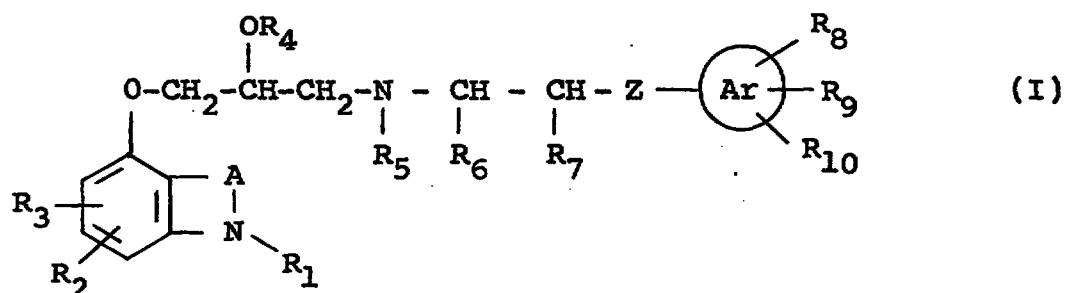


Heterocyclic oxypropanolamine derivatives, processes
for their preparation and medicaments containing these
compounds

The present invention concerns new heterocyclic
 5 oxypropanolamine derivatives of the general formula I



in which R_1 signifies hydrogen, a lower alkyl, aralkyl
 or lower alkanoyl group, R_2 and R_3 , which can be the
 same or different, each signify hydrogen, a lower alkyl,
 10 hydroxyalkyl, alkoxycarbonyl or alkanoyloxyalkyl group,
 as well as together an alkylene radical, R_4 signifies
 hydrogen, a lower alkanoyl group or an aroyl group,
 R_5 signifies hydrogen, a lower alkyl group or an aralkyl
 group, R_6 signifies hydrogen or a lower alkyl group, R_7
 15 signifies hydrogen, a hydroxyl group or a lower alkyl
 group, Z signifies a valency bond, a methylene group,
 an oxygen or sulphur atom, Ar signifies a carbocyclic
 aryl radical or a pyridyl radical, R_8 , R_9 and R_{10} ,
 which can be the same or different, each signify
 20 hydrogen, halogen, a hydroxyl group, a lower alkanoyl
 group, a lower alkyl group, a lower alkenyl group, a

lower alkoxy group, an aralkoxy group, an allyloxy group, a lower alkylthio group, an aminocarbonyl group, an aminosulphonyl group, a lower alkanoylamino group or R_8 and R_9 together a lower alkylenedioxy group or R_8 together with R_7 also a $-\text{CH}_2-\text{O}-$ group and A signifies the group X_1-Y_1 , in which X_1 signifies a methylene or $-\text{NR}_{11}$ radical, whereby R_{11} signifies hydrogen or a lower alkyl group and Y_1 a methylene radical or the group $>\text{C} = \text{Q}$, whereby Q stands for oxygen or sulphur, or the group $\text{X}_2=\text{Y}_2$, in which X_2 and Y_2 can be the same or different and each stands for a nitrogen atom or $=\overset{|}{\text{C}}\text{R}_{12}$ groups, whereby R_{12} represents hydrogen, a lower alkyl or alkoxy carbonyl group, whereby, in the case in which $\text{X}_2=\text{Y}_2$ represents a $-\text{CH}=\text{N}-$ group and R_1 an alkyl or aralkyl group, because of the ability of indazoles to tautomerise, this can also be localised on the nitrogen atom standing for Y_2 , with the proviso that in each case Y_1 is connected with the radical $=\text{N}-\text{R}_1$ of the general formula I, whereby for case that Q signifies an oxygen atom or $\text{X}_2=\text{Y}_2$ an $-\text{CR}_{12}=\text{CR}_{12}-$ group, either the two radicals R_2 and R_3 cannot simultaneously be hydrogen atoms or R_7 and R_8 together must form a $-\text{CH}_2-\text{O}-$ bridge, as well as their pharmacologically acceptable salts.

Since the compounds of the formula I possess asymmetric carbon atoms, the subject of the invention is also the optically-active forms and racemic mixtures of these compounds.

The compounds of the formula I and their pharmacologically acceptable salts possess, in the case of low toxicity, outstanding vasodilatory properties which manifest themselves essentially in a lowering of the blood pressure; furthermore, an inhibition of adrenergic β -receptors is observed. Therefore, the compounds according to the invention are especially suitable for the treatment and prophylaxis of cardiac and circulatory diseases.

10 In published German Patent Specifications Nos. 19 48 507; 21 13 379; 22 30 426; 26 19 164; 26 51 574; 27 00 193 and 28 30 211, as well as in Swiss Patent Specification No. 483 423, are described and claimed compounds of similar structure and action. By changing
15 of the heterocyclic phenolic part, as well as of the aminopropoxy side chain, a surprising improvement of action was achieved.

By a lower alkyl group of the substituents R_1 , R_2 , R_3 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} and R_{12} are to be
20 understood straight-chained or branched groups with 1 to 4 carbon atoms, such as e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl or n-hexyl radicals. However, the methyl or ethyl group especially comes into question. The alkylene radical possibly
25 formed by the substituents R_2 and R_3 together has 3 - 4, preferably 3 carbon atoms.

By alkenyl groups are to be understood unsaturated

hydrocarbon radicals with up to 6 C-atoms, especially the allyl and methylvinyl radical.

Hydroxyalkyl groups of the substituents R_2 and R_3 contain 1 - 4 carbon atoms; the 2-hydroxyethyl
5 and the hydroxymethyl radical is preferred.

Alkoxy groups of the substituents R_8 , R_9 and R_{10} contain 1 - 6, preferably 1 - 4 carbon atoms, such as e.g. the methoxy, ethoxy, propoxy, butoxy or pentoxy group. The methoxy, ethoxy and propoxy group are
10 preferred.

As alkoxycarbonyl groups of the substituents R_2 , R_3 and R_{12} , there come into question especially the methoxycarbonyl and ethoxycarbonyl group.

Alkylthio groups of the substituents R_8 , R_9 and R_{10} are groups with 1 - 6, preferably 1 - 4 carbon
15 atoms. The methylmercapto radical is preferred.

Alkanoyl radicals of the substituents R_1 , R_4 , R_8 , R_9 and R_{10} , as well as the alkanoyl part of the alkanoyloxyalkyl groups in the definitions of the
20 substituents R_2 and R_3 and of the alkanoylamino radicals of the substituents R_8 , R_9 and R_{10} contain 1 - 8, preferably 1 - 5 carbon atoms, whereby their alkyl groups can be straight-chained or branched. The formyl, acetyl or the pivaloyl radical are preferred. As alkanoyloxy-
25 alkyl groups, alkanoyloxymethyl groups are especially preferred.

By an aroyl group in the definition of the

substituent R_4 is preferably to be understood the benzoyl radical, which can be substituted one or more times by halogen, alkyl groups with 1 - 4 carbon atoms or alkoxy groups with 1 - 4 carbon atoms.

5 By an aralkyl group in the definition of the substituents R_1 and R_5 , as well as by an aralkoxy group in the definition of the substituents R_8 , R_9 and R_{10} , are to be understood radicals which, as aryl part, have a phenyl or naphthyl radical and, as alkyl part, a
10 straight-chained or branched, saturated hydrocarbon chain with 1 - 4 carbon atoms. The benzyl radical is especially preferred.

The carbocyclic radical Ar can be a phenyl or also a naphthyl radical, whereby the phenyl radical is
15 especially preferred.

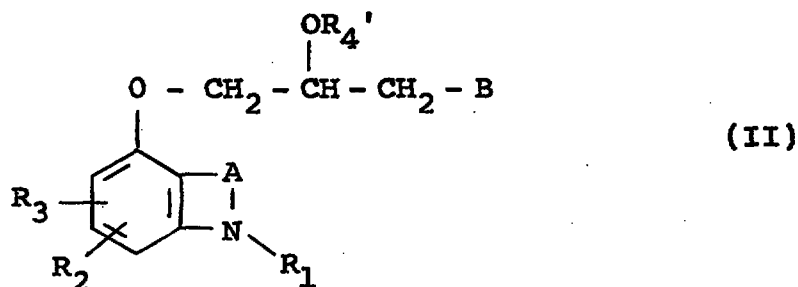
As lower alkylenedioxy radical jointly formed by the substituents R_8 and R_9 , there preferably come into question the methylenedioxy and ethylenedioxy group.

The symbol A in general formula I has, in partic-
20 ular, the meaning that, as heterocycles, there are to be understood benzimidazolin-2-one, benzimidazolin-2-thione, benzimidazole, benztriazole, indole, indoline and indazole.

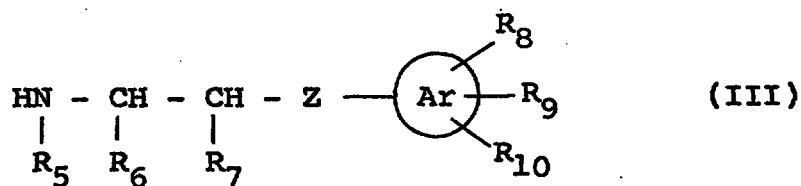
By halogen in the sense of the invention is under-
25 stood fluorine, chlorine, bromine and iodine, especially fluorine, chlorine and bromine.

The preparation of the new compounds of the general formula I is characterised in that, in per se known manner, one either

a) reacts a compound of the formula II

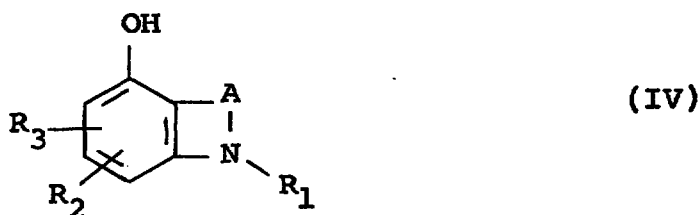


in which R_1 , R_2 , R_3 and A have the above-mentioned meaning, B represents a reactive group and R_4' has the
 5 above-given meaning for R_4 or, together with B, represents a valency bond, with a compound of the general formula III

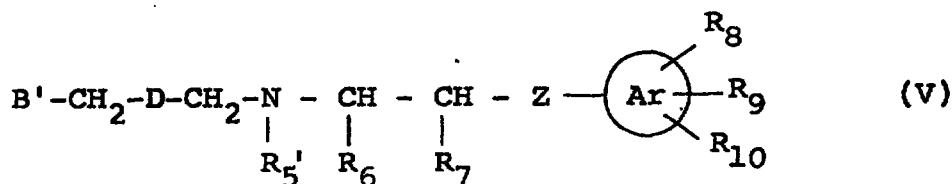


in which R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , Z and Ar have the
 10 above-given meaning, or

b) reacts a compound of the formula IV

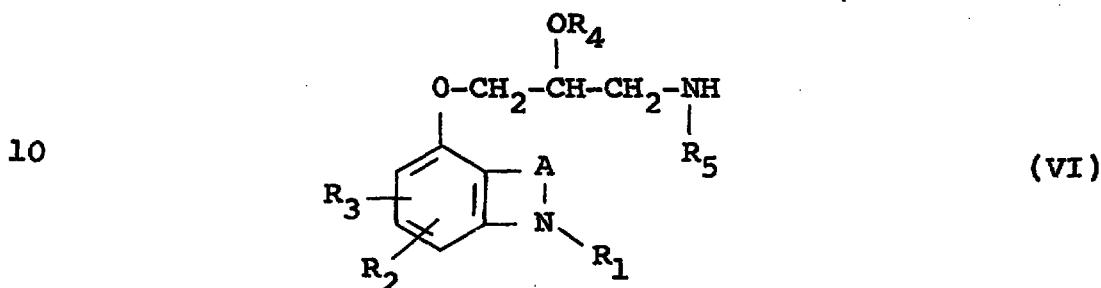


in which R_1 , R_2 , R_3 and A have the given meaning, with a compound of the general formula:-

