

PATENT SPECIFICATION

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- (21) Application No. 37072/75/ (22) Filed 9 Sept. 1975 /
 (31) Convention Application No's: 7413789 (32) Filed 1 Nov. 1974 /
 7506348 4 June 1975 in /
 (33) Sweden (SE)
 (44) Complete Specification published 19 July 1978
 (51) INT CL² C07C 93/00 121/60
 (52) Index at acceptance
 C2C 200; 202; 220; 227; 22Y; 29X; 29Y; 30Y;
 322; 326; 32Y; 360; 362; 364; 365; 36Y;
 43X; 452; 455; 456; 45Y; 500; 502; 509;
 50Y; 620; 624; 633; 634; 650; 652; 662;
 682; 699; 790; 79Y; LF; LY

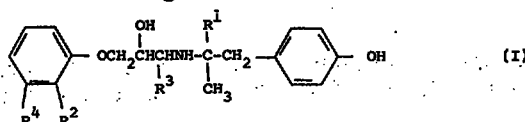
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(54) NEW ARYLOXY N-ARALKYL PROPANOLAMINES, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

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

The present invention relates to new aryloxy N-aralkyl propanolamines, useful as potent β -receptor blocking compounds, to their preparation, to pharmaceutical preparations containing them and to a method for treating symptoms and signs of cardiovascular disorders by blocking the β -receptors of the heart by administering them to mammals, excluding man. The new compounds are those of the general formula:



wherein R¹ is hydrogen or methyl and R² is hydrogen, methyl, ethyl, propyl, allyl, methoxy, propargyloxy, cyano or pyrrolyl linked via its nitrogen atom to the benzene ring, R³ is hydrogen, methyl or ethyl, and R⁴ is hydrogen or methyl, provided that R² and R⁴ are not both hydrogen, and salts thereof.

The new compounds have valuable pharmacological properties. Thus they block cardiac β -receptors, as shown 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 anesthetized cat at an intravenous dose of 0.002 to 2 mg/kg. They also block the vascular β -receptors as shown 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 anesthetized cat at an intravenous dose of 0.002 to 2 mg/kg or more. The compounds have also stimulating properties on β -receptors, i.e. they show intrinsic activity. This property is especially pronounced in vascular β -receptors, causing dilatation of peripheral blood vessels.

The new compounds can be used in the treatment of arrhythmias, angina pectoris and hypertension. The peripheral vasodilatation is especially valuable for the two last mentioned indications.

Compounds according to the present invention include:

- 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-o-methylphenoxy-propanol-2;
- 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-o-ethylphenoxy-propanol-2;
- 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-o-propylphenoxy-propanol-2;
- 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-o-allylphenoxy-propanol-2;
- 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-o-propargyloxyphenoxy-propanol-2;
- 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-o-cyanophenoxy-propanol-2;
- 3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-o-methylphenoxy-propanol-2;
- 3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-o-ethylphenoxy-propanol-2;
- 3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-o-propylphenoxy-propanol-2;

- 3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-*o*-allylphenoxy-propanol-2;
 3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-*o*-propargyloxyphenoxy-propanol-2;
 3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-*o*-cyanophenoxy-propanol-2;
 5 3-ethyl-3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-*o*-allylphenoxy-propanol-2;
 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-*o*,*m*-dimethylphenoxy-propanol-2;
 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-*o*-methoxyphenoxy-propanol-2;
 3-methyl-3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-*o*-ethylphenoxy-propanol-2;
 3-methyl-3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-*o*-cyanophenoxy-propanol-2;
 10 3-methyl-3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-*o*-methylphenoxy-propanol-2;
 3-methyl-3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-*o*-allylphenoxy-propanol-2; and
 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-*m*-methylphenoxy-propanol-2.

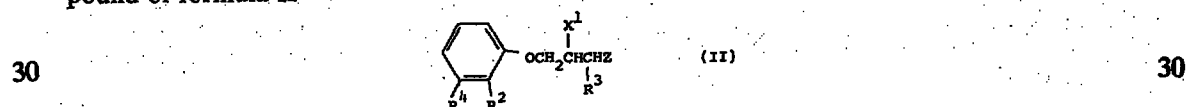
In preferred compounds of the invention R² is propargyloxy, cyano, methyl or methoxy and R¹, R³ and R⁴ are each hydrogen.

- 15 Salt forming acids may be used in preparing therapeutically acceptable salts of the compounds, e.g. hydrohalogen acids, sulfuric acid, phosphoric acid, nitric acid, perchloric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxy or sulfonic acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, or pyrovic acid, phenylacetic, benzoic, *p*-aminobenzoic, anthranilic, *p*-hydroxybenzoic, salicylic or *p*-aminosalicylic acid, embonic acid (i.e. panonic acid), methanesulfonic, ethane-
 20 sulfonic, hydroxyethane sulfonic, ethylenesulfonic, halogenbenzenesulfonic, toluenesulfonic, naphthylsulfonic, or sulfanilic acid, methionine, tryptophane, lysine or arginine.

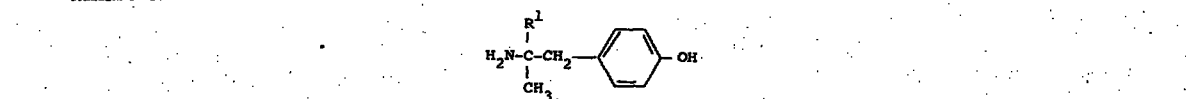
The compounds of the invention are intended to be administered orally or parenterally for acute and chronic treatment of above mentioned cardiovascular disorders.

- 25 The biological effects of the new compounds have been tested, and the different tests carried out will be shown and explained below.

