness. The residue was dissolved in 2M hydrochloric acid and the mixture was washed twice with diethyl ether. The aqueous phase was made alkaline with sodium hydroxide and extracted with methylene chloride. After drying and evaporation the residue was dissolved in ethyl acetate and diethyl ether containing HCl was added to pH 4. The hydrochloride was filtered off and isolated. After having been recrystallised from acetone, 2.6 g of 1-isopropylamino-3-[4'-(2-methoxycarbonylaminoethoxy)-phenoxy]-propan-2-ol-hydrochloride were obtained, m.p. 108°. The structure was determined using NMR.



EXAMPLE 2.

The starting material of Example 1 was prepared as follows. 20.0 g of N,N-dibenzyl-2-chloroethylamine hydrochloride and 27.6 g of potassium carbonate were mixed in 250 ml of acetonitrile. The mixture was refluxed for 15 min. and 13.8 g of 4-benzyloxyphenol were added, whereupon the mixture was refluxed for 5 hours whilst stirring. After filtration and evaporation, the residue was recrystallized from petroleum ether. 18.4 g of 1-(N,N-dibenzylamino)-2-(4'-benzyloxyphenoxy)-ethane was obtained. Its structure was determined by NMR.

The product obtained was dissolved in 185 ml of 95% ethanol and 5.5 ml of concentrated HCl. After hydrogenation over a palladised charcoal catalyst, filtration, evaporation, and recrystallisation from isopropanol/diethyl ether 5.8 g of 4-β-aminoethoxyphenol was obtained, m.p. 175°. The structure was determined by NMR.

The resulting 4-β-aminoethoxyphenol and 6.3 g of sodium bicarbonate were mixed in 25 ml of water and cooled on an ice bath. 5.3 g of chloroformic acid methyl ester were added whilst stirring. The mixture was stirred at room temperature for 3 hours and then extracted with methylene chloride. The methylene chloride phase was dried and evaporated. The resulting diacylated product was then hydrolysed overnight with 2M sodium hydroxide solution. The mixture was acidified with hydrochloric acid and extracted with methylene chloride. After drying and evaporation 3.9 g of 4-β-methoxycarbonylaminoethoxyphenol was obtained as a yellow oil. The structure was determined by NMR.

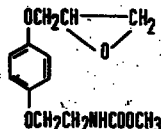
The resulting 4-β-methoxycarbonylaminoethoxyphenol was dissolved in 30 ml of epichlorohydrin and 1.8 g of potassium carbonate were added. The mixture was refluxed for 2 hours. After filtration and evaporation 4.1 g of 1,2-epoxy-3-(4'-β-

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methoxycarbonylaminoethoxyphenoxy)-propan-2-ol were obtained as an oil which crystallised, m.p. 65°. The structure was determined by NMR.



EXAMPLE 3.
(Method B).

10 g of 4-(2-methoxycarbonylaminoethoxy)-phenyl glycidyl ether in 100 ml of ethanol were saturated with gaseous ammonia and the mixture was heated in an autoclave on a boiling waterbath for 4 hours. The solvent was evaporated and the residue was dissolved in ethylacetate and hydrogen chloride gas was introduced. The hydrochloride then precipitated and it was filtered off and dissolved in 50 ml of ethanol to which isopropylamine and 15 g of K_2CO_3 had been added. The mixture was heated in an autoclave at 130° for 10 hours whereupon the solvent was evaporated and the residue was mixed with 100 ml of 2N HCl and 100 ml of diethyl ether. The aqueous phase was separated off and was made alkaline with 2N NaOH and extracted with ethyl acetate. The solvent phase was dried over K_2CO_3 , whereupon 1-isopropylamino-3-[4-(2-methoxycarbonylaminoethoxy)-phenoxy]-propan-2-ol was obtained and converted to its hydrochloride, by introducing diethyl ether containing HCl to pH 4, which was recrystallized from acetone, m.p. 108°.

EXAMPLE 4.
(Method C).

2.4 g of Na were dissolved in 100 ml of ethanol, whereupon 19.0 g of 4-(2-methoxycarbonylaminoethoxy)-phenol and 15.5 g of 1-isopropylamino-3-chloropropan-2-ol were added. The mixture was heated in an autoclave on a boiling waterbath for 15 hours. Thereupon it was filtered and the filtrate was evaporated to dryness. The residue was made acidic with 2N HCl and extracted with diethyl ether, whereupon the aqueous phase was made alkaline with 2N NaOH and extracted with ethyl acetate. The ethyl acetate was dried over $MgSO_4$ and 1-(isopropylamino-3-[4-(2-methoxycarbonylaminoethoxy)-phenoxy]-propan-2-ol obtained which was converted to its hydrochloride as described in Example 1 above, m.p. 107°.