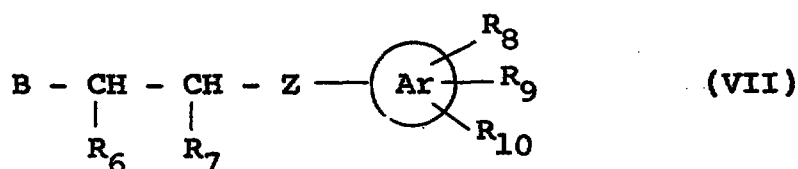


in which R_6 , R_7 , R_8 , R_9 , R_{10} , Z and Ar have the above-given meaning, B' represents a reactive group, D stands for $>CO-$ or $>CH-OR_4$ group, whereby R_4 has the above-given meaning for R_4 or also, together with B', signifies a valency bond and R_5 has the above-given meaning for R_5 or also, together with B', can represent a single bond, and, if D signifies the $>C=O$ group, subsequently reduces;

c) reacts a compound of the formula IV

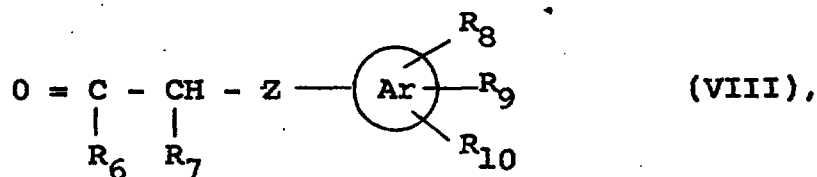


in which R_1 , R_2 , R_3 , R_4 , R_5 and A have the above-given meaning, with a compound of the formula VII



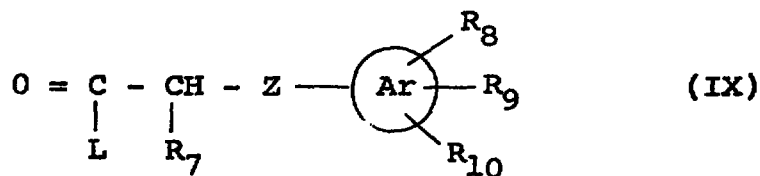
15 in which B, R_6 , R_7 , R_8 , R_9 , R_{10} , Z and Ar have the given meaning, or

d) hydrogenates a mixture of a compound of formula VI with a compound of the formula VIII



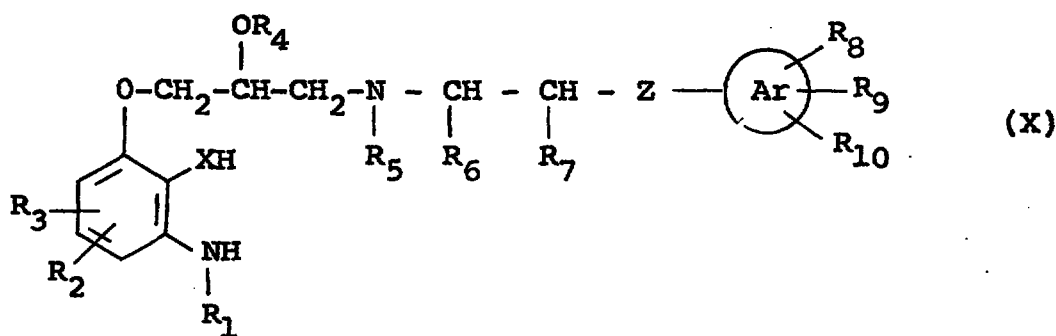
in which R_6 , R_7 , R_8 , R_9 , R_{10} , Z and Ar have the given meanings, or

e) reacts a compound of the formula VI with a compound of the formula IX



in which R_7 , R_8 , R_9 , R_{10} , Z and Ar have the given meaning and L represents a reactive residue, and subsequently reduces the amide obtained, or

f) reacts a compound of the formula X



in which R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , Z and Ar have the given meaning, XX_1 or HX_2 represent, for the case in which A signifies the group X_1-Y_1 , a compound in which $\text{X} = \text{X}_1$, with a compound of the general formula XIa



in which Y_1 has the above-given meaning, L_1 signifies a hydrogen atom, the hydroxyl group or a reactive residue T and L_2 a hydrogen atom or a reactive residue T, or, for the case in which the group $\text{X}_2 = \text{Y}_2$, a compound in

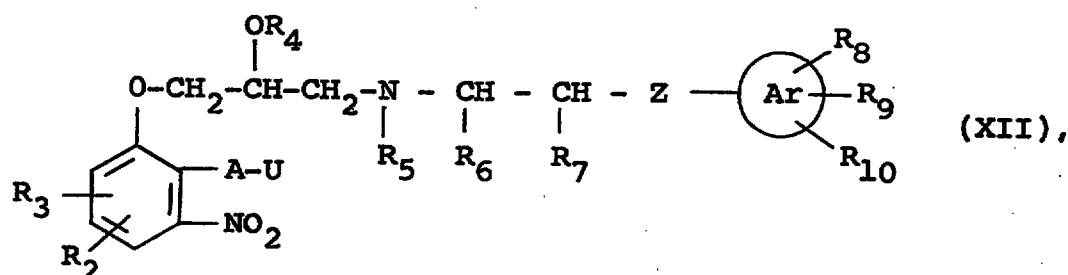
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which $X = HX_2$, with a compound of the general formula XIb



in which L_1 and Y_2 have the above-given meaning, L_2' represents a hydrogen atom or a reactive residue T and L_3 a hydrogen atom or, together with L_2' , an oxygen atom, and cyclises; or

g) reduces and cyclises a compound of the formula XII



10 in which $R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, Z, A$ and Ar have the given meaning and U represents a group which can be split off, and possibly subsequently, in a compound obtained of the general formula I, converts one of the radicals $R_1, R_2, R_3, R_4, R_5, R_8, R_9, R_{10}$ or R_{12} according to usual methods into another radical $R_1, R_2, R_3, R_4, R_5, R_8, R_9, R_{10}$ or R_{12} defined by the claim above and, if desired, converts the compounds obtained into their pharmacologically acceptable salts.

Reactive residues B in compounds of the general formulae II and VII, as well as B' in compounds of the general formula V, are, in particular, acid residues, e.g. of hydrohalic acids and sulphonic acids. Chlorides, mesyloxy and tosyloxy radicals are especially preferred.

Reactive residues L in compounds of the general formula IX are, in particular, acid residues, e.g. of hydrohalic acids or hydrazoic acid or of lower alkane carboxylic acids, lower alkoxy or aryloxy groups, amino or imidazolyl groups. Chlorides, azides and imidazolyl residues are especially preferred.

The reactive residues T and U in compounds of the formulae XIa, XIb and XII stand for all residues which can be nucleophilically substituted. Such residues are preferably halogen atoms, such as chlorine or bromine, amino, imidazolyl, lower alkoxy, lower acyloxy, phenoxy groups, mercapto and lower alkoxythiocarbonyl groups. For example, as compounds of the general formula XIa, carbonyl halides, urea, N,N'-carbonyl-diimidazole, as well as for the case in which Q stands for sulphur, thiocarbonyl halides, thiourea or also xanthogenates, can be used. Compounds of the general formula XIa can also be prepared in situ in the reaction solution from other compounds, e.g. carbon disulphide in alkaline solution. As compounds of the general formula XIb, there come into question, for example, carboxylic acids, such as formic acid or acetic acid, carboxylic acid

esters or also carboxylic acid halides. However, compounds of general formula XIb can also be prepared in situ in the reaction mixture from other compounds, e.g. inorganic nitrite in aqueous mineral acid, lower alkyl
5 nitrous acid esters in organic solvents.

The processes according to the invention are preferably carried out in a solvent inert under the reaction conditions, e.g. water, methanol, ethanol, n-butanol, dioxan, dimethylformamide or hexamethyl-
10 phosphoric acid triamide, optionally in the presence of an acid-binding agent. The reactions can also be achieved by mixing of the reaction components without solvents. The reactions are carried out at room temperature or with heating, optionally under a protective
15 gas atmosphere.

The reduction of the group $>C=O$ standing for D possibly to be carried out preferably takes place by catalytic hydrogenation with noble metal or nickel catalysts or by means of complex metal hydrides, such
20 as e.g. sodium borohydride.

The hydrogenation of an amine of the formula VI with a carbonyl compound of the formula VIII according to process d) is carried out in a suitable solvent (e.g. methanol) in the presence of a catalyst (e.g.
25 Raney nickel).

The reduction of the amides obtained according to process e) preferably takes place by means of complex metal hydrides, e.g. lithium aluminium hydride.

The starting compounds used in the processes according to the invention are, as a rule, compounds known from the literature. New compounds are generally obtained analogously to the processes described for the preparation of these known compounds. Thus, for example, the amines of the general formula III can be prepared by reaction of haloalkyl nitriles with corresponding phenols, naphthols or aryl compounds (e.g. chloroacetonitrile and phenol) and subsequent hydrogenation in the presence of ammonia.

The amines of the general formula VI can be obtained from the corresponding (2,3-epoxypropoxy) derivatives by reaction with liquid ammonia.

Reactive compounds of the general formula VII, e.g. *p*-toluenesulphonic acid esters, are, as a rule, prepared from the corresponding phenols, naphthols, aryl or pyridyl compounds by reaction with haloalcohols and subsequent esterification with *p*-toluenesulphonic acid.

The carbonyl compounds of the general formula VIII and the reactive acid derivatives of the general formula IX are obtained e.g. from corresponding phenols, naphthols, aryl and pyridyl compounds by reaction with suitable haloalkyl compounds.

The conversion optionally to be carried out subsequently of one of the substituents R_1 , R_2 , R_3 , R_4 , R_5 , R_8 , R_9 , R_{10} or R_{12} in compounds of the general formula I into another radical R_1 , R_2 , R_3 , R_4 , R_5 , R_8 , R_9 , R_{10} or

R_{12} defined in the claims, there come into question, for example, the subsequent acylation of an OH group to an alkanoyloxy or aroyloxy group, the reduction of an alkoxycarbonyl group to a hydroxymethyl radical, the hydrolysis of an alkanoyloxymethyl group to a hydroxymethyl radical, the reduction of an alkanoyloxymethyl group to a methyl substituent or the splitting off of a benzyl group.

The esterification of a hydroxyl group standing for $-OR_4$ can take place in per se usual manner by reaction with an acid halide or acid anhydride, optionally in the presence of an acid-binding agent, such as e.g. pyridine or triethylamine.

The reduction possibly to be carried out of compounds of the general formula I, in which R_2 and/or R_3 represent an alkoxycarbonyl or an alkanoyloxymethyl group, to compounds of the formula I, in which R_2 and/or R_3 represent a hydroxymethyl or methyl substituent, expediently takes place by means of complex metal hydrides, such as e.g. lithium aluminium hydride, or by catalytic hydrogenation by means of noble metal catalysts or Raney nickel.

The hydrolysis of alkanoyloxymethyl groups R_2 and/or R_3 in compounds of the general formula I to hydroxymethyl radicals R_2 and/or R_3 can take place in per se known manner under acidic or alkaline conditions.

The splitting off of a benzyl group represented

by R_1 and R_5 or contained in R_8 , R_9 or R_{10} takes place, for example, by hydrogenation in the presence of noble metal catalysts.

For the conversion of the compounds of the formula I into their pharmacologically acceptable salts, one preferably reacts these in an organic solvent with an inorganic or organic acid, e.g. hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, acetic acid, citric acid, maleic acid or benzoic acid.

The compounds of the formula I according to the invention can be obtained in the form of a racemic mixture. The separation of the racemate into the optically-active forms takes place according to known methods via the diastereomeric salts. As active acids, there can mainly be used tartaric acid, malic acid, camphoric acid and camphorsulphonic acid.

For the preparation of medicaments, the compounds of the formula I are mixed in per se known manner with suitable pharmaceutical carrier materials, aroma, flavouring and colouring materials and formed, for example, as tablets or dragees or, with the addition of appropriate adjuvants, suspended or dissolved in water or oil, e.g. olive oil.

The new compounds of the formula I according to the invention can be administered enterally or parenterally in liquid or solid form. As injection medium, it is preferred to use water which contains the additives

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conventional in injection solutions, such as stabilisation agents, solubilising agents or buffers. Additives of this kind are e.g. tartrate and citrate buffers, ethanol, complex formers (such as ethylenediamine-tetraacetic acid and its non-toxic salts), high molecular polymers (such as liquid polyethylene oxide) for viscosity regulation. Solid carrier materials are e.g. starch, lactose, mannitol, methyl cellulose, talc, highly-dispersed silicic acids, high molecular fatty acids (such as stearic acid), gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats and solid high molecular polymers (such as polyethylene glycols); compositions suitable for oral administration can, if desired, contain flavouring and/or sweetening agents.

The dosage administered depends upon the age, the state of health and the weight of the recipient, the extent of the disease, the nature of further treatments possibly carried out simultaneously, the frequency of the treatments and the nature of the desired action. Usually, the daily dosage of the active compounds amounts to 0.1 - 50 mg./kg. of body weight. Normally, 0.5 - 40 and preferably 1.0 - 20 mg./kg./day in one or more administrations per day are effective in order to achieve the desired results.