The new compounds may be obtained according to methods known *per se*. Thus, a compound of formula II



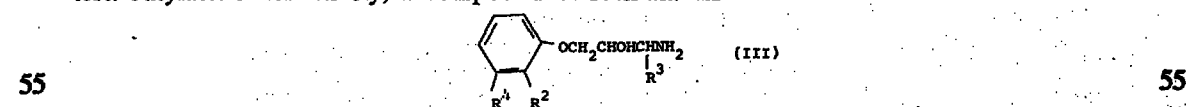
- 35 wherein R², R³ and R⁴ have the meaning given above, X¹ is a hydroxy group, Z is a reactive, esterified hydroxy group, or X¹ and Z together from an epoxy group can be reacted with an amine of the formula



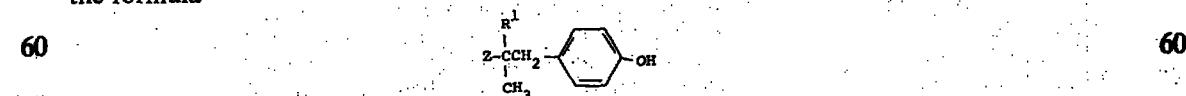
- 40 wherein R¹ has the same meaning as given above.

- A suitable reactive, esterified hydroxy group is a hydroxy group esterified with a strong, inorganic or organic acid, preferably a hydrohalogen acid, such as hydrochloric acid, hydrobromic acid, or hydroiodic acid; sulfuric acid or a strong organic sulfonic acid, e.g. benzene-
 45 sulfonic acid, 4-bromobenzenesulfonic acid, or 4-toluenesulfonic acid. Thus, Z is preferably chloro, bromo or iodo.

- This reaction is carried out conventionally. As 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
 50 and alkali metal alcoholates such as sodium methylate, potassium ethylate and potassium tert.-butylate. Alternatively, a compound of formula III



- 55 wherein R², R³ and R⁴ have the meanings given above, can be reacted with a compound of the formula

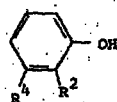


- 60 wherein R¹ and Z have the same meanings as given above.

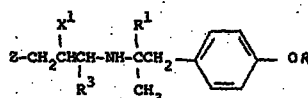
- This reaction is carried out conventionally, preferably in the presence of a basic condensing agent and/or an excess of an amine. Suitable basic condensing agents are e.g. alkali metal
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alcoholates, preferably sodium or potassium alcoholate, or also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

Alternatively, a compound of formula IV



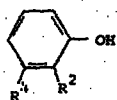
wherein R^2 and R^4 have the same meanings as given above can be reacted with a compound of formula V



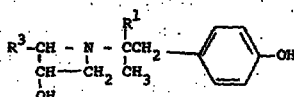
wherein Z, X^1 and R^1 and R^3 have the same meanings as given above and R is a splitable, protecting group.

This reaction is carried out conventionally. In those cases where reactive esters are used as starting material, the compound of formula IV may suitably be used in the form of its metal phenolate such as an alkali metal phenolate, preferably sodium phenolate, or one works in the presence of an acid binding agent, preferably a condensing agent, which can form a salt of the compound of formula IV as an alkali metal alcoholate.

Alternatively, a compound of formula IV



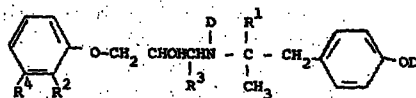
wherein R^2 and R^4 have the same meanings as given above, can be reacted with a compound of formula VI



wherein R^1 and R^3 have the same meanings as given above.

This reaction is carried out conventionally. Thus, the reaction is carried out under alkaline conditions in a suitable solvent, such as benzyl alcohol by boiling the reaction mixture for several hours. Thereby the phenol is primarily converted to its metal phenolate such as an alkali metal phenolate before it is added to the compound of formula VI.

Alternatively, one may split off the labile groups D_1 and D_2 from a compound of formula



each D, which may be the same or different is hydrogen or a labile group D_1 or D_2 , but are not both hydrogen, D_1 and D_2 being groups which may be replaced by hydrogen in a known manner.

Suitable splitable residues are especially those which are splitable by solvolysis, reduction, pyrolysis or fermentation.

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

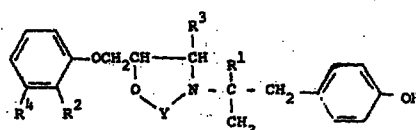
Residues splitable by hydrolysis are e.g. an acyl residue, which can be present, as a carboxy group derivative, e.g. an oxycarbonyl residue such as alkoxycarbonyl residue, e.g. tert-butoxycarbonyl residue, or ethoxycarbonyl residue; an aralkoxycarbonyl residue such as phenyl lower alkoxycarbonyl residue, e.g. a carbobenzyloxy residue; a halogencarbonyl residue, e.g. a chlorocarbon residue; or an arylsulphonyl residue such as a toluenesulfonyl or bromobenzenesulfonyl residue or as halogenated, such as fluorinated, lower alkanoyl residues such as formyl-, acetyl- or trifluoroacetyl residues or a benzyl residue or a cyano group or a silyl residue, such as a trimethylsilyl residue.

Of the above mentioned residues which are removable to leave a hydroxy group, residues splitable by hydrolysis are preferred, e.g. an oxycarbonyl residue, lower alkanoyl residue or benzoyl residue.

Residues which can be removed by hydrolysis to leave an amino group include an alkylidene or benzylidene residue or a phosphorylidene group as a triphenylphosphorylidene group.

Residues removable by hydrolysis to leave a hydroxy group and/or amino group may also be substituted on to a methylene carbon. Substituents on the methylene carbon may be e.g. aliphatic or aromatic residues such as alkyl, as mentioned above, aryl e.g. phenyl or pyridyl. The hydrolysis may be carried out conventionally, suitably in a basic or preferably in an acid medium.

Compounds having residues being splittable by hydrolysis include the compounds of formula VII



wherein R^1 , R^2 , R^3 and R^4 have the same meanings as given above and Y is a carbonyl or thiocarbonyl residue.

The hydrolysis is carried out in an analogous way, e.g. in the presence of a hydrolysing agent, e.g. in the presence of an acidic agent such as diluted mineral acids, such as sulfuric acid or hydrohalogen acid, or in the presence of basic agents such as alkali metal hydroxides, such as sodium hydroxide. Oxycarbonyl residues, aryl sulfonyl residues and cyano groups may also be split off by means of acidic agents such as a hydrohalogen acid, suitably hydrobromic acid. Preferably, the splitting may take place using diluted hydrobromic acid, possibly in a mixture with acetic acid. Cyano groups are preferably split off by means of hydrobromic acid at an elevated temperature, as in boiling hydrobromic acid, according to the "bromocyano method" (v. Braun). A tert.-butoxycarbonyl residue may be split off under anhydrous conditions by means of treatment with a suitable acid, such as trifluoroacetic acid. Acidic agents are preferably used in the hydrolysis of compounds of formula VI.