EXAMPLE 5.
(Method E).

As described in Example 4, N-benzyl-1-isopropylamino-3-[4-(2-methoxycarbonylaminoethoxy)-phenoxy]-propan-2-ol was prepared from 4-(2-methoxycarbonylaminoethoxy)-phenol and N-benzyl-1-isopropylamino-3-chloropropan-2-ol-*p*-hydroxybenzoate, 10 g of the resulting compound were dissolved in 100 ml of ethanol, 0.5 g. of palladised charcoal (10%) catalyst were added and hydrogenation was carried out until the estimated amount of H_2 had been absorbed. After filtration, the mixture was evaporated to dryness and the residue of 1-isopropylamino-3-[4-(2-methoxycarbonylaminoethoxy)-phenoxy]-propan-2-ol was converted to its hydrochloride as described in Example 1, m.p. 108°.

EXAMPLE 6.
(Method F).

11 g of 1-amino-3-[4-(2-methoxycarbonylaminoethoxy)-phenoxy]-propan-2-ol prepared as described in Example 3, were dissolved in 80 ml of methanol containing 5 g of acetone. The solution was cooled on an icebath and 10 g of sodium borohydride was added, little by little. The temperature was allowed to rise to room temperature and after 1 hour, 200 ml of H_2O were added and the mixture was extracted with ethyl acetate. The ethyl acetate phase was dried over K_2CO_3 and the resulting 1-isopropylamino-3-[4-(2-methoxycarbonylaminoethoxy)-phenoxy]-propan-2-ol was converted to its hydrochloride by introducing diethyl ether containing HCl to pH 4, isolating the precipitate and recrystallizing it from acetone, m.p. 108°.

EXAMPLE 7.
(Method G).

10 g of 1-isopropylamino-3-[4-(2-chloroethoxy)-phenoxy]-propan-2-ol, 8 g of methylcarbamate and 15 g of K_2CO_3 were mixed in 100 ml of acetonitrile and were refluxed for 5 hours whilst stirring. Filtration and evaporation gave crude 1-isopropylamino-3-[4-(2-methoxycarbonylaminoethoxy)-phenoxy]-propan-2-ol which was dissolved in ethyl acetate and converted to its hydrochloride by introducing diethyl ether containing HCl and recrystallizing the precipitate from acetone, m.p. 108° .

EXAMPLE 8.
(Method D).

0.116 moles of 4- β -methoxycarbonylaminoethoxyphenol were mixed with 0.080 moles of 1-isopropyl-3-azetidinol, 0.500 moles of benzylalcohol and 0.003 moles of KOH. The mixture was refluxed at 140° for 6 hours whilst stirring and then cooled and extracted with 2M HCl. The aqueous phase was made alkaline and then extracted with chloroform. After drying and evaporation, the residue was dissolved in diethyl ether and to the solution, diethyl ether containing HCl was added. The hydrochloride was filtered off and washed with acetone. The hydrochloride of 1-isopropylamino-3-[4'-(2-methoxycarbonylaminoethoxy)-phenoxy]-propan-2-ol was obtained, m.p. 108° .

EXAMPLE 9.

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

1-isopropylamino-3-[4'-(2-methoxycarbonylaminoethoxy)-phenoxy]-propan-2-ol . 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 active compound of formula I 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 of formula I.

EXAMPLE 10.

1-isopropylamino-3-[4'-(2-methoxycarbonylaminoethoxy)-phenoxy]-propan-2-ol 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 admixed and the resulting mixtures was pressed into tablets (10,000) each of which contain 25 mg of active substance. The tablets have a breaking score to enable a dose other than 25 mg to be given.

EXAMPLE 11.

Granules were prepared from 1-isopropylamino-3-[4-(2-methoxycarbonylaminoethoxy)-phenoxy]-propan-2-ol 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 were pressed into 10,000 biconvex tablets. These tablets were first coated with a 10% alcoholic solution of shellac and then with an aqueous solution containing saccharose (45%), gum arabicum (5%), gelatine (4%) and dyestuff

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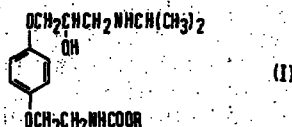
(0.2%). Talc and sugar powder were used for powdering after the first five coatings. The coating was then coated with a 66% sugar syrup and polished with a 10% carnauba wax solution in carbon tetrachloride.

EXAMPLE 12.

1 - Isopropylamino-3-[4 - (2-methoxycarbonylaminoethoxy)-phenoxy] - propan-2-ol hydrochloride (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 per ml, was used for filling ampoules, which were sterilized by heating at 120°C for 20 minutes.