Besides the compounds set out in the following Examples, in the scope of the present Application are

also preferred:

- 4-{2-hydroxy-3-[2-(2,6-dimethoxyphenoxy)-ethylamino]-propoxy}-7-methyl-3-propyl-2-benzimidaxolinone.
- 4-{2-hydroxy-3-[2-(2-allyloxyphenoxy)-ethylamino]-propoxy}-6-methylindole.
- 4-{2-hydroxy-3-[2-(2-methylthiophenoxy)-ethylamino]-propoxy}-1-formylindoline.
- 4-{2-hydroxy-3-[2-(2-sulphamylphenoxy)-ethylamino]-propoxy}-indazole
- 10 4-{2-hydroxy-3-[2-(3,4-ethylenedioxyphenyl)-ethylamino]-propoxy}-indazole
- 4-{2-hydroxy-3-[2-(3-ethoxy-4-methoxyphenyl)-ethylamino]-propoxy}-indazole
- 4-{2-hydroxy-3-[2-(3,4,5-trimethoxyphenyl)-ethylamino]-propoxy}-indazole
- 15 4-{2-hydroxy-3-[2-(3-methoxy-4-hydroxyphenyl)-ethylamino]-propoxy}-indazole
- 4-{2-hydroxy-3-[2-(3-hydroxy-4-n-butoxyphenyl)-ethylamino]-propoxy}-indazole
- 20 4-{2-hydroxy-3-[2-(3,4-dihydroxyphenyl)-ethylamino]-propoxy}-indazole
- 4-{2-hydroxy-3-[3-(3,4-dimethoxyphenyl)-propylamino]-propoxy}-indazole
- 4-{2-hydroxy-3-[1-(3,4-dimethoxyphenyl)-propyl-2-amino]-propoxy}-indazole
- 25 1-methyl-4-{2-hydroxy-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propoxy}-indazole

1-methyl-4-{2-hydroxy-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propoxy}-indoline.

4-{2-hydroxy-3-[2-(2-methoxyphenylthio)-ethylamino]-propoxy}-1-formylindoline

5 4-{2-benzoyloxy-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propoxy}-indazole

4-{2-hydroxy-3-[1-(3,4-dihydroxyphenyl)-2-amino-1-propanol]-propoxy}-6-methylindole.

The following Examples show some of the numerous
10 process variations which can be used for the synthesis of the compounds according to the invention. However, they are not to represent a limitation of the subject matter of the invention.

Example 1.

15 4-{2-Hydroxy-3-[2-(2-methoxyphenoxy)-propylamino]-propoxy}-7-methyl-2-benzimidazolinone hydrochloride.

12.3 g. 2,3-Diamino-1-{2-hydroxy-3-[2-methoxyphenoxy)-propylamino]-propoxy}-4-methylbenzene trihydrochloride are dissolved in 500 ml. water. One passes
20 phosgene into this solution for 45 minutes at room temperature, then flushes with nitrogen and filters off with suction. The crystallisate is recrystallised from 300 ml. ethanol/200 ml. methanol, with the addition of active charcoal. There are obtained 5.0 g. (46% of
25 theory) of title compound of m.p. 228 - 230°C.

The starting material necessary herefor is obtained as follows:

30.5 g. 2,3-Dinitro-1-(2,3-epoxypropoxy)-4-methyl-
benzene and 32.6 g. N-benzyl-2-(2-methoxyphenoxy)-
propylamine are boiled under reflux for 3 hours in 500 ml.
ethanol. The reaction mixture is hydrogenated over 10 g.
5 10% palladium-charcoal in 1 l. ethanol at 50°C. and
30 bar. One frees from catalyst, acidifies with 2N
hydrochloric acid, clarifies with active charcoal and
evaporates to dryness. One obtains 59 g. 2,3-diamino-1-
{2-hydroxy-3-[2-(2-methoxyphenoxy)-propylamino]-propoxy}-
10 4-methylbenzene trihydrochloride.

Example 2.

Analogously to Example 1, from phosgene and the
correspondingly substituted 1-propoxy-2,3-diamino-
benzene derivative are obtained

designation	Yield % of theory	m.p. °C. (solvent)
a) 4-[2-hydroxy-3-(3,4-dimethoxy-phenethylamino)-propoxy]-7-methyl-2-benzimidazolinone hydrochloride from 2,3-diamino-1-[2-hydroxy-3-(3,4-dimethoxyphenethylamino)-propoxy]-4-methylbenzene trihydrochloride	42	204 - 206 (isopropanol/ methanol)

designation	yield % of theory	m.p. °C. (solvent)
b) 4-{2-hydroxy-3-[2-(2-hydroxy-phenoxy)-ethylamino]-propoxy}-7-methyl-2-benzimidazolinone hydrochloride from 2,3-diamino-1-{2-hydroxy-3-[2-(2-hydroxyphenoxy)-ethylamino]-propoxy}-4-methyl-benzene trihydrochloride	67	262 - 263 (methanol/ water)
c) 6,7-dimethyl-4-{2-hydroxy-3-[2-(2-methylphenoxy)-ethylamino]-propoxy}-2-benzimidazolinone hydrochloride from 2,3-diamine-4,5-dimethyl-1-{2-hydroxy-3-[2-(2-methylphenoxy)-ethylamino]-propoxy}-benzene trihydrochloride	34	273 - 274 (methanol/ water)
d) 4-{2-hydroxy-3-[2-(2-methoxyphenoxy)-ethylamino]-propoxy}-7-methyl-2-benzimidazolinone hydrochloride from 2,3-diamino-1-{2-hydroxy-3-[2-(2-methoxyphenoxy)-ethylamino]-propoxy}-4-methyl-benzene trihydrochloride	62	202 - 203 (ethanol/ methanol)
e) 4-[2-hydroxy-3-(benzo[b]-1,4-dioxan-2-yl-methylamino)-propoxy]-2-benzimidazolinone hydrochloride from 2,3-diamino-1-[2-hydroxy-3-(benzo[b]-1,4-dioxan-1-yl-methylamino)-propoxy]-benzene trihydrochloride		
f) 4-[2-hydroxy-3-(2-phenoxy-ethylamino)-propoxy]-7-methyl-2-benzimidazolinone hydrochloride from 2,3-diamino-1-[2-hydroxy-3-(2-phenoxy-ethylamino)-propoxy]-4-methyl-benzene trihydrochloride	56	231 - 233 (ethanol/ methanol)

designation	yield % of theory	m.p. °C. (solvent)
g) 4-[2-hydroxy-3-(2-phenoxy-ethylamino)-propoxy]-6-methyl-2-benzimidazolinone hydrochloride from 2,3-diamino-1-[2-hydroxy-3-(2-phenoxyethylamino)-propoxy]-5-methyl-benzene trihydrochloride	52	250 - 252 (ethanol/ methanol)
h) 4-{2-hydroxy-3-[2-(2-methoxyphenoxy)-ethylamino]-propoxy}-6-methyl-2-benzimidazolinone hydrochloride from 2,3-diamino-1-{2-hydroxy-3-[2-(2-methoxyphenoxy)-ethylamino]-propoxy}-5-methyl-benzene trihydrochloride	87	213 - 215 (ethanol)
i) 4-[2-hydroxy-3-(3,4-dimethoxyphenethylamino)-propoxy]-6-methyl-2-benzimidazolinone hydrochloride from 2,3-diamino-1-[2-hydroxy-3-(3,4-dimethoxyphenethylamino)-propoxy]-5-methyl-benzene trihydrochloride	15	260 - 262 (ethanol)
j) 4-{2-hydroxy-3-[2-(2-allyloxyphenoxy)-ethylamino]-propoxy}-7-methyl-2-benzimidazolinone hydrochloride from 2,3-diamino-1-{2-hydroxy-3-[2-(2-allyloxyphenoxy)-ethylamino]-propoxy}-4-methyl-benzene trihydrochloride		

Example 3.

4-{2-Hydroxy-1-[2-(2-methoxyphenoxy)-propylamino]-propoxy}-7-methylbenzimidazole hydrochloride.

14.7 g. 2,3-Diamino-1-{2-hydroxy-3-[2-(2-methoxy-

phenoxy)-propylamino]-propoxy}-4-methylbenzene trihydrochloride are boiled under reflux for 3 hours in 80 ml. formic acid. One clarifies with active charcoal and evaporates to dryness. The resultant formyl compound is saponified in 50 ml. 2N hydrochloric acid at boiling temperature. After evaporating to dryness, the residue is recrystallised from 50 ml. ethanol with the addition of active charcoal. One obtains 5.6 g. (41% of theory) of title compound of m.p. 103 - 105°C.

10 Example 4.

Analogously to Example 3, from formic acid and the correspondingly substituted 1-propoxy-2,3-diaminobenzene derivative, one obtains

designation	Yield % of theory	m.p. °C. (solvent)
a) 4-[2-hydroxy-3-(3,4-dimethoxyphenethylamino)-propoxy]-benzimidazole hydrochloride from 2,3-diamino-1-[2-hydroxy-3-(3,4-dimethoxyphenethylamino)-propoxy]-benzene trihydrochloride	50	255 - 256 (ethanol)

designation	Yield % of theory	m.p. °C. (solvent)
b) 4-[2-hydroxy-3-(3,4-dimethoxy-phenethylamino)-propoxy]-7-methylbenzimidazole hydrochloride from 2,3-diamino-1-[2-hydroxy-3-(3,4-dimethoxyphenethylamino)-propoxy]-4-methyl-benzene trihydrochloride	20	254 - 256 (ethanol/ water)
c) 4-{2-hydroxy-3-[2-(2-hydroxy-phenoxy)-ethylamino]-propoxy}-7-methylbenzimidazole hydrochloride from 2,3-diamino-1-{2-hydroxy-3-[2-(2-hydroxyphenoxy)-ethylamino]-propoxy}-4-methylbenzene trihydrochloride	92	229 - 231 (water)
d) 6,7-dimethyl-4-{2-hydroxy-3-[2-(2-methylphenoxy)-ethylamino]-propoxy}-benzimidazole hydrochloride from 2,3-diamino-4,5-dimethyl-1-{2-hydroxy-3-[2-(2-methylphenoxy)-ethylamino]-propoxy}-benzene trihydrochloride	17	106 - 109 (ethanol/ ethyl acetate)
e) 4-{2-hydroxy-3-[2-(2-methoxy-phenoxy)-ethylamino]-propoxy}-7-methylbenzimidazole hydrochloride from 2,3-diamino-1-{2-hydroxy-3-[2-(2-methoxyphenoxy)-ethylamino]-propoxy}-4-methylbenzene trihydrochloride	62	219 - 221 (ethanol/ methanol)
f) 4-{2-hydroxy-3-[2-(2-methoxy-phenoxy)-ethylamino]-propoxy}-benzimidazole hydrochloride from 2,3-diamino-1-{2-hydroxy-3-[2-(2-methoxyphenoxy)-ethylamino]-propoxy}-benzene trihydrochloride	17	115 - 118 (ethanol)

designation	Yield % of theory	m.p. °C. (solvent)
g) 4-[2-hydroxy-3-(4-phenyl-2-butylamino)-propoxy]-benzimidazole hydrochloride from 2,3-diamino-1-[2-hydroxy-3-(4-phenyl-2-butylamino)-propoxy]-benzene trihydrochloride	77	amorphous
h) 4-[2-hydroxy-3-(2-phenoxyethylamino)-propoxy]-benzimidazole hydrochloride from 2,3-diamino-1-[2-hydroxy-3-(2-phenoxyethylamino)-propoxy]-benzene trihydrochloride	10	amorphous
i) 4-[2-hydroxy-3-(benzo[b]-1,4-dioxan-2-yl-methylamino)-propoxy]-benzimidazole hydrochloride from 2,3-diamino-1-[2-hydroxy-3-(benzo[b]-1,4-dioxan-2-yl-methylamino)-propoxy]-benzene trihydrochloride	19	105 - 107 (isopropanol/ methanol)
j) 4-{2-hydroxy-3-[2-(2-methoxyphenoxy)-propylamino]-propoxy}-benzimidazole hydrochloride from 2,3-diamino-1-{2-hydroxy-3-[2-(2-methoxyphenoxy)-propylamino]-propoxy}-benzene trihydrochloride	59	115 - 118 (ethanol)

Example 5.

4-[2-Hydroxy-3-(3,4-dimethoxyphenethylamino)-propoxy]-2,7-dimethylbenzimidazole hydrochloride.

14.6 g. 2,3-Diamino-1-[2-hydroxy-3-(3,4-dimethoxyphenethylamino)-propoxy]-4-methylbenzene trihydrochloride are heated under reflux for 3 hours in 50 ml. glacial

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acetic acid. It is clarified with active charcoal and completely evaporated. The residue is boiled under reflux for 2 hours in 40 ml. 2N hydrochloric acid and subsequently evaporated to dryness. One purifies over
5 a silica gel column with chloroform/methanol 8:2 as elution agent and finally crystallises from 100 ml. ethanol 2.2 g. (19% of theory) of title compound of m.p. 167 - 169°C.