Residues splittable by ammonolysis are especially halogenocarbonyl residues, such as chlorocarbonyl. The ammonolysis may be carried out conventionally, e.g. by means of an amine containing at least one hydrogen atom bounded to the nitrogen atom, such as a mono- or di-lower alkylamine e.g. methylamine or dimethylamine, or especially ammonia, preferably at an elevated temperature. Instead of ammonia, one may use an agent which releases ammonia such as hexamethylene tetraamine.

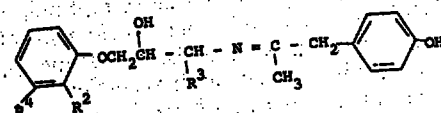
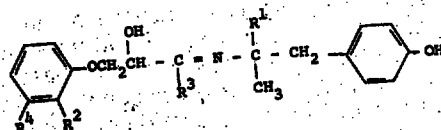
Residues splittable by reduction are e.g. an α -arylalkyl residue, such as a benzyl residue or an α -aralkoxycarbonyl residue such as a benzyl-oxycarbonyl residue, which may be split off conventionally by means of hydrogenolysis, especially by catalytically activated hydrogen, such as by hydrogen in the presence of hydrogenating catalysts, e.g. Raney-nickel. Other residues splittable by hydrogenolysis are 2-halogenalkoxycarbonyl residues such as 2,2,2-trichloroethoxycarbonyl or 2-iodoethoxy- or 2,2,2-tri-bromoethoxycarbonyl residues, which may be split off conventionally, suitably by means of a metallic reduction (so called nascent hydrogen). Nascent hydrogen may be obtained by the influence of metal or metal alloys, such as amalgam, on compounds which release hydrogen such as carboxy acids, alcohols or water, zinc or zinc alloys together with acetic acid are preferably used. Hydrogenolysis of 2-halogenalkoxycarbonyl residues may also take place using chromium or chromium (II) compounds as chromium (II) chloride or chromium (II) acetate.

Another residue splittable by reduction is an arylsulfonyl group such as a toluenesulfonyl group, which may be split conventionally by reduction using nascent hydrogen, e.g. by means of an alkali metal, such as lithium or sodium, in liquid ammonia, and suitably may be split off from a nitrogen atom. In carrying out this reduction, one has to take care that other reducing groups are not influenced.

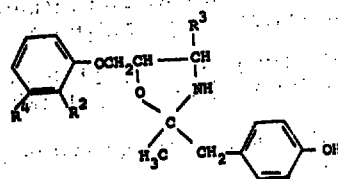
Residues splittable by pyrolysis, especially residues splittable from the nitrogen atom, are in substituted or unsubstituted carbamoyl groups. Suitable substituents are e.g. lower alkyl or aryl lower alkyl such as methyl or benzyl or aryl, such as phenyl, the pyrolysis is carried out conventionally, taking care of other thermally susceptible groups.

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

In a still further alternative method, a Schiff's base of formula VIII or IX

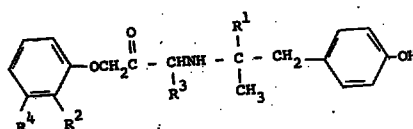


or a cyclic tautomer corresponding to formula IX of formula X



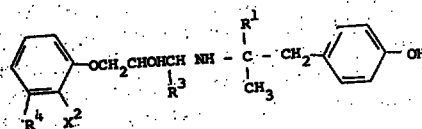
can be reduced, wherein R^1 , R^2 , R^3 and R^4 have the same meanings as given above, the compounds of formula IX and X perhaps both being present together. The use of compounds IX and/or X gives rise to compounds of formula I in which R^1 is only hydrogen. This reduction is carried out conventionally e.g. using a di-light metal hydride, such as sodium borohydride, lithium aluminium hydride, or using 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, one has to take care that other reducible groups are not affected.

Alternatively, the oxo group in a compound of formula XI



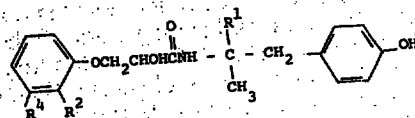
wherein R^1 , R^2 , R^3 and R^4 have the same meanings as given above, can be reduced to a hydroxy group. This reduction is carried out conventionally, especially using a di-light metal hydride, as mentioned above, or by the "Meerwein-Ponndorf-Verley method" or a modification thereof, suitably using an alkanol as a reaction component and as solvent, e.g. isopropanol, and using a metal alkanolate, as a metal isopropanolate, e.g. aluminium isopropanolate.

Alternatively, in a compound of formula XII



wherein R^1 , R^3 and R^4 have the same meanings as given above, and wherein X^2 is a residue transformable to a residue R^2 , one transforms X^2 to R^2 .

Alternatively, the oxo group in a compound of formula XIII



wherein R^1 , R^2 and R^4 have the meaning as given above, and R^3 is hydrogen, may be reduced to two hydrogen atoms.

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

Depending on the process conditions and the starting material, the end product is obtained either in free base form or in the form of its acid addition salt, and both 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, in a manner known *per se*, be transformed into free base compounds using e.g. basic agents such as alkali or ion exchangers. On the other hand, the free bases obtained may form salts with organic or inorganic acids. In the preparation of acid addition salts, preferably such acids are used which form therapeutically acceptable salts. Such acids are e.g. hydrohalogen acids, sulfuric acid, phosphoric acid, nitric acid, perchloric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxy or sulfonic acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic or pyruvic acid, phenylacetic, benzoic, *p*-aminobenzoic, antranilic, *p*-hydroxybenzoic, salicylic or *p*-aminosalicylic acid, embonic acid (i.e. pantoic acid), methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenesulfonic acids, halogenbenzenesulfonic, toluenesulfonic, naphthylsulfonic acids, or sulfanilic acid; methionine, tryptophane, lysine or arginine.