WHAT WE CLAIM IS:—

1. An amine of the formula I



wherein

R is methyl or ethyl.

2. 1-isopropylamino-3-[4'-(2-methoxycarbonylaminoethoxy)-phenoxy]-propan-2-ol.

3. An amine according to claim 1 or 2 in the form of its dextro-rotating optical antipode.

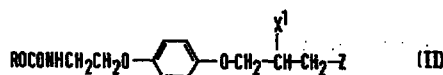
4. An amine according to claim 1 or 2 in the form of its levo-rotating optical antipode.

5. An amine according to any one of claims 1 to 4 in the form of its free base.

6. A salt of an amine according to any one of claims 1 to 4.

7. A therapeutically acceptable salt of an amine according to any one of claims 1 to 4.

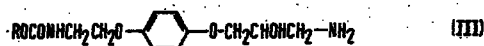
8. A process for the preparation of an amine as defined in claim 1 which comprises reacting a compound of formula II



wherein

R is as defined in claim 1, X¹ is hydroxy, and Z is a reactive, esterified hydroxy group, or X¹ and Z together form an epoxy group, with isopropylamine.

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



wherein

R is as defined in claim 1 with a compound of formula IV



wherein

Z is a reactive esterified hydroxy group.

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



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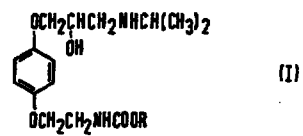
(0.2%). Talc and sugar powder were used for powdering after the first five coatings. The coating was then coated with a 66% sugar syrup and polished with a 10% carnauba wax solution in carbon tetrachloride.

EXAMPLE 12.

1 - Isopropylamino-3-[4 - (2-methoxycarbonylaminoethoxy)-phenoxy] - propan-2-ol hydrochloride (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 per ml, was used for filling ampoules, which were sterilized by heating at 120°C for 20 minutes.

WHAT WE CLAIM IS:—

1. An amine of the formula I



wherein

R is methyl or ethyl.

2. 1-isopropylamino-3-[4'-(2-methoxycarbonylaminoethoxy)-phenoxy]-propan-2-ol.

3. An amine according to claim 1 or 2 in the form of its dextro-rotating optical antipode.

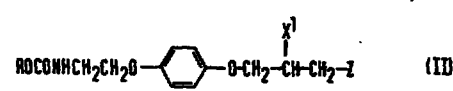
4. An amine according to claim 1 or 2 in the form of its levo-rotating optical antipode.

5. An amine according to any one of claims 1 to 4 in the form of its free base.

6. A salt of an amine according to any one of claims 1 to 4.

7. A therapeutically acceptable salt of an amine according to any one of claims 1 to 4.

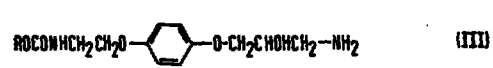
8. A process for the preparation of an amine as defined in claim 1 which comprises reacting a compound of formula II



wherein

R is as defined in claim 1, X¹ is hydroxy, and Z is a reactive, esterified hydroxy group, or X¹ and Z together form an epoxy group, with isopropylamine.

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



wherein

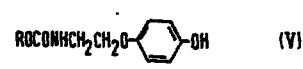
R is as defined in claim 1 with a compound of formula IV



wherein

Z is a reactive esterified hydroxy group.

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





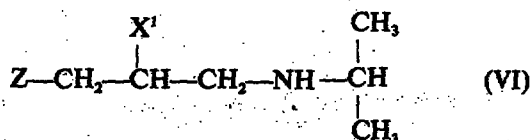
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wherein

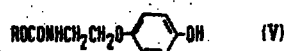
R is as defined in claim 1 with a compound of formula VI



wherein

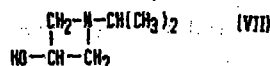
Z and X¹ are as defined in claim 8.

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



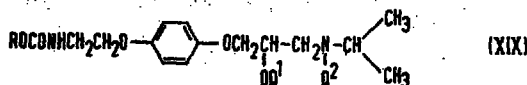
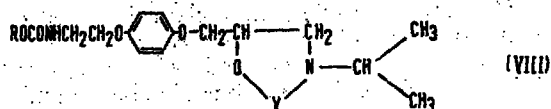
wherein