The diamine used as starting material is obtained
10 as follows:

26.0 g. N-Benzyl-3,4-dimethoxyphenethylamine and 24.3 g. 2,3-dinitro-1-(2,3-epoxypropoxy)-4-methylbenzene are boiled under reflux for 4 hours in 300 ml. ethanol. The reaction mixture is diluted with
15 300 ml. ethanol and hydrogenated at 50°C. and 30 bar pressure over 7.0 g. 10% palladium-charcoal. One frees from catalyst, acidifies with 2N hydrochloric acid and, after evaporation, obtains the amorphous diamine salt.

20 Example 6.

Analogous to Example 5, from acetic acid and correspondingly substituted 1-propoxy-2,3-diaminobenzene derivatives is obtained:

	Designation	Yield % of theory	m.p. °C. (solvent)
5 10	a) 4-{2-hydroxy-3-[2-(2-propoxy- phenoxy)-ethylamino]-propoxy}- 2,7-dimethylbenzimidazole hydrochloride from 2,3-diamino-4-methyl-1-{2- hydroxy-3-[2-(2-propoxy- phenoxy)-ethylamino]- propoxy}-benzene trihydro- chloride	44	143 - 145 (alcohol/ ethyl acetate)
15 20	b) 4-{2-hydroxy-3-[2-(2-methoxy- 4-methylphenoxy)-ethylamino]- propoxy}-2,7-dimethylbenz- imidazole hydrochloride from 2,3-diamino-4-methyl-1-{2- hydroxy-3-[2-(2-methoxy-4- methylphenoxy)-ethylamino]- propoxy}-benzene trihydro- chloride	62	165 - 167 (ethanol)

Example 7.

25 4-[2-Hydroxy-3-(3,4-dimethoxyphenethylamino)-propoxy]-
benzotriazole hydrochloride.

14.1 g. 2,3-Diamino-1-[2-hydroxy-3-(3,4-dimethoxy-
phenethylamino)-propoxy]-benzene trihydrochloride are
dissolved in 10 ml. water and 3.5 ml. glacial acetic
30 acid, cooled to 5°C. and mixed with 2.07 g. sodium
nitrite in 3.6 ml. water. One subsequently stirs for
2.5 hours at room temperature. The resultant sodium
chloride is precipitated out by the addition of 480 ml.
isopropanol. After filtration, it is evaporated,
35 purified over a silica gel column (elution agent
methanol/ethyl acetate 2:1 v/v), mixed with ethereal

hydrochloric acid and crystallised from ethanol. One obtains 1.26 g. (10% of theory) of title compound of m.p. 123 - 124°C.

Example 8.

5 Analogously to Example 7, from sodium nitrite and the correspondingly substituted 1-propoxy-2,3-diaminobenzene derivative are obtained:

designation	Yield % of theory	m.p. °C. (solvent)
a) 4-[2-hydroxy-3-(3,4-dimethoxyphenethylamino)-propoxy]-7-methylbenzotriazole hydrochloride from 2,3-diamino-1-[2-hydroxy-3-(3,4-dimethoxyphenethylamino)-propoxy]-4-methylbenzene trihydrochloride	16	184 - 186 (isopropanol)
b) 4-{2-hydroxy-3-[2-(2-methoxyphenoxy)-ethylamino]-propoxy}-benzotriazole hydrochloride from 2,3-diamino-1-{2-hydroxy-3-[2-(2-methoxyphenoxy)-ethylamino]-propoxy}-benzene trihydrochloride	25	113 - 115 (methanol/ ether)
c) 4-{2-hydroxy-3-[2-(2-methoxyphenoxy)-ethylamino]-propoxy}-7-methylbenzotriazole hydrochloride from 2,3-diamino-1-{2-hydroxy-3-[2-(2-methoxyphenoxy)-ethylamino]-propoxy}-4-methylbenzene trihydrochloride	48	109 - 111 (isopropanol/ methanol)

	designation	Yield % of theory	m.p. °C. (solvent)
5 10	d) 4-{2-hydroxy-3-[2-(2-hydroxy- phenoxy)-ethylamino]-propoxy}- benzotriazole hydrochloride from 2,3-diamino-1-{2-hydroxy-3-[2- (2-hydroxyphenoxy)-ethylamino]- propoxy}-benzene trihydrochloride	14	200 - 203 (ethanol/ methanol)
15	e) 4-[2-hydroxy-3-(2-methoxyphen- ethylamino)-propoxy]-benzo- triazole hydrochloride from 2,3-diamino-1-[2-hydroxy-3-(2- methoxyphenethylamino)-propoxy]- benzene trihydrochloride	21	82 - 85 (ethanol/ ethyl acetate)
20 25	f) 4-{2-hydroxy-3-[2-(2-methoxy- phenoxy)-propylamino]-propoxy}- benzotriazole hydrochloride from 2,3-diamino-1-{2-hydroxy-3-[2- (2-methoxyphenoxy)-propyl- amino]-propoxy}-benzene tri- hydrochloride	62	amorphous
30	9) 4-{2-hydroxy-3-[2-(2-allyloxy- phenoxy)-propylamino]-propoxy}- benzotriazole hydrochloride from 2,3-diamino-1-{2-hydroxy-3-[2- (2-allyloxyphenoxy)-propyl- amino]-propoxy}-benzene tri- hydrochloride	15	143 - 145 (ethanol/ ethyl acetate)

Example 9.

35 4-[2-Hydroxy-3-(3,4-dimethoxyphenethylamino)-propoxy]-
benzimidazoline-2-thione hydrochloride.

17.4 g. 2,3-Diamino-1-[2-hydroxy-3-(3,4-dimethoxy-
phenethylamino)-propoxy]-benzene trihydrochloride are
dissolved in 450 ml. chloroform and 50 ml. ethanol and
40 mixed dropwise at room temperature with 3.2 ml. thio-
phosgene in 30 ml. chloroform.

After 2 hours, it is treated with active charcoal and evaporated to dryness. One purifies over a silica gel column (chloroform/methanol 8:2) and obtains 10 g. (62% of theory) of uniform product. After taking up in isopropanol and mixing with ethereal hydrochloric acid, the title compound of m.p. 108 - 110°C. is precipitated out with ethyl acetate.

Example 10.

Analogously to Example 9, from thiophosgene and the correspondingly substituted 1-propoxy-2,3-diaminobenzene derivative are obtained:

designation	Yield % of theory	m.p. °C. (solvent)
15 a) 4-[2-hydroxy-3-(3,4-dimethoxyphenethylamino)-propoxy]-7-methyl-benzimidazoline-2-thione hydrochloride 20 from 2,3-diamino-1-[2-hydroxy-3-(3,4-dimethoxyphenethylamino)-propoxy]-4-methylbenzene trihydrochloride		
25 b) 4-{2-hydroxy-3-[2-(2-methoxyphenoxy)-propylamino]-propoxy}-7-methyl-benzimidazoline-2-thione benzoate 30 from 2,3-diamino-1-{2-hydroxy-3-[2-(2-methoxyphenoxy)-propylamino]-propoxy}-4-methylbenzene trihydrochloride	14	169 - 170 (ethanol/ether)
35 c) 4-{2-hydroxy-3-[2-(2-methylphenoxy)-ethylamino]-propoxy}-benzimidazoline-2-thione hydrochloride from 2,3-diamino-1-{2-hydroxy-3-[2-(2-methylphenoxy)-ethylamino]-propoxy}-benzene trihydrochloride		

Example 11.

4-{2-Hydroxy-3-[2-(2-hydroxyphenoxy)-ethylamino]-propoxy}-6,7-cyclopentenobenzimidazolin-2-one hydrochloride.

- 5 One passes phosgene for 1 hour into the solution of 6.5 g. (0.0175 mol) 4,5-diamino-6-{2-hydroxy-3-[2-(2-hydroxyphenoxy)-ethylamino]-propoxy}-indane hydrochloride in 250 ml. water and 100 ml. tetrahydrofuran, subsequently flushes thoroughly with nitrogen, filters,
- 10 takes up the precipitate in a dilute aqueous sodium hydroxide solution, washes with methylene chloride, adjusts the aqueous phase to pH 7, extracts with methylene chloride, evaporates, takes up in acetone and precipitates out the hydrochloride with ethereal hydrochloric acid.
- 15 One obtains 2.8 g. of the title compound (36% of theory) as amorphous salt of m.p. 145 - 155°C.

The diamino compound used as starting product can be prepared in the following manner:

- 20 The condensation of 5-amino-6-(2,3-epoxypropoxy)-4-nitroindane and N-benzyl-2-(2-benzyloxyphenoxy)-ethylamine gives 5-amino-6-{3-[N-benzyl-2-(2-benzyloxyphenoxy)-ethylamino]-2-hydroxypropoxy}-4-nitroindane as oil.

- 25 By hydrogenation and hydrogenolytic debenzylation of the above compound as hydrochloride in methanolic solution over 10% palladium-charcoal one obtains 4,5-

diamino-6-{2-hydroxy-3-[2-(2-hydroxyphenoxy)-ethyl-amino]-propoxy}-indane hydrochloride of m.p. 193 - 195°C.

Example 12.

4-{3-[2-(3,4-dimethoxyphenyl)-ethylamino]-2-hydroxy-
5 propoxy}-6,7-cyclopentenobenzimidazolin-2-one hydro-
chloride.

Analogous to the process described in Example 1,
one obtains from phosgene and 4,5-diamino-6-{3-[2-(3,4-
dimethoxyphenyl)-ethylamino]-2-hydroxypropoxy}-indane
10 hydrochloride the title compound as hydrochloride of
m.p. 193 - 195°C.

The diamine compound used as starting product
can be prepared in the following manner:

By reaction of 5-amino-6-(2,3-epoxypropoxy)-4-
15 nitroindane and 3,4-dimethoxyphenethylamine one obtains
5-amino-6-{3-[2-(3,4-dimethoxyphenyl)-ethylamino]-2-
hydroxypropoxy}-4-nitroindane of m.p. 230 - 236°C.
(as hydrochloride).

The hydrogenation of the above compound in
20 methanolic solution over platinum dioxide gives 4,5-
diamino-6-{3-[2-(3,4-dimethoxyphenyl)-ethylamino]-2-
hydroxypropoxy}-indane, which is isolated as amorphous
hydrochloride.

Example 13.

25 4-[2-Hydroxy-3-(2-phenoxypropylamino)-propoxy]-6,7-
cyclopentenobenzimidazolin-2-one hydrochloride.

Analogous to the process described in Example 1,

one obtains from phosgene and 4,5-diamino-6-[2-hydroxy-3-(2-phenoxypropylamino)-propoxy]-indane hydrochloride, the title compound as hydrochloride of m.p. 261 - 263°C.

The diamino compound used as starting product can
5 be prepared as follows:

The condensation of 5-amino-6-(2,3-epoxypropoxy)-4-nitroindane and N-benzyl-2-phenoxypropylamine gives 5-amino-6-[3-(N-benzyl-2-phenoxypropylamino)-2-hydroxy-propoxy]-4-nitroindane of m.p. 70 - 80°C. (as amorphous
10 hydrochloride).

By hydrogenation and hydrogenolytic debenzylation of above compound in methanolic solution over 10% palladium-charcoal, one obtains 4,5-diamino-6-[2-hydroxy-3-(2-phenoxypropylamino)-propoxy]-indane hydro-
15 chloride of m.p. 153 - 155°C.

Example 14.

4-{2-Hydroxy-3-[2-(2-hydroxyphenoxy)-ethylamino]-propoxy}-6,7-cyclopentenobenzimidazole.

A mixture of 4.1 g. (0.01 mol) 4,5-diamino-6-{2-
20 hydroxy-3-[2-(2-hydroxyphenoxy)-ethylamino]-propoxy}-indane hydrochloride and 35 ml. formamide is heated to reflux for 40 minutes, evaporated, mixed with water, extracted with methylene chloride, the extract evaporated and triturated with ethyl acetate. One obtains
25 1.3 g. of title compound of m.p. 182 - 183°C.

Example 15.

4-{2-Hydroxy-3-[(1-methyl-3-phenyl)-propylamino]-propoxy}-6-methylindole benzoate.