These or other salts of the new compounds e.g. picrates, may be used to purify the free bases as the free base can be transformed into a salt, the salt separated and a more pure base then released from the salt.

Unless the context requires otherwise, references in this specification to the compounds includes free bases and salts.

In a still further alternative process for producing a compound of the invention, one may react an aldehyde of the formula XIX



wherein R^2 and R^4 have the same meaning as given above, and R^3 is hydrogen with an amine of the formula



wherein R^1 has the same meanings as given above, in the presence of a suitable reducing agent, such as one of the above mentioned. This produces a compound of formula VII as an intermediate, which then is reduced by the procedure described above.

It is also possible to react, in a manner known *per se*, an amine of the formula III with an aldehyde or a ketone of the formula

in the presence of a suitable reducing agent, such as one of the above mentioned to produce compounds wherein R^1 is hydrogen. This gives a compound of formula IX or X as an intermediate, which then is reduced by the procedure described above.

The new compounds may, depending on the choice of starting materials and process, be obtained as pure optical antipodes or as racemates or, if they contain at least two asymmetric carbon atoms, as a mixture of isomers.

The isomer mixtures (racemate mixtures) obtained may, depending on physical-chemical differences of the component isomers, be separated into racemates containing 2 isomers only, e.g. by means of chromatography and/or fraction crystallisation.

The racemates obtained can be separated into individual isomers according to known methods, e.g. by recrystallisation from an optically active solvent, by means of microorganisms, or by a reaction with optically active acids forming salts of the compound and separating the salts thus obtained, e.g. by means of their different solubility. The individual isomers may then be released from the salt by the use of a suitable agent. Suitable optically active acids are e.g. the L- and D-forms of tartaric acid, di-*o*-tolyltartaric acid, malic acid, mandelic acid, camphor sulfonic acid or china acid. Preferably the isomer having the greater pharmacological activity is isolated.

The starting materials are known or may, if they should be new, be obtained according to processes known *per se*.

In clinical use, the compounds of the invention are administered normally orally, rectally or by injection in the form of a pharmaceutical preparation, which contains an active component either as free base or as pharmaceutically acceptable, non-toxic acid addition salts, e.g. the hydrochloride lactate, acetate, sulphamate in combination with a pharmaceutical

carrier and such preparations form a further aspect of the present invention.

The carrier may be a solid, semisolid 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 0.2 to 50% by weight in preparations for oral administration.

5 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 be mixed with a solid, pulverulent carrier, e.g. with lactose, saccharose, sorbitol, mannitol, starch, e.g. potato starch, corn starch or amylopectin, cellulose derivatives or gelatine, as well as with an anti-friction agent such as magnesium stearate, calcium stearate or a polyethyleneglycol wax and be pressed into tablets. If coated tablets are required, the above described core may be coated with a concentrated solution of sugar, which may also contain e.g. gum arabic, gelatine, talc or titanium dioxide. The tablets may also be coated with a laquer dissolved in an easily volatile organic solvent or mixture of solvents. To this coating, a dye may be added in order to distinguish easily between tablets with different active compounds or with different amounts of the active compound present.

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

15 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.

20 Liquid preparations for oral administration may be present in the form of syrups or suspensions, e.g. solutions containing 0.2% by weight to 20% by weight of the active substance described, the remainder 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.

25 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 of 0.5% by weight to 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may suitably be available in different dosage unit ampoules.

30 The preparation of pharmaceutically acceptable tablets for peroral use is carried out in accordance with the following method:

35 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 therapeutic compound and necessary auxiliary agents are mixed continuously with the binding agent solution and are moistened so that the solution is uniformly divided in the mass without overmoistening any parts. The amount of solvent is usually so chosen that the mass obtains a consistency similar to that of wet snow. The moistening of the pulverulent mixture with the binding agent solution causes the particles to gather together slightly to aggregates and the real granulating process is carried out in such a way that the mass is pressed through a sieve in the form of a net of stainless steel having a mesh size of about 1 mm. The mass is then placed in thin layers on a tray to be dried in a drying cabinet. This drying takes place over 10 hours and has to be standardized carefully as the degree of moisture of the granulate is of utmost importance for the following process and for the properties of the tablets. Drying in a fluid bed may possibly be used. In this case, the mass is not put on a tray but is poured into a container having a net bottom.

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

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

50 The cleaned tablet punching machine is provided with a selected set of punches and dies, and the necessary adjustment for the weight of the tablets and the degree of compression is made. 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 of disintegrate in water. Especially as regards the two latter properties the choice of compression pressure (0.5 to 5 ton) needs careful selection. When the right adjustment is made, 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.

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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 coating. This means that these 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 consist of glass or plastic gallipots but boxes, tubes and specific dosage adapted packages can also be used.

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

The following Examples illustrate the invention, Temperature is given in °C.

Example 1

Preparation of 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-*o*-methylphenoxy-propanol-2. 2.5 g of 1,2-epoxy-3-*o*-methylphenoxy propane were mixed with 1.5 g of 1-(4-hydroxyphenyl)-2-amino-propane and 25 ml of isopropanol and the total solution was refluxed for 1.5 hours. The solution was thereupon evaporated *in vacuo*. The base thus obtained was dissolved in acetone and the hydrochloride was precipitated using HCl in ether. The hydrochloride was filtered off and washed with acetonitrile. The yield of 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-*o*-methylphenoxy-propanol-2 was 1.4 g. Melting point 112°C. The structure was determined using NMR.

Example 2

3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-*o*-ethylphenoxypropanol-2 was prepared according to Example 1 using 1,2-epoxy-3-*o*-ethylphenoxy-propane and 1-(4-hydroxyphenyl)-2-amino-propane as starting materials. Melting point of its hydrochloride was 143°C, its structure was determined by NMR and equivalent weight.

Example 3

3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-*o*-allylphenoxy-propanol-2 was prepared according to Example 1 using 1,2-epoxy-3-*o*-allylphenoxy-propane and 1-(4-hydroxyphenyl)-2-amino-propane as starting material. Melting point of tartrate was 71°C. Its structure was determined by NMR and equivalent weight.