R is as defined in claim 1 with a compound of formula VII

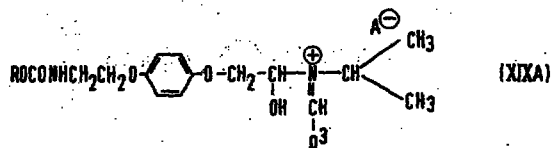


12. A process for the preparation of an amine as defined in claim 1 which comprises

(i) solvolysis of a compound of the general formula

where R is as defined in claim 1 and Q¹ and Q², which may be the same or different, each is hydrogen (with the proviso that both Q¹ and Q² do not represent hydrogen), or an acyl, cyano or silyl group; or of a compound of general formula

where R is as defined in claim 1 and Y is a carbonyl or thiocarbonyl residue; or of a compound of the general formula

where R is as defined in claim 1 =CH-Q³ is an alkylidene, benzylidene or phosphorylidene group and A is an anion; or(ii) reduction of a compound of general formula XIX where R is as defined in claim 1 and Q¹ and Q², which may be the same or different, each is hydrogen (with the proviso that both Q¹ and Q² do not represent hydrogen), or an α-aryl-alkyl, α-alkoxy-carbonyl, 2-halogeno-alkoxycarbonyl or an arylsulphonyl group; or(iii) pyrolysis or fermentation of a compound of general formula XIX where R is as defined in claim 1 and Q¹ and Q², which may be the same or different, each is hydrogen (with the proviso that both Q¹ and Q² do not represent hydrogen) or a carbamoyl or alkylcarbamoyl, aralkylcarbamoyl or arylcarbamoyl group.

13. A process for the preparation of an amine as defined in claim 1 which comprises reducing a Schiff's base of the formulae IX or X

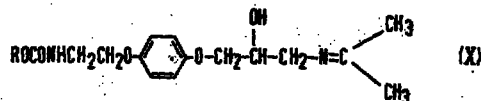
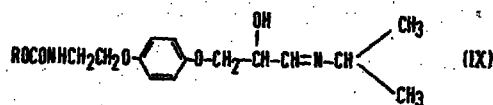
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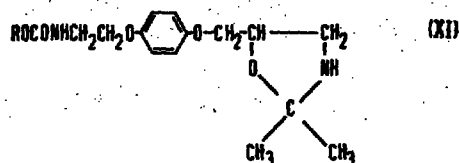
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or a cyclic-tautomer of formula XI corresponding to that of formula X



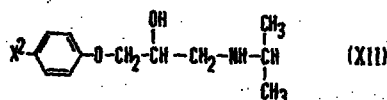
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wherein

R is as defined in claim 1 and where the compounds of formula X and XI may exist together.

14. A process for the preparation of an amine as defined in claim 1 which comprises converting a compound of formula XII

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wherein

(1) X^2 is $\text{Z}-\text{CH}_2\text{CH}_2\text{O}-$ and the compound XII is reacted with a compound ROCONH_2 , where R is as defined in claim 1 and Z is as defined in claim 8, or

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(2) X^2 is $\text{H}_2\text{NCH}_2\text{CH}_2\text{O}-$ and the compound XII is reacted with a compound ROCOCl where R is as defined in claim 1 and Z is as defined in claim 8, or

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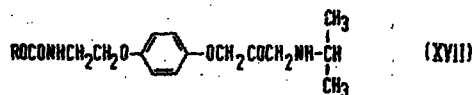
(3) X^2 is $\text{Z}'\text{CONHCH}_2\text{CH}_2\text{O}-$ and the compound XII is reacted with a compound $\text{R}-\text{Z}^2$ where R is as defined in claim 1, one of Z' and Z^2 is Z as defined in claim 8 and the other of Z' and Z^2 is OH, or

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(4) X^2 is OH and the compound XII is reacted with a compound $\text{ROCONHCH}_2\text{CH}_2-\text{Z}$ where R is as defined in claim 1 and Z is as defined in claim 8.

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15. A process for the preparation of an amine as defined in claim 1 which comprises hydrogenating a compound of formula XVII



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16. A process according to any one of claims 8 to 15 where the amine is prepared in the form of a racemate and the racemate is separated into its individual isomeric components.

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17. A process according to any one of claims 8 to 16 wherein the amine is prepared in the form of a salt and the salt is converted to the free base or wherein the amine is prepared in the form of a free base and the free base is converted to a salt.

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18. A process according to claim 17 wherein the amine is isolated in the form of a therapeutically acceptable salt.

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19. A process according to any one of claims 8 to 15 substantially as hereinbefore described in any one of Examples 1 and 3 to 8.

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20. An amine as defined in claim 1 or salt thereof obtained by a process according to any one of claims 8 to 19.

21. An amine as defined in claim 1 or therapeutically acceptable salt thereof obtained by a process according to any one of claims 8 to 19.



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22. A pharmaceutical preparation comprising as an active ingredient, an amine or salt according to any one of claims 1 to 5, 7 or 21 together with a therapeutically acceptable carrier.

23. A composition according to claim 22, substantially as hereinbefore described in any one of Examples 9 to 12.

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