4.9 g. 4-(2,3-Epoxypropoxy)-6-methylindole (see
5 published Federal Republic of Germany Patent Application
No. 25 08 251) and 3.7 g. (1-methyl-3-phenyl)-propyl-
amine are stirred for 18 hours in 50 ml. n-butanol,
evaporated in a vacuum and shaken up with 1N lactic
acid and ether. After precipitation of the base with
10 dilute aqueous sodium hydroxide solution, it is
extracted with ether/ethyl acetate 1:1 and purified
chromatographically over silica gel with methylene
chloride/methanol 9:1. The base obtained is dissolved
in ethyl acetate, mixed with an equivalent amount of
15 benzoic acid and filtered off with suction. One
obtains 2.0 g. (18% of theory) 4-{2-hydroxy-3-[(1-
methyl-3-phenyl)-propylamino]-propoxy}-6-methylindole
benzoate of m.p. 119 - 122°C.

Example 16.

20 In a manner analogous to that described in
Example 15, one obtains:

designation	Yield % of theory	m.p. °C. (solvent)
a) 4-{2-hydroxy-3-[2-(3,4-dimethoxy-phenyl)-ethylamino]-propoxy}-6-methylindole benzoate from 4-(2,3-epoxypropoxy)-6-methylindole and 2-(3,4-dimethoxy-phenyl)-ethylamine	27	147 - 148 (ethyl acetate)
b) 4-{2-hydroxy-3-[2-(2-pyridinyl)-ethylamino]-propoxy}-6-methylindole di-p-nitrobenzoate from 4-(2,3-epoxypropoxy)-6-methylindole and 2-(2-pyridinyl)-ethylamine	16	146 (methanol)
c) 4-[2-hydroxy-3-(2-phenoxyethyl-amino)-propoxy]-6-methylindole benzoate from 4-(2,3-epoxypropoxy)-6-methylindole and 2-phenoxyethylamine	16	123 - 125 (ether)
d) 4-{2-hydroxy-3-[(1-methyl-2-phenyl)-ethylamino]-propoxy}-6-methylindole benzoate from 4-(2,3-epoxypropoxy)-6-methylindole and (1-methyl-2-phenyl)-ethylamine	20	125 - 128 (ethyl acetate)
e) 4-{2-hydroxy-3-[2-(2-methoxyphenoxy)-ethylamino]-propoxy}-6-methylindole from 4-(2,3-epoxypropoxy)-6-methylindole and 2-(2-methoxyphenoxy)-ethylamine	19	123 - 125 (ethyl acetate)
f) 4-{2-hydroxy-3-[2-(4-carbamidophenoxy)-ethylamino]-propoxy}-6-methylindole from 4-(2,3-epoxypropoxy)-6-methylindole and 2-(4-carbamidophenoxy)-ethylamine	19	128 - 130 (methanol)

designation	Yield % of theory	m.p. °C. (solvent)
g) 4-[2-hydroxy-3-(benzo[b]-1,4-dioxan-2-yl-methylamino)-propoxy]-6-methylindole p-chlorobenzoate from 4-(2,3-epoxypropoxy)-6-methylindole and 2-(aminomethyl)-1,4-benzo[b]-dioxan	14	168 - 170 (ethyl acetate)
h) 4-[2-hydroxy-3-(2-phenoxy-N-benzylpropylamino)-propoxy]-6-methylindole from 4-(2,3-epoxypropoxy)-6-methylindole and 2-phenoxy-N-benzylpropylamine	95	oil
i) 4-{2-hydroxy-3-[2-(2-methoxyphenoxy)-N-benzylpropylamino]-propoxy}-6-methylindole from 4-(2,3-epoxypropoxy)-6-methylindole and 2-(2-methoxyphenoxy)-N-benzylpropylamine	95	oil
j) 4-{2-hydroxy-3-[2-(5-carbamido-2-pyridoxy)-N-benzylethylamino]-propoxy}-6-methylindole from 4-(2,3-epoxypropoxy)-6-methylindole and 2-(5-carbamido-2-pyridoxy)-N-benzylethylamine	76	oil
k) 4-{2-hydroxy-3-[2-(2-benzyloxyphenoxy)-ethylamino]-propoxy}-6-methylindole from 4-(2,3-epoxypropoxy)-6-methylindole and 2-(2-benzyloxyphenoxy)-ethylamine	16	oil
l) 4-{2-hydroxy-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propoxy}-6-methoxycarbonylindole from 4-(2,3-epoxypropoxy)-6-methoxycarbonylindole and 2-(3,4-dimethoxyphenyl)-ethylamine	59	145 - 147 (isopropanol/ ether)

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	designation	Yield % of theory	m.p. °C. (solvent)
5 10	m) 4-{2-hydroxy-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propoxy}-6-hydroxymethyl-indole from 4-(2,3-epoxypropoxy)-6-hydroxymethylindole and 2-(3,4-dimethoxy-phenyl)-ethylamine	35	60 amorphous
15	n) 4-{2-hydroxy-3-[2-(2-allyloxyphenoxy)-ethylamino]-propoxy}-6-methylindole from 4-(2,3-epoxypropoxy)-6-methylindole and 2-(allyloxyphenoxy)-ethylamine	36	125 (methanol)

20 Example 17.

4-[2-Hydroxy-3-(2-phenoxypropylamino)-propoxy]-6-methylindole p-chlorobenzoate.

One hydrogenates 8 g. 4-[2-hydroxy-3-(2-phenoxy-N-benzylpropylamino)-propoxy]-6-methyl indole (preparation see Example 16 h) in 200 ml. methanol and 5 ml. triethylamine at room temperature and 1 bar hydrogen pressure over 2 g. 10% palladium-charcoal, filters, evaporates, dissolves the remaining residue in 50 ml. ethyl acetate and mixes with the calculated amount of p-chlorobenzoic acid. After filtering off with suction and recrystallisation, one obtains 4.3 g. 4-[2-hydroxy-3-(2-phenoxypropylamino)-propoxy]-6-methylindole p-chlorobenzoate of m.p. 134 - 136°C.

Example 18.

In a manner analogous to that described in Example 17, one obtains:

5	designation	Yield % of theory	m.p. °C. (solvent)
10	a) 4-{2-hydroxy-3-[2-(2-methoxy-phenoxy)-propylamino]-propoxy}-6-methylindole from 4-{2-hydroxy-3-[2-(2-methoxy-phenoxy)-N-benzylpropylamino]-propoxy}-6-methylindole (see Example 16 i)	58	104 - 106 (ethyl acetate)
15	b) 4-{2-hydroxy-3-[2-(5-carbamido-2-pyridoxy)-ethylamino]-propoxy}-6-methylindole di-p-chloro-benzoate from 4-{2-hydroxy-3-[2-(5-carbamido-2-pyridoxy)-N-benzylethylamino]-propoxy}-6-methylindole (see Example 16j)	10	141 - 143 (isopropanol)
25	c) 4-{2-hydroxy-3-[2-(2-hydroxy-phenoxy)-ethylamino]-propoxy}-6-methylindole benzoate from 4-{2-hydroxy-3-[2-(2-benzyloxy-phenoxy)-ethylamino]-propoxy}-6-methylindole (see Example 16k)	72	85 - 90 (methanol)
30			

Example 19.

4-{2-Hydroxy-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propoxy}-6-hydroxymethylindole.

One drops a solution of 5.0 g. 4-{2-hydroxy-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propoxy}-6-methoxycarbonylindole (preparation see Example 16l) in 150 ml. absolute tetrahydrofuran to a suspension of 2.3 g.

lithium aluminium hydride in 50 ml. absolute tetrahydrofuran, stirs for 12 hours at room temperature, decomposes, while cooling, with sodium chloride solution and 10N aqueous sodium hydroxide solution, filters, washes with tetrahydrofuran and evaporates. The residue is purified over a silica gel column with methylene chloride/methanol 9:1. The base is precipitated out with ether and filtered off with suction. There are obtained 2.4 g. 4-{2-hydroxy-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propoxy}-6-hydroxymethylindole of sinter point 60°C. (51% of theory).

Example 20.

2-Ethoxycarbonyl-4-[2-hydroxy-3-(3-phenylpropylamino)-propoxy]-6-methylindole.

3.6 g. 2-Ethoxycarbonyl-4-(2,3-epoxypropoxy)-6-methylindole (published Federal Republic of Germany Patent Application No. 26 26 890) and 1.76 g. 3-phenylpropylamine are stirred at room temperature in 5 ml. hexamethylphosphoric acid triamide until the reaction is complete, taken up in water and ether, the ether phase extracted with 1N tartaric acid and the base liberated with potassium carbonate solution. After shaking out with ether, drying and evaporating, there remain 2.0 g. 2-ethoxycarbonyl-4-[2-hydroxy-3-(3-phenylpropylamino)-propoxy]-6-methylindole of m.p. 127°C. (33% of theory).

Preparation of the acetate:

1.4 g. 2-Ethoxycarbonyl-4-[2-hydroxy-3-(3-phenylpropylamino)-propoxy]-6-methylindole are dissolved in 10 ml. ethyl acetate with gentle warming, mixed with 0.2 ml. acetic acid and, after cooling, filtered off with suction. One obtains 1.3 g. 2-ethoxycarbonyl-4-[2-hydroxy-3-(3-phenylpropylamino)-propoxy]-6-methylindole as acetate of m.p. 155°C.

Example 21.

In a manner analogous to that described in Example 20, one obtains:

	designation	Yield % of theory	m.p. °C. (solvent)
15	a) 2-ethoxycarbonyl-4-{2-hydroxy-3-[(1-methyl-3-phenyl)-propylamino]-propoxy}-6-methylindole from	28	133 - 134 (ethyl acetate)
20	2-ethoxycarbonyl-4-(2,3-epoxypropoxy)-6-methylindole and (1-methyl-3-phenyl)-propylamine		
25	b) 2-ethoxycarbonyl-4-{2-hydroxy-3-[2-(2-pyridinyl)-ethylamino]-propoxy}-6-methylindole benzoate from	20	129 - 131 (ethyl acetate)
	2-ethoxycarbonyl-4-(2,3-epoxypropoxy)-6-methylindole and 2-(2-pyridinyl)-ethylamine		
30	c) 2-ethoxycarbonyl-4-{2-hydroxy-3-[2-(4-pyridinyl)-ethylamino]-propoxy}-6-methylindole from	32	133 - 134 (ether)
35	2-ethoxycarbonyl-4-(2,3-epoxypropoxy)-6-methylindole and 2-(4-pyridinyl)-ethylamine		

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designation	Yield % of theory	m.p. °C. (solvent)
d) 2-ethoxycarbonyl-4-[2-hydroxy-3-(2-phenoxyethylamino)-propoxy]-6-methylindole benzoate from 2-ethoxycarbonyl-4-(2,3-epoxy-propoxy)-6-methylindole and 2-phenoxyethylamine	24	147 (ethyl acetate)
e) 2-ethoxycarbonyl-4-{2-hydroxy-3-[(1-methyl-2-phenoxy)-ethylamino]-propoxy}-6-methylindole benzoate from 2-ethoxycarbonyl-4-(2,3-epoxy-propoxy)-6-methylindole and 1-methyl-2-phenoxyethylamine	23	135 - 137 (ether)
f) 2-ethoxycarbonyl-4-{2-hydroxy-3-[2-(2-methoxyphenoxy)-ethylamino]-propoxy}-6-methylindole from 2-ethoxycarbonyl-4-(2,3-epoxy-propoxy)-6-methylindole and 2-(2-methoxyphenoxy)-ethylamine	21	145 - 147 (ethyl acetate)
g) 2-ethoxycarbonyl-4-{2-hydroxy-3-[2-(4-carbamidophenoxy)-ethylamino]-propoxy}-6-methylindole acetate from 2-ethoxycarbonyl-4-(2,3-epoxy-propoxy)-6-methylindole and 2-(4-carbamidophenoxy)-ethylamine	18	160 - 165 (ethyl acetate)
h) 2-ethoxycarbonyl-4-[2-hydroxy-3-(benzo[b]-1,4-dioxan-2-yl-methylamino)-propoxy]-6-methylindole from 2-ethoxycarbonyl-4-(2,3-epoxy-propoxy)-6-methylindole and 2-(aminomethyl)-1,4-benzo[b]-dioxan	25	135 - 137 (ether)

Example 22.

4-[2-Hydroxy-3-(3-phenylpropylamino)-propoxy]-indazole.

5 g. 4-(2,3-epoxypropoxy)-indazole and 25 g. 3-phenylpropylamine are stirred for 20 hours at 50°C.

- 5 One distils off excess amine in a vacuum, triturates the residue with ether, filters off with suction and recrystallises from ethyl acetate. There are obtained 4.3 g. 4-[2-hydroxy-3-(3-phenylpropylamino)-propoxy]-indazole of m.p. 122 - 124°C. (50% of theory).

10 Example 23.

4-{2-Hydroxy-3-[(1-methyl-2-phenoxy)-ethylamino]-propoxy}-indazole.