Example 4

3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-*o*-propargyloxy phenoxy-propanol-2 was prepared according to Example 1 using 1,2-epoxy-3-*o*-propargyloxyphenoxy-propane and 1-(4-hydroxyphenyl)-2-amino-propane as starting material. The *p*-hydroxybenzoate salt was also prepared.

Example 5

3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-*o*-cyanophenoxy-propanol-2 was prepared according to Example 1 using 1,2-epoxy-3-*o*-cyanophenoxy-propane and 2-(4-hydroxyphenyl)-1-methylethylamine as starting materials. The hydrochloride was obtained as a water soluble oil and its structure was determined using NMR.

Example 6

3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-*o*-methylphenoxy-propanol-2 was prepared according to Example 1, using 1,2-epoxy-3-*o*-methylphenoxypropane and 2-(4-hydroxyphenyl)-1,1-dimethylethyl amine as starting materials. The hydrochloride was obtained as a water soluble oil and its structure was determined using NMR.

Example 7

3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-*o*-ethylphenoxy-propanol-2 was prepared according to Example 1 using 1,2-epoxy-3-*o*-ethylphenoxypropane and 2-(4-hydroxyphenyl)-1,1-dimethylethylamine as starting materials. The melting point of the hydrochloride was 154°C.

Example 8

3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-*o*-allylphenoxy-propanol-2 was prepared according to Example 1, using 1,2-epoxy-3-*o*-allylphenoxy propane and 2-(4-hydroxyphenyl)-1,1-dimethylethyl amine as starting materials. The melting point of the hydrochloride was 140°C.

Example 9

3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-3-*o*-propargyloxy phenoxypropanol-2 was prepared according to Example 1, using 1,2-epoxy-3-*o*-propargyloxyphenoxypropane and 2-(4-hydroxyphenyl)-1,1-dimethylethylamine as starting materials.

Example 10

3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-*o*-cyanophenoxy propanol-2 was prepared according to Example 1, using 1,2-epoxy-3-*o*-cyanophenoxypropane and 2-(4-hydroxyphenyl)-1,1-dimethylethylamine as starting materials. Melting point 144°C (HCl).

Example 11

3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-*o,m*-dimethylphenoxy-propanol-2 was pre-

pared in accordance with Example 1 using 1,2-epoxy-3-*o,m*-dimethylphenoxypropane and 2-(4-hydroxyphenyl)-1-methylethylamine, as starting materials. Melting point 125°C (HCL).
 Example 12

3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-*o*-methoxyphenoxy-propanol-2 was prepared in accordance with Example 1 using 1,2-epoxy-3-*o*-methoxyphenoxy-propane and 2-(4-hydroxyphenyl)-1-methylethylamine as starting materials. Melting point 114°C (HCL).

Example 13
 3-methyl-3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-*o*-ethylphenoxy-propanol-2 was prepared in accordance with Example 1 using 1,2-epoxy-1-methyl-3-*o*-ethylphenoxy-propane and 2-(4-hydroxyphenyl)-1-methylethylamine, as starting materials. The hydrochloride was obtained as a water soluble oil and its structure was determined using NMR.

Example 14
 3-methyl-3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-*o*-cyanophenoxy-propanol-2 was prepared in accordance with Example 1 above using 1,2-epoxy-1-methyl-3-*o*-cyanophenoxy-propane and 2-(4-hydroxyphenyl)-1-methylethylamine as starting materials. The hydrochloride was obtained as a water soluble oil and its structure was determined using NMR.

Example 15
 3-ethyl-3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-*o*-allylphenoxy-propanol-2 was prepared in accordance with Example 1 above using 1,2-epoxy-1-ethyl-3-*o*-allylphenoxy-propane and 2-(4-hydroxyphenyl)-1-methylethylamine as starting materials. The hydrochloride was obtained as a water soluble oil and its structure was determined using NMR.

Example 16
 3-methyl-3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-*o*-methylphenoxy-propanol-2 was prepared in accordance with Example 1 above using 1,2-epoxy-1-methyl-3-*o*-methylphenoxy-propane and 2-(4-hydroxyphenyl)-1,1-dimethylethylamine as starting materials. The hydrochloride was obtained as a water soluble oil and its structure was determined using NMR.

Example 17
 3-methyl-3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-*o*-allylphenoxy-propanol-2 was prepared in accordance with Example 1 above using 1,2-epoxy-1-methyl-3-*o*-allylphenoxy-propane and 2-(4-hydroxyphenyl)-1,1-dimethylethylamine as starting materials. Melting point 172°C (HCL).

Example 18
 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-*m*-methylphenoxy-propanol-2 was prepared in accordance with Example 1 using 1,2-epoxy-3-*m*-methylphenoxypropane and 2-(4-hydroxyphenyl)-1-methylethylamine as starting materials. Melting point 150°C (HCL).

Example 19
 Preparation of 3-[1-methyl-2-(4-hydroxyphenyl)ethylamino]-1-*o*-allylphenoxy butanol-2. 2.5 g of 2,3-epoxy-1-*o*-allylphenoxy butane were mixed with 1.5 g of 1-methyl-2-(4-hydroxyphenyl)ethylamine and 25 ml of isopropanol and the total solution was refluxed for 100 hours. The solution was thereupon evaporated *in vacuo*. The base thus obtained was dissolved in trichloroethylene and the hydrochloride was precipitated using HCL in ether. Water was added and the mixture was titrated with 1M HCL. The pH was determined with a glass electrode and the values were plotted against ml HCL. At a band in the curve the water phase was separated, fresh water was added and the procedure was repeated until the next band in the curve. This water phase was separated, made alkaline with NH₄OH and extracted with methylene chloride. The organic phase was washed with water, dried and evaporated. The hydrochloride was precipitated with ether HCL. The ether was decanted and the product solidified upon evaporation in high vacuum. The yield of 3-[1-methyl-2-(4-hydroxyphenyl)ethylamino]-1-*o*-allylphenoxy butanol-2HCL was 1.6 g. Melting point 70°C. The structure was determined using NMR.