- 5 g. 4-(2,3-Epoxypropoxy)-indole and 4.17 g. 1-methyl-2-phenoxyethyl)-amine are heated in 10 ml. 1,2-dimethoxyethane for 20 hours at 50°C. After trituration with acetone, suction filtration and recrystallisation from isopropanol, one obtains 3.7 g. 4-{2-hydroxy-3-[(1-methyl-2-phenoxy)-ethylamino]-propoxy}-indazole of m.p. 175 - 177°C. (41% of theory).

20 Example 24.

2-Benzyl-2-{2-hydroxy-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propoxy}-indazole.

- 17 g. 2-Benzyl-4-(2,3-epoxypropoxy)-indazole and 20 g. 2-(3,4-dimethoxyphenyl)-ethylamine are stirred for 20 hours at 70°C. One dissolves off excess amine by stirring with ether and filters off with suction. There are obtained 19.1 g. of title compound of m.p. 101 - 102°C. (74% of theory).

Example 25.

In a manner analogous to that described in Example 24, one obtains:

5	designation	yield % of theory	m.p. °C. (solvent)
10	2-benzyl-4-{2-hydroxy-3-[2-(2-benzyloxyphenoxy)-ethylamino]-propoxy}-indazole from 2-benzyl-4-(2,3-epoxypropoxy)-indazole and 2-(2-benzyloxyphenoxy)-ethylamine	91	81 - 83 (ethanol)

Example 26.

15 2-Benzyl-4-[2-hydroxy-3-(2-phenoxyethylamino)-propoxy]-indazole.

5 g. 2-Benzyl-4-(2,3-epoxypropoxy)-indazole and 2.6 g. 2-phenoxyethylamine are heated for 48 hours to 50°C. in 10 ml. 1,2-dimethoxyethane. One evaporates, dissolves in methylene chloride and purifies chromatographically over a silica gel column with the elution agents methylene chloride/ethyl acetate 8:2 and ethyl acetate. After evaporation, there are obtained 4.2 g. of the title compound as viscous oil.

Example 27.

25 In a manner analogous to that described in Example 26, one obtains:

designation	yield % of theory	m.p. °C. (solvent)
a) 2-benzyl-4-{2-hydroxy-3-[2-(2-methoxy-phenoxy)-ethylamino]-propoxy}-indazole from 2-benzyl-4-(2,3-epoxypropoxy)-indazole and 2-(2-methoxy-phenoxy)-ethylamine	52	oil
b) 2-benzyl-4-{2-hydroxy-3-[2-(2-methoxy-phenoxy)-propylamino]-propoxy}-indazole from 2-benzyl-4-(2,3-epoxypropoxy)-indazole and 2-(2-methoxy-phenoxy)-propylamine	83	oil
c) 2-benzyl-4-{2-hydroxy-3-[2-(4-pyridyl)-ethylamino]-propoxy}-indazole from 2-benzyl-4-(2,3-epoxypropoxy)-indazole and 2-(4-pyridyl)-ethylamine	51	oil
d) 2-benzyl-4-[2-hydroxy-3-(benzo[b]-1,4-dioxan-2-yl-methyl-amino)-propoxy]-indazole from 2-benzyl-4-(2,3-epoxypropoxy)-indazole and 2-(aminomethyl)-1,4-benzo[b]-dioxan	47	oil
e) 2-benzyl-4-{2-hydroxy-3-[2-(3,4-ethylenedioxyphenyl)-ethylamino]-propoxy}-indazole from 2-benzyl-4-(2,3-epoxypropoxy)-indazole and 2-(3,4-ethylene-dioxyphenyl)-ethylamine	76	165 - 168 (isopropanol)
f) 2-benzyl-4-(2-hydroxy-3-[2-(3-ethoxy-4-methoxyphenyl)-ethyl-amino]-propoxy)-indazole from 2-benzyl-4-(2,3-epoxypropoxy)-indazole and 2-(3-ethoxy-4-methoxyphenyl)-ethylamine	85	oil

Designation	yield % of theory	m.p. °C. (solvent)
g) 2-benzyl-4-{2-hydroxy-3-[2-(3,4,5-trimethoxyphenyl)-ethylamino]-propoxy}-indazole from 2-benzyl-4-(2,3-epoxypropoxy)-indazole and 2-(3,4,5-trimethoxyphenyl)-ethylamine	88	oil
h) 2-benzyl-4-(2-hydroxy-3-[2-(4-benzyloxy-3-methoxyphenyl)-ethylamino]-propoxy)-indazole from 2-benzyl-4-(2,3-epoxypropoxy)-indazole and 2-(4-benzyloxy-3-methoxyphenyl)-ethylamine	78	96 - 98 (methanol)
i) 2-benzyl-4-{2-hydroxy-3-[2-(3-benzyloxy-4-butoxyphenyl)-ethylamino]-propoxy}-indazole from 2-benzyl-4-(2,3-epoxypropoxy)-indazole and 2-(3-benzyloxy-4-butoxyphenyl)-ethylamine	80	oil
j) 2-benzyl-4-{2-hydroxy-3-[2-(3,4-dibenzyloxyphenyl)-ethylamino]-propoxy}-indazole from 2-benzyl-4-(2,3-epoxypropoxy)-indazole and 2-(3,4-dibenzyloxyphenyl)-ethylamine	84	oil
k) 2-benzyl-4-{2-hydroxy-3-[2-(2-pyridoxy)-ethylamino]-propoxy}-indazole from 2-benzyl-4-(2,3-epoxypropoxy)-indazole and 2-(2-pyridoxy)-ethylamine	64	oil

Example 28.

2-Benzyl-4-{2-hydroxy-3-[2-(2-hydroxyphenoxy)-N-benzyl-propylamino]-propoxy}-indazole.

4.2 g. 2-Benzyl-4-(2,3-epoxypropoxy)-indazole and
 5 3.85 g. 2-(2-hydroxyphenoxy)-N-benzylpropylamine are
 boiled under reflux for 4 d in 30 ml. dioxan under
 nitrogen. One evaporates, dissolves in methylene
 chloride and purifies chromatographically over a silica
 gel column. After evaporation, there remain 5.8 g. of
 10 the title compound as viscous oil (72% of theory).

Example 29.

In a manner analogous to that described in
 Example 28, one obtains:

15	designation	yield % of theory	m.p. °C. (solvent)
20	2-benzyl-4-{2-hydroxy-3-[2-(4-acetamidophenoxy)-N-benzyl-ethylamino]-propoxy}-indazole from 2-benzyl-4-(2,3-epoxypropoxy)-indazole and 2-(4-acetamidophenoxy)-N-benzylethylamine	67	oil

The 2-benzyl-4-(2,3-epoxypropoxy)-indazole used as
 starting product can be obtained as follows:

25 One introduces, with cooling and under a nitrogen
 atmosphere, 9.2 g. sodium hydride-paraffin (55 - 60%
 suspension) into a solution of 47.1 g. 2-benzyl-4-

hydroxyindazole in 250 ml. dimethylformamide, after the ending of H₂ evolution adds 19 ml. epibromohydrin dropwise thereto and stirs for 16 hours at room temperature. Thereafter, one stirs into 1.5 l. water, extracts with methylene chloride and purifies over a silica gel column with methylene chloride/methanol 99:1. After trituration with ligroin:ether (1:1 v/v) and suction filtration, there are obtained 30 g. 2-benzyl-4-(2,3-epoxypropoxy)-indazole of m.p. 66 - 68°C. (51% of theory).

Example 30.

4-{2-Hydroxy-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propoxy}-indazole.

19.1 g. 2-Benzyl-4-{2-hydroxy-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propoxy}-indazole (preparation Example 24) are hydrogenated in 700 ml. methanol and 22.4 ml. concentrated hydrochloric acid over 2 g. 10% palladium-charcoal. After filtering off with suction, it is evaporated, dissolved in water, rendered alkaline with aqueous sodium hydroxide solution and extracted with methylene chloride. The organic phase is evaporated, trituated with ether and filtered off with suction.

There are obtained 9.1 g. of title compound of m.p. 118 - 119°C. (59% of theory).

One obtains the hydrochloride of m.p. 157 - 159°C.
by dissolving in ethanol and adding ethereal hydro-
chloric acid.

In a manner analogous to that described above,
one obtains:

5

designation	Yield % of theory	m.p. °C. (solvent)
a) 4-{2-hydroxy-3-[2-(2-hydroxy- phenoxy)-ethylamino]-propoxy}- indazole from 2-benzyl-4-{2-hydroxy-3-[2-(2- benzyloxyphenoxy)-ethylamino]- propoxy}-indazole (see Example 25)	41	137 - 139 (isopropanol)
b) 4-[2-hydroxy-3-(2-phenoxyethyl- amino)-propoxy]-indazole from 2-benzyl-4-[2-hydroxy-3-(2- phenoxyethylamino)-propoxy]- indazole (see Example 26)	88	134 - 135 (ethyl acetate)
c) 4-{2-hydroxy-3-[2-(2-methoxy- phenoxy)-ethylamino]-propoxy}- indazole from 2-benzyl-4-{2-hydroxy-3-[2-(2- methoxyphenoxy)-ethylamino]- propoxy}-indazole (see Example 27a)	82	106 - 107 (ethyl acetate)
d) 4-{2-hydroxy-3-[2-(2-methoxy- phenoxy)-propylamino]-propoxy}- indazole from 2-benzyl-4-(2-hydroxy-3-[2-(2- methoxyphenoxy)-propylamino]- propoxy)-indazole (see Example 27b)	58	127 - 128 (ethyl acetate)

designation	yield % of theory	m.p. °C. (solvent)
e) 4-{2-hydroxy-3-[2-(4-pyridyl)-ethylamino]-propoxy}-indazole from 2-benzyl-4-{2-hydroxy-3-[2-(4-pyridyl)-ethylamino]-propoxy indazole (see Example 27c)	72	123 - 125 (ethyl acetate)
f) 4-[2-hydroxy-3-(benzo[b]-1,4-dioxan-2-yl-methylamino)-propoxy]-indazole from 2-benzyl-4-[2-hydroxy-3-(benzo[b]-1,4-dioxan-2-yl-methylamino)-propoxy]-indazole (see Example 27d)	54	142 - 143 (ethyl acetate)
g) 4-{2-hydroxy-3-[2-(2-hydroxyphenoxy)-propylamino]-propoxy}-indazole from 2-benzyl-4-{2-hydroxy-3-[2-(2-hydroxyphenoxy)-N-benzylpropylamino]-propoxy}-indazole (see Example 28)	57	92 - 95 (ethyl acetate)
h) 4-{2-hydroxy-3-[2-(4-acetamidophenoxy)-ethylamino]-propoxy}-indazole from 2-benzyl-4-{2-hydroxy-3-[2-(4-acetamidophenoxy)-N-benzylethylamino]-propoxy}-indazole (see Example 29)	49	130 - 133 (ethanol/ water)
i) 4-{2-hydroxy-3-[2-(3,4-ethylenedioxyphenyl)-ethylamino]-propoxy}-indazole from 2-benzyl-4-{2-hydroxy-3-[2-(3,4-ethylenedioxyphenyl)-ethylamino]-propoxy}-indazole (see Example 27e)	59	125 - 126 (ethyl acetate)

designation	yield % of theory	m.p. °C. (solvent)
j) 4-{2-hydroxy-3-[2-(3-ethoxy-4-methoxyphenyl)-ethylamino]-propoxy}-indazole from 2-benzyl-4-{2-hydroxy-3-[2-(3-ethoxy-4-methoxyphenyl)-ethylamino]-propoxy}-indazole (see Example 27f)	73	118 - 119 (ethyl acetate)
k) 4-{2-hydroxy-3-[2-(3,4,5-trimethoxyphenyl)-ethylamino]-propoxy}-indazole from 2-benzyl-4-{2-hydroxy-3-[2-(3,4,5-trimethoxyphenyl)-ethylamino]-propoxy}-indazole (see Example 27g)	63	171 - 172 (ethyl acetate)
l) 4-{2-hydroxy-3-[2-(4-hydroxy-3-methoxyphenyl)-ethylamino]-propoxy}-indazole from 2-benzyl-4-{2-hydroxy-3-[2-(4-benzyloxy-3-methoxyphenyl)-ethylamino]-propoxy}-indazole (see Example 27h)	57	139 - 141 (isopropanol/ ethyl acetate)
m) 4-{2-hydroxy-3-[2-(4-butoxy-3-hydroxyphenyl)-ethylamino]-propoxy}-indazole from 2-benzyl-4-{2-hydroxy-3-[2-(3-benzyloxy-4-butoxyphenyl)-ethylamino]-propoxy}-indazole (see Example 27i)	55	94 - 97 (ethyl acetate)
n) 4-{2-hydroxy-3-[2-(3,4-dihydroxyphenyl)-ethylamino]-propoxy}-indazole acetate from 2-benzyl-4-{2-hydroxy-3-[2-(3,4-dibenzyloxyphenyl)-ethylamino]-propoxy}-indazole (see Example 27 j)	46	160 - 162 (ethanol)

	designation	yield % of theory	m.p. °C. (solvent)
5 10	o) 4-{2-hydroxy-3-[2-(2-pyridyl- oxy)-ethylamino]-propoxy}- indazole from 2-benzyl-4-{2-hydroxy-3-[2- (2-pyridoxy)-ethylamino]- propoxy}-indazole (see Example 27 <u>k</u>)	52	113 - 115 (ethyl acetate)

Example 31.