Example 20
 A syrup containing 2% (weight per volume of active substance) was prepared from the following ingredients:

3-[2-(4-hydroxyphenyl)-1-methylethylamino]-	2.0 g
-1- <i>o</i> -methylphenoxy-propanol-2 HCL (active substance)	0.6 g
Saccharine	30.0 g
Sugar	5.0 g
Glycerine	0.1 g
Flavouring agent	10.0 g
Ethanol 96%	100.0 ml
Distilled water	ad

Sugar, saccharine and the ether salt of the invention were dissolved in 60 g of warm water. After cooling, glycerine and solution of flavouring agents dissolved in ethanol were added. To the mixture water was then added to 100 ml.

The above mentioned active substance may be replaced with other pharmaceutically accept-

able acid addition salts.

Example 21

3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino-1-*o*-allylphenoxy]-propanol-2 hydrochloride (250 g) (active substance) 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 mixed and the mixture thus obtained was pressed into 10,000 tablets each of which contain 25 mg of active substance. The tablets are provided with a breaking score to give a dose other than 25 mg when broken.

Example 22

Granules were prepared from 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-*o*-propargyloxyphenoxy-propanol-2-*p*-hydroxybenzoate (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 was pressed into 10,000 biconvex tablets. These tablets are first coated with a 10% alcoholic solution of shellac and then with an aqueous solution containing saccharose (45%), gum arabic (5%), gelatine (4%) and a 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 23

3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-3-*o*-ethylphenoxy-propanol-2-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 in filling ampoules, which were sterilized by heating at 120°C for 20 minutes.

Biological effects

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

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

Table 1 below shows affinity values and intrinsic β -mimetic activity in reserpinized cats and effects on blood pressure in conscious dogs of compound of the present invention. Corresponding values for propranolol, (1-isopropylamino-3-(1-naphthoxy)-propanol-2, and metoprolol, (1-isopropylamino-3-[4-(2-methoxyethyl)phenoxy]-propanol-2), are shown for comparison.

Table 1 also shows pA_2 measured on rats. pA_2 is -log of the concentration of an antagonist which leads to the fact that the dose of noradrenaline has to be doubled in order to obtain the same effect of noradrenaline as one obtains without the antagonist or

$$pA_2 = \log (dr - 1) - \log (\text{antagonist})$$

$$\text{wherein } dr \text{ is dose ratio} = \frac{ED_{50} \text{ of noradrenaline (antagonist)}}{ED_{50} \text{ of noradrenaline (control)}}$$

and all concentrations are given in mol/l. pA_2 is thus a measure of α -receptor-effect where higher pA_2 > higher α -effect.

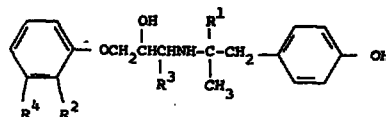
TABLE 1

5	Compound	Reserpinized cat		Intrinsic activity beats/min	Conscious dog BP in mm Hg after 1.5 mg/kg i.v.		pA ₂	5
		Block of isopren. ED ₅₀ mg/kg	PR		Supine	Erect		
	Propranolol	0.1	0.1	0	+5	0	—	
	Metoprolol	0.2	4.7	0	-5	-3	—	
10	Ex 1	0.07	0.07	+16	-22	-19	6.8	10
	2	0.11	0.15	+32	-40	-35	7.2	
	3	0.7	1.1	+33	—	—	7.2	
	5	0.04	0.1	+33	-40	-19	6.7	
	6	0.06	0.3	+62	-16	-25	5.8	
15	7	0.05	0.04	+38	—	—	6.8	15
	8	0.11	0.09	+39	-40	-20	6.4	
	10	0.025	0.04	+42	—	—	6.3	
	11	0.24	0.2	+6	—	—	—	
	12	0.04	0.5	+40	—	—	—	
20	13	0.12	0.5	+18	—	—	6.2	20
	14	0.3	1.0	+40	—	—	6.0	
	15	5.1	3.3	+2	—	—	6.6	
	16	1.3	8.5	+9	—	—	6.2	
	17	2.5	0.6	+3	—	—	7.4	
25	18	0.2	0.4	+10	—	—	—	25
	19	0.5	0.6	+28	-33	-45	—	

The experiments demonstrate that the compounds tested are potent β -receptor antagonists with or without intrinsic β -mimetic activity. The compounds also decrease blood pressure in conscious dogs significantly more than propranolol and metoprolol. The pronounced hypotensive effect in conscious dogs of the new compounds depends on a vasodilating effect in combination with cardiac beta-receptor blockade.

WHAT WE CLAIM IS:—

1. A compound of the general formula I



wherein R¹ is hydrogen or methyl and R² is hydrogen, methyl, ethyl, propyl, allyl, methoxy, propargyloxy, cyano or pyrrolyl linked via its nitrogen atom to the benzene ring, R³ is hydrogen, methyl or ethyl, and R⁴ is hydrogen or methyl, provided that R² and R⁴ are not both hydrogen, and salts thereof.

2. A compound according to Claim 1 in the form of a mixture of isomers.
3. A compound according to Claim 1 in the form of an individual isomer.
4. A compound according to Claim 1 in the form of a racemic mixture.
5. A compound according to Claim 3 in the form of an optically active isomer.
6. A compound according to any one of the preceding claims in the form of the free base.
7. A compound according to any one of Claims 1-5 in the form of a salt.
8. A compound according to any one of Claims 1-5 in the form of a therapeutically acceptable salt.
9. A compound according to any one of the preceding claims wherein R² is methyl, ethyl, propyl, allyl or propargyloxy.
10. A compound according to Claim 9 wherein R² is propargyloxy or methyl, and R¹, R³ and R⁴ are each hydrogen.
11. A compound according to any one of Claims 1-8 wherein R² is hydrogen, methoxy, cyano or pyrrolyl.
12. A compound according to Claim 11 wherein R² is cyano or methoxy and R¹, R³ and R⁴ are each hydrogen.
13. 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-o-methyl-phenoxy-propanol-2.
14. 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-o-ethyl-phenoxy-propanol-2.
15. 3-[1-methyl-2-(4-hydroxyphenyl)ethylamino]-1-o-propyl-phenoxy-propanol-2.
16. 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-o-allyl-phenoxy-propanol-2.



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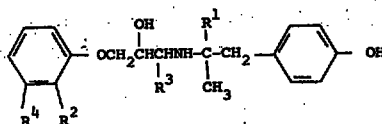
TABLE 1

Compound	Reserpinized cat		Intrinsic activity beats/min	Conscious dog BP in mm Hg after 1.5 mg/kg i.v.		pA ₂
	Block of isopren. ED ₅₀ mg/kg	PR		Supine	Erect	
Propranolol	0.1	0.1	0	+5	0	—
Metoprolol	0.2	4.7	0	-5	-3	—
Ex 1	0.07	0.07	+16	-22	-19	6.8
2	0.11	0.15	+32	-40	-35	7.2
3	0.7	1.1	+33	—	—	7.2
5	0.04	0.1	+33	-40	-19	6.7
6	0.06	0.3	+62	-16	-25	5.8
7	0.05	0.04	+38	—	—	6.8
8	0.11	0.09	+39	-40	-20	6.4
10	0.025	0.04	+42	—	—	6.3
11	0.24	0.2	+6	—	—	—
12	0.04	0.5	+40	—	—	6.2
13	0.12	0.5	+18	—	—	6.0
14	0.3	1.0	+40	—	—	6.6
15	5.1	3.3	+2	—	—	6.2
16	1.3	8.5	+9	—	—	7.4
17	2.5	0.6	+3	—	—	—
18	0.2	0.4	+10	—	—	—
19	0.5	0.6	+28	-33	-45	—

The experiments demonstrate that the compounds tested are potent β -receptor antagonists with or without intrinsic β -mimetic activity. The compounds also decrease blood pressure in conscious dogs significantly more than propranolol and metoprolol. The pronounced hypotensive effect in conscious dogs of the new compounds depends on a vasodilating effect in combination with cardiac beta-receptor blockade.

WHAT WE CLAIM IS:—

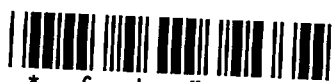
1. A compound of the general formula I



wherein R¹ is hydrogen or methyl and R² is hydrogen, methyl, ethyl, propyl, allyl, methoxy, propargyloxy, cyano or pyrrolyl linked via its nitrogen atom to the benzene ring, R³ is hydrogen, methyl or ethyl, and R⁴ is hydrogen or methyl, provided that R² and R⁴ are not both hydrogen, and salts thereof.

2. A compound according to Claim 1 in the form of a mixture of isomers.
3. A compound according to Claim 1 in the form of an individual isomer.
4. A compound according to Claim 1 in the form of a racemic mixture.
5. A compound according to Claim 3 in the form of an optically active isomer.
6. A compound according to any one of the preceding claims in the form of the free base.
7. A compound according to any one of Claims 1-5 in the form of a salt.
8. A compound according to any one of Claims 1-5 in the form of a therapeutically acceptable salt.
9. A compound according to any one of the preceding claims wherein R² is methyl, ethyl, propyl, allyl or propargyloxy.
10. A compound according to Claim 9 wherein R² is propargyloxy or methyl, and R¹, R³ and R⁴ are each hydrogen.
11. A compound according to any one of Claims 1-8 wherein R² is hydrogen, methoxy, cyano or pyrrolyl.
12. A compound according to Claim 11 wherein R² is cyano or methoxy and R¹, R³ and R⁴ are each hydrogen.
13. 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-o-methyl-phenoxy-propanol-2.
14. 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-o-ethyl-phenoxy-propanol-2.
15. 3-[1-methyl-2-(4-hydroxyphenyl)ethylamino]-1-o-propyl-phenoxy-propanol-2.
16. 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-o-allyl-phenoxy-propanol-2.

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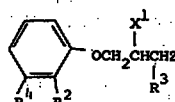
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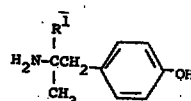
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17. 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-o-propargyloxyphenoxy-propanol-2.
18. 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-o-cyano-phenoxy-propanol-2.
19. 3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-o-methyl-phenoxy-propanol-2.
20. 3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-o-ethyl-phenoxy-propanol-2.
21. 3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-o-propyl-phenoxy-propanol-2.
22. 3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-o-allyl-phenoxy-propanol-2.
23. 3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-[o-propargyloxyphenoxy]-propanol-2.
24. 3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-o-cyanophenoxy-propanol-2.
25. 3-ethyl-3-[1-methyl-2-(4-hydroxyphenyl)ethylamino]-1-o-allylphenoxy-propanol-2.
26. 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-o-m-dimethylphenoxy-propanol-2.
27. 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-o-methoxy-phenoxy-propanol-2.
28. 3-methyl-3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-o-ethylphenoxy-propanol-2.
29. 3-methyl-3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-o-cyanophenoxy-propanol-2.
30. 3-methyl-3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-o-methylphenoxy-propanol-2.
31. 3-methyl-3-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-1-o-allylphenoxy-propanol-2.
32. 3-[2-(4-hydroxyphenyl)-1-methylethylamino]-1-m-methylphenoxy-propanol-2.
33. 3-[1-methyl-2-(4-hydroxyphenyl)ethylamino]-1-o-allylphenoxy-butanol-2.
34. A compound according to any one of claims 13-33, in the form of the free base.
35. A compound according to any one of claims 13-33, in the form of a salt.
36. A compound according to claim 35, in the form of a therapeutically active salt.
37. A compound according to any one of claims 13-36, in the form of a mixture of isomers.
38. A compound according to any one of claims 13-36, in the form of an individual isomer.
39. A compound according to any one of claims 13-36, in the form of a racemic mixture.
40. A compound according to claim 38, in the form of an optically active isomer.
41. A process for the preparation of a compound as defined in claim 1, wherein a compound of formula II

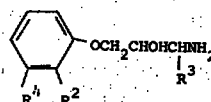


wherein R², R³ and R⁴ are as defined in claim 1, X¹ is a hydroxy group and Z is a reactive, esterified hydroxy group, or X¹ and Z together form an epoxy group, is reacted with an amine of formula

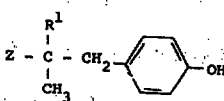


wherein R¹ is as defined in claim 1.