4-{2-Hydroxy-3-[1-(3,4-dimethoxyphenyl)-propyl-2-
amino]-propoxy}-indazole.

15 A mixture of 4 g. 2-benzyl-4-(3-amino-2-hydroxy-
propoxy)-indazole and 3 g. 3,4-dimethoxyphenylacetone
is hydrogenated in 100 ml. methanol in the presence of
1.5 g. 10% palladium-charcoal. After take up of 1 mol
hydrogen, 10 ml. concentrated hydrochloric acid are
20 added thereto and shaken until a further 1 mol hydrogen
is taken up.

After suction filtration and evaporation, one
takes up in water and methylene chloride. After
separation of the aqueous phase, it is rendered alkaline
25 and extracted with methylene chloride/methanol 10:1.
After drying and evaporating, the diastereomeric
mixture obtained is recrystallised from ethyl acetate.
There are thus obtained 1.1 g. of fraction A of the
title compound of m.p. 110 - 112°C. (21% of theory).

30 By evaporation of the mother liquor and

89

trituration with ether, there are obtained, after suction filtration, 1.5 g. of fraction B of the title compound of m.p. 66 - 73°C. (29% of theory).

The 2-benzyl-4-(3-amino-2-hydroxypropoxy)-indazole used as starting product can be obtained as follows:

12 g. 2-Benzyl-4-(2,3-epoxypropoxy)-indazole are shaken in an autoclave in 100 ml. liquid ammonia for 8 hours at 50°C. After taking up with ethyl acetate, filtering with suction and subsequently washing, one obtains 9.3 g. of the title compound of m.p. 113 - 115°C. (73% of theory).

Example 31b.

4-{2-Hydroxy-3-[3-(3,4-dimethoxyphenyl)-propylamino]-propoxy}-indazole benzoate.

6.6 g. 4-(3-Amino-2-hydroxypropoxy)-indazole (crude product) are stirred in 80 ml. methylene chloride for 48 hours at room temperature in the presence of 3.1 ml. triethylamine with 5.1 g. 3-(3,4-dimethoxyphenyl)-propionyl chloride. After shaking out with water, drying and evaporating, there remain 9.1 g. 4-{2-hydroxy-3-[3-(3,4-dimethoxyphenyl)-propionamido]-propoxy}-indole (m.p. 148 - 150°C., from nitromethane).

The crude product obtained is stirred in 120 ml. anhydrous tetrahydrofuran with 1.7 g. lithium aluminium hydride under an atmosphere of nitrogen for 26 hours at 60°C. After the usual decomposition and

working up, the oil obtained is purified over a silica gel column (elution agent ethyl acetate:methanol 9:1 - 6:4). After evaporation of the desired fractions, 1.7 g. of colourless oil is obtained. By dissolving
5 in ethanol and adding the calculated amount of benzoic acid, after evaporation and the addition of ether, there are obtained 1.75 g. 4-{2-hydroxy-3-[3-(3,4-dimethoxyphenyl)-propylamino]-propoxy}-indazole benzoate of m.p. 131 - 134°C. (15% of theory).

10 The 4-(3-amino-2-hydroxypropoxy)-indazole used as starting product can be obtained as follows:

5.1 g. 1-Acetyl-4-(3,4-epoxypropoxy)-indazole, dissolved in 50 ml. methanol, are stirred in an autoclave with 250 ml. liquid ammonia for 8 hours at 50°C.
15 One treats the solution obtained with active charcoal, evaporates and obtains 6.6 g. of the title compound as crude product which, without further purification, can be used in the next step.

Example 32.

20 1-Pivaloyl-4-{2-pivaloyloxy-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propoxy}-indazole hydrochloride.

One stirs a mixture of 4.2 g. 4-{2-hydroxy-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propoxy}-indazole hydrochloride (preparation see Example 30), 4.2 ml.
25 pivalic anhydride and 35 ml. pivalic acid for 50 - 60 hours at 75°C. The solid mass obtained is stirred with ligroin. There remain 4.1 g. of the title compound of m.p. 155 - 158°C. (69% of theory).

Example 33.

4-{2-Pivaloyloxy-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propoxy}-indazole.

4.0 g. 1-Pivaloyl-4-{2-pivaloyloxy-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propoxy}-indazole hydrochloride (preparation see Example 32) are heated under reflux for 2.5 hours with 150 ml. isopropylamine. One evaporates, dissolves in ether, shakes with 1N aqueous sodium hydroxide solution and purifies the organic phase chromatographically over a silica gel column (elution agent: methylene chloride/ethyl acetate 1:1. There are obtained 2.7 g. of the title compound as oil (85% of theory).

Example 34.

15 4-{2-Hydroxy-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propoxy}-1-formylindoline benzoate.

2.2 g. 4-(2,3-Epoxypropoxy)-1-formylindoline and 1.8 g. 2-(3,4-dimethoxyphenyl)-ethylamine are stirred at room temperature for 18 hours in 50 ml. n-butanol, evaporated in a vacuum and taken up in ether and 1N lactic acid. The aqueous phase is rendered alkaline with 2N aqueous sodium hydroxide solution and extracted with methylene chloride. After drying and evaporating, there remain 4 g. of crude product. This is purified over a silica gel column with methylene chloride/methanol 95:5. 1.3 g. of purified base are thus obtained which are dissolved

in 50 ml. ethyl acetate and mixed with the equivalent amount of benzoic acid. After suction filtration, there remain 1.3 g. 4-{2-hydroxy-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propoxy}-1-formylindoline benzoate of m.p. 136 - 138°C. (24% of theory).

Example 35.

In a manner analogous to that described in Example 34, one obtains:

10	designation	Yield % of theory	m.p. °C. (solvent)
15	a) 4-{2-hydroxy-3-[2-(4-fluorophenoxy)-ethylamino]-propoxy}-1-formylindoline benzoate from 4-(2,3-epoxypropoxy)-1-formylindoline and 2-(4-fluorophenoxy)-ethylamine	20	121 - 123 (ethyl acetate)
20	b) 4-{2-hydroxy-3-[2-(2-methoxyphenoxy)-propoxy]-1-formylindoline benzoate from 4-(2,3-epoxypropoxy)-1-formylindoline and 2-(2-methoxyphenoxy)-ethylamine	19	78 - 79 (ethyl acetate)
25	c) 4-{2-hydroxy-3-[2-(2-methoxyphenoxy)-N-benzyl-propylamino]-propoxy}-1-formylindoline from 4-(2,3-epoxypropoxy)-1-formylindoline and 2-(2-methoxyphenoxy)-N-benzyl-propylamine	90	oil
30			
35			

	designation	Yield % of theory	m.p. °C. (solvent)
5 10	d) 4-{2-hydroxy-3-[2-(2-benzyl- oxyphenoxy)-N-benzylethyl- amino]-propoxy}-1-formyl- indoline from 4-(2,3-epoxypropoxy)-1- formylindoline and 2-(2- benzyloxyphenoxy)-N-benzyl- ethylamine	95	oil
15	e) 4-[2-hydroxy-3-(2-phenyl- ethylamino)-propoxy]-1- formylindoline from 4-(2,3-epoxypropoxy)-1- formylindoline and 2-phenyl- ethylamine	18	121 - 123 (ethyl acetate)
20 25	f) 4-{2-hydroxy-3-[2-(2-chloro- phenoxy)-ethylamino]- propoxy}-1-formylindoline from 4-(2,3-epoxypropoxy)-1- formylindoline and 2-(2- chlorophenoxy)-ethylamine	15	104 - 107 (ethyl acetate)
30	g) 4-{2-hydroxy-3-[2-(2-methyl- thiophenoxy)-ethylamino]- propoxy}-1-formylindoline from 4-(2,3-epoxypropoxy)-1- formylindoline and 2-(methyl- thiophenoxy)-ethylamine	20	129 - 130 (methanol)

Example 36.

35 4-{2-Hydroxy-3-[2-(2-methoxyphenoxy)-propylamino]-
propoxy}-1-formylindoline benzoate.

One hydrogenates 6.7 g. 4-{2-hydroxy-3-[2-(2-
methoxy)-N-benzylpropylamino]-propoxy}-1-formylindoline

(preparation see Example 35 c) in 250 ml. ethanol and 20 ml. triethylamine at room temperature and 1 bar hydrogen pressure over 2 g. 10% palladium-charcoal, filters, evaporates and dissolves the remaining residue in 50 ml. ethyl acetate and mixes with the equivalent amount of benzoic acid. After suction filtration, one obtains 2.1 g. 4-{2-hydroxy-3-[2-(2-methoxyphenoxy)-propylamino]-propoxy}-1-formylindoline benzoate of m.p. 131 - 133°C. (31% of theory).

10 Example 37.

In a manner analogous to that described in Example 37, one obtains:

15	designation	Yield % of theory	m.p. °C. (solvent)
20	4-{2-hydroxy-3-[2-(2-hydroxyphenoxy)-ethylamino]-propoxy}-1-formylindoline acetate from 4-{2-hydroxy-3-[2-(2-benzyloxyphenoxy)-N-benzylethylamino]-propoxy}-1-formylindoline (see Example 35d)	41	171 - 173 (ethyl acetate)

25 The starting materials needed for the preparation of the above compounds are obtained as follows:

4-(2,3-Epoxypropoxy)-1-formylindoline.

48.6 g. 2-Benzyloxy-6-nitrotoluene, dissolved in 670 ml. dimethylformamide, are mixed with 29.9 g. para-formaldehyde and subsequently 200 ml. 1N potassium

tert.-butylate solution are added thereto dropwise.

After stirring for 1 hour at room temperature, it is stirred into 3 l. ice water and extracted with ether. The ethereal phase is dried with sodium sulphate and
5 evaporated in a vacuum. There remain 62 g. 2-benzyloxy-6-nitrophenylethanol, which is used in the next stage as crude product.

62 g. 2-Benzyloxy-6-nitrophenylethanol are dissolved in 500 ml. anhydrous pyridine and, while
10 cooling to about 10°C., mixed with 47.7 g. *p*-toluene sulphonyl chloride. One allows to increase to room temperature and stirs for about 10 hours for complete reaction. The reaction mixture is stirred into ice water. After suction filtration, washing with water
15 and drying, there remain 74 g. *p*-toluenesulphonic acid 2-(2-benzyloxy-6-nitrophenyl)-ethyl ester of m.p. 96 - 98°C. (86% of theory, referred to 2-benzyloxy-6-nitrotoluene).

74 g. *p*-toluenesulphonic acid 2-(2-benzyloxy-6-
20 nitrophenyl)-ethyl ester are dissolved in 2 l. ethylene glycol monomethyl ether, mixed with 5 g. 10% palladium-active charcoal and hydrogenated at room temperature and 1 bar hydrogen pressure. After removal of the catalyst, it is evaporated and the residue formylated
25 with a mixture of 227 ml. acetic anhydride and 91 ml. formic acid [according to C.W. Huffmann, J. org. Chem., 23, 727(1958)]. After the reaction, it is decomposed

with ice water and extracted with ethyl acetate. The organic phase is neutralised, dried with sodium sulphate and evaporated in a vacuum. The remaining residue is mixed with 320 ml. epichlorohydrin and with
5 173 ml. 2N sodium methylate solution. After stirring overnight, it is evaporated and the residue dissolved in water and ethyl acetate. From the ethyl acetate residue are obtained, by trituration with isopropanol and suction filtration, 15.8 g. 4-(2,3-epoxypropoxy)-
10 1-formylindoline; m.p. 88 - 89°C. (42% of theory).

Example 38.

Tablets were prepared; each tablet contains 10 mg. 4-{2-hydroxy-3-[2-(2-methoxyphenoxy)-ethylamino]-propoxy}-7-methyl-2-benzimidazolinone hydrochloride.
15 The tablets were prepared according to the following formulation:

	4-{2-hydroxy-3-[2-(2-methoxyphenoxy)-ethylamino]-propoxy}-7-methyl-2-benzimidazolinone hydrochloride	10 g.
20	lactose	80 g.
	starch	29 g.
	magnesium stearate	1 g.