42. A process for the preparation of a compound as defined in claim 1, wherein a compound of formula III

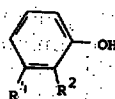


wherein R², R³ and R⁴ are as defined in claim 1 is reacted with a compound of the formula



wherein R¹ is as defined in claim 1 and Z is as defined in claim 41.

43. A process for the preparation of a compound as defined in claim 1 wherein a compound of formula IV



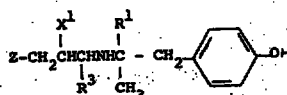


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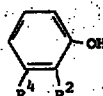
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wherein R^2 and R^4 are as defined in claim 1, is reacted with a compound of formula V

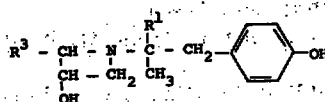


wherein R^1 and R^3 are as defined in claim 1, and Z and X^1 are as defined in claim 41.

44. A process for the preparation of a compound as defined in claim 1, wherein a compound of the formula IV

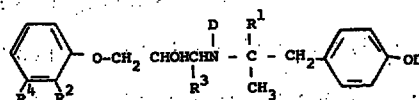


wherein R^2 and R^4 are as defined in claim 1, is reacted with a compound of the formula VI



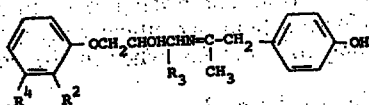
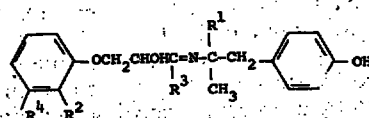
wherein R^1 and R^3 are as defined in claim 1.

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

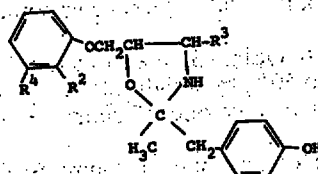


each D, which may be the same or different is hydrogen or a labile group D_1 or D_2 but are not both hydrogen, D_1 and D_2 being groups which may be replaced by hydrogen in a known manner.

46. A process for the preparation of a compound as defined in claim 1, which comprises reducing a Schiff's base of the formula VIII or, when R^1 is hydrogen, of formula IX

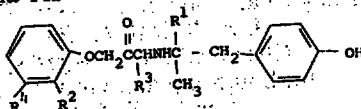


or, when R^1 is hydrogen, a cyclic tautomer of formula X corresponding to the compound of formula IX



wherein R^1 , R^2 , R^3 and R^4 are as defined in claim 1, it being possible for the compounds IX and X to be present simultaneously.

47. A process for the preparation of a compound as defined in claim 1, which comprises reducing a compound of formula XI





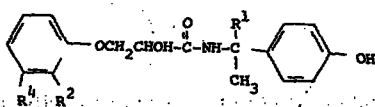
wherein R¹, R², R³ and R⁴ are as defined in claim 1.

48. A process for the preparation of a compound as defined in claim 1, wherein, in a compound of formula XII



wherein R¹, R³ and R⁴ are as defined in claim 1, and X² is a residue transformable into R² as defined in claim 1, X² is transformed into R² by methods known *per se*.

49. A process for the preparation of a compound as defined in claim 1, which comprises reducing the keto group to a methylene group in a keto compound of formula



where R¹, R² and R⁴ are as defined in claim 1.

50. A process according to any one of claims 41-49, in which the compound is prepared in the form of the free base.

51. A process according to any one of claims 41-49 in which the compound is prepared in the form of a salt.

52. A process according to any one of claims 41-49, in which the compound is prepared in the form of a therapeutically acceptable salt.

53. A process according to any one of claims 41-52, in which the compound is prepared in the form of a mixture of isomers.

54. A process according to any one of claims 41-53, in which an individual isomer is isolated.

55. A process according to any one of claims 41-53, in which the compound is obtained as a racemic mixture.

56. A process according to any one of claims 41-53, in which an optically active isomer is isolated.

57. A process according to any one of claims 41-56, in which a compound as defined in claim 9 or 10 is prepared.

58. A process according to any one of claims 41-56 in which a compound as defined in claim 11 or 12 is prepared.

59. A process according to any one of claims 41-49, substantially as hereinbefore described with reference to any one of the Examples 1-19.

60. A compound obtained by a process according to any one of claims 41-59.

61. A compound obtained by a process according to claim 57.

62. A compound obtained by a process according to claim 58.

63. A pharmaceutical preparation comprising a compound according to any one of claims 1-40 or 59-61 together with a pharmaceutically acceptable carrier or diluent.

64. A preparation according to claim 63, wherein the compound comprises 0.1 to 95% by weight of the preparation.

65. A preparation according to claim 63, in a form suitable for administration by injection wherein the compound comprises 0.5% to 20% by weight of the preparation.

66. A preparation according to claim 65, for parenteral application which comprises an aqueous solution of a water soluble salt of the compound in an amount of 0.5-10% by weight of the preparation.

67. A preparation according to claim 63, in a form suitable for oral administration wherein the compound comprises 0.2% to 50% by weight of the preparation.

68. A preparation according to any one of claims 63-67, wherein the compound is as defined in claim 9 or 10 or 61.

69. A preparation according to any one of claims 63-67, wherein the compound is as defined in claim 11 or 12 or 62.

70. A preparation according to claim 63, substantially as hereinbefore described with reference to any one of the Examples 20-23.

71. A method of blocking the β -receptors of the heart of a mammal excluding man which comprises administering to the mammal a compound according to any one of claims 1-40, or 59-61 or a preparation according to any one of claims 63-70.

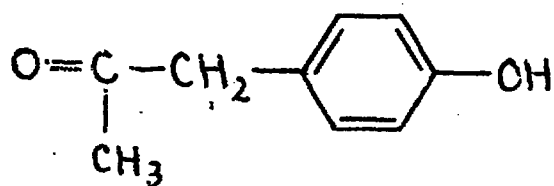
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ERRATUM

SPECIFICATION NO 1518689

Page 6, line 42, *after formula insert*THE PATENT OFFICE
26 February 1980

Bas 74096/1