The above compound was finely powdered and mixed with lactose and starch. The mixture was granulated
25 in the usual manner. Magnesium stearate was added to the granulate and the mixture was pressed to give 1000 tablets with an individual weight of 0.12 g.

Example 39.

In a manner analogous to that described in Example 23, one obtains:

5	designation	yield % of theory	m.p. °C. (solvent)
10	a) 4-{2-hydroxy-3-[2-(2-allyl- phenoxy)-ethylamino]-propyl}- indazole from 4-(2,3-epoxypropoxy)- indazole and 2-(2-allyl- phenoxy)-ethylamine	47	125 - 126 (ethyl acetate)
15	b) 4-{2-hydroxy-3-[2-(2-allyl- oxyphenoxy)-ethylamino]- propoxy}-indazole from 4-(2,3-epoxypropoxy)- indazole and 2-(2-allyloxy- phenoxy)-ethylamine	45	137 - 139 (ethyl acetate)
20			

Experimental protocol.

Rabbits were narcotised with 26% urethane 5 ml./kg.
A catheter was implanted into the A. femoralis for the
continuous measurement of the arterial blood pressure.
25 The measurement of the blood pressure took place by
means of an electromechanical pressure convertor
(Statham P 23 Db). The impulses were recorded on a
direct recorder and evaluated after calibration with
a mercury manometer.

30 After determination of the initial value, both
neck pulse arteries (A. carotis) were occluded for
2 minutes and, in this way, the blood pressure

temporarily increased (carotid sinus relief reflex - CSR). Subsequently, the test substance was injected i.v. in the lowest test dosage (0.125 mg./kg.) and 8 minutes later the CSR reflex again initiated. At intervals of, in each case, 15 minutes, the test substance was again injected in logarithmically increasing dosage (Factor 2) and the CSR again initiated.

Substances which, under these conditions, weaken the increase of the blood pressure under CSR can be regarded as vasodilatory. For the assessment of the blood pressure-lowering action quality, there was calculated for the test substances the dosage which weakened the CSR reflex by 30 mm.Hg (ED₋₃₀ mm.Hg).

b) Testing for β -blocking activity.

Rabbits were fixed in wooden cages, the heart frequency was obtained from them via insert electrodes and read off on a frequency counting device (measurement time 15 seconds). Via an ear vein there was first injected 1 μ g./kg. of isoprenaline i.v., which brings about an increase of the heart frequency of about 210 beats/min. to about 370 beats/min. Subsequently, the test substances were administered i.v. in increasing dosage (see Method a) and the heart frequency after isoprenaline again read off. The inhibition of the isoprenaline tachycardia is to be regarded as a measure of the β -blockade. The dosage of the test

substances was determined which weakened the increase of isoprenaline by 50% (HD_{50}).

The data from both experiments are given in Table 1. The calculation of the equieffective dosages
5 ($ED_{-30 \text{ mm.Hg}}$ or HD_{50}) was carried out on a logarithmic basis of 4 - 6 or 6 - 10 individual experiments. The dosages calculated from both experiments (HD_{50} and $ED_{-30 \text{ mm.Hg}}$) were compared with one another.

All tested substances possess strong β -blocking
10 properties and, in addition, a marked blood pressure-lowering quality.

Since both actions are desired, the appearance of both effects should be brought about by dosages lying as close together as possible since otherwise the
15 usefulness of a 2nd quality of action (because of relative underdosing) would not be relevant. From a theoretical point of view, a quotient of 1 appears to be optimal. Since, however, clinical experiences are not yet available, all substances with quotients which
20 do not differ too much from 1 are of interest.

Table 1

Vasodilatory and β -blocking activity of the substances according to the invention in comparison with the commercial product PROPRANOLOL = 1-isopropylamino-3-(1-naphthyloxy)-2-propanol

5

10

15

20

25

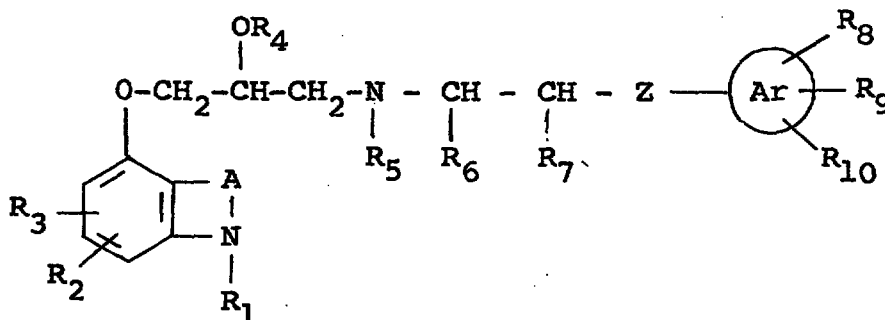
Example No.	ED ₋₃₀ mm.Hg (vasodilat.Act.) (μ g/kg i.v.)	HD ₅₀ (β -blocking Act.) (μ g/kg i.v.)	HD ₅₀
			ED ₋₃₀ mm.Hg
2 d	641	406	0.63
3	1410	2485	1.76
4 a	3420	762	0.22
4 b	1910	3460	1.81
4 c	2240	5222	2.33
4 f	1660	931	0.51
4 h	3170	1338	0.42
4 i	5790	4338	0.75
7	3060	544	0.18
11	1160	233	0.20
15	400	59	0.15
16 a	1359	160	0.12
16 b	1580	487	0.31
16 c	1920	569	0.30
16 l	280	105	0.36
18 c	420	252	0.60
30 f	1980	154	0.21
34	3780	1253	0.33
35 b	1620	991	0.61
Propranolol	> 3550	393	< 0.11



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CLAIMS

1. Heterocyclic oxypropanol derivatives of the general formula I



5 in which

R_1 signifies hydrogen, an aralkyl, C_{1-6} alkyl or C_{1-8} alkanoyl group,

R_2 and R_3 , which can be the same or different, each signify hydrogen, an alkoxy carbonyl, C_{1-6} alkyl, C_{1-4} hydroxyalkyl or (C_{1-8} alkanoyl)oxyalkyl group, as well as together signify an alkylene radical with up to 6 C-atoms,

R_4 signifies hydrogen, a C_{1-8} alkanoyl group or an aroyl group,

15 R_5 signifies hydrogen, a C_{1-6} alkyl group or an aralkyl group,

R_6 signifies hydrogen or a C_{1-6} alkyl group,

R_7 signifies hydrogen, a hydroxyl group or a C_{1-6} alkyl group,

20 Z signifies a valency bond, a methylene group, an oxygen or sulphur atom,

Ar signifies a carbocyclic aryl radical or a pyridyl radical,



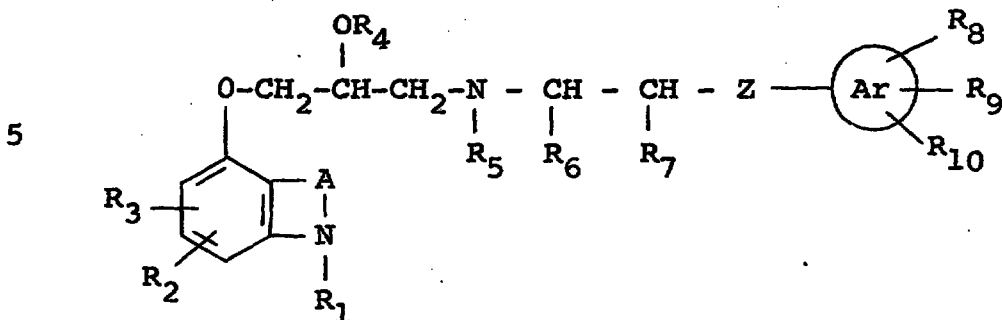
- R_8 , R_9 and R_{10} which can be the same or different, each signify hydrogen, halogen, a hydroxy group, a C_{1-8} alkanoyl group, a C_{1-6} alkyl group, an alkenyl group with up to 8 C-atoms, a C_{1-6} alkoxy group, an aralkoxy group, the allyloxy group, a C_{1-6} alkylthio group, an aminocarbonyl group, an amino-sulphonyl group, a C_{1-8} alkanoylamino group or R_8 and R_9 together signify a lower alkylenedioxy group or R_8 together with R_7 also a $-CH_2-O-$ group and
- 10 A signifies the group X_1-Y_1 , in which X_1 represents a methylene or $-NR_{11}$ radical, whereby R_{11} signifies hydrogen or a C_{1-6} alkyl group, and Y_1 represents a methylene radical or the group $>C=Q$, whereby Q stands for oxygen or sulphur; or the group
- 15 $X_2=Y_2$, in which X_2 and Y_2 can be the same or different and each stands for a nitrogen atom or for a $=CR_{12}$ group, whereby R_{12} represents hydrogen, an alkoxy carbonyl group or a C_{1-4} alkyl group, whereby for the case in which $X_2=Y_2$ represents a $-CH=N-$ group and R_1 an aralkyl
- 20 group or a C_{1-6} alkyl group, because of the ability to tautomerise of the indoles, this can also be localised on the nitrogen atom standing for Y_2 , with the proviso that in each case Y_1 is connected to the radical $N-R_1$ of the general formula I, whereby for the case in which
- 25 Q signifies an oxygen atom or $X_2=Y_2$ a $-CR_{12}=CR_{12}-$ group, either the two residues R_2 and R_3 cannot simultaneously be hydrogen or R_7 and R_8 must together form a



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-CH₂-O- bridge, as well as their pharmacologically compatible salts.

2. Process for the preparation of aminopropanol derivatives of the general formula I

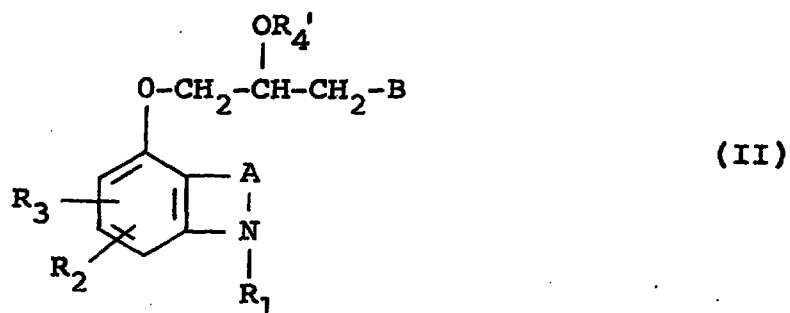


in which R₁ signifies hydrogen, an aralkyl, C₁₋₄ alkyl or C₁₋₈ alkanoyl group, R₂ and R₃, which can be the same or different, each signify hydrogen, an alkoxy-carbonyl, C₁₋₆ alkyl, C₁₋₄ hydroxyalkyl or (C₁₋₈ alkanoyl)-oxyalkyl group, as well as together signify an alkylene radical with up to 6 C-atoms, R₄ signifies hydrogen, a C₁₋₈ alkanoyl group or an aroyl group, R₅ signifies hydrogen, a C₁₋₆ alkyl group or an aralkyl group, R₆ signifies hydrogen or a C₁₋₆ alkyl group, R₇ signifies hydrogen, a hydroxyl group or a C₁₋₆ alkyl group, Z signifies a valency bond, a methylene group, an oxygen or sulphur atom, Ar signifies a carbocyclic aryl radical or a pyridyl radical, R₈, R₉ and R₁₀, which can be the same or different, each signify hydrogen, halogen, a hydroxyl group, a C₁₋₈ alkanoyl group, a C₁₋₆ alkyl group, an alkenyl group with up to 6 C-atoms, a C₁₋₆ alkoxy group, an aralkoxy group, the allyloxy

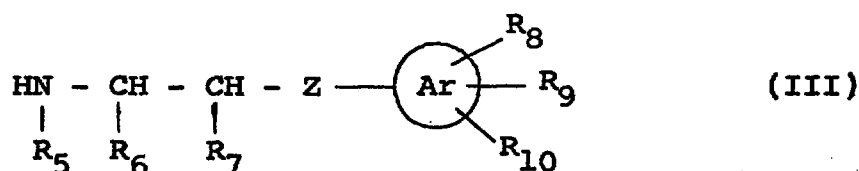


group, a C_{1-6} alkylthio group, an aminocarbonyl group, an aminosulphonyl group, a C_{1-8} alkanoylamino group or R_8 and R_9 together signify a lower alkylenedioxy group or R_8 together with R_7 also signifies a $-CH_2-O-$ group and A signifies the group X_1-Y_1 , in which X_1 signifies a methylene or $-NR_{11}$ radical, whereby R_{11} signifies hydrogen or a C_{1-6} alkyl group and Y_1 signifies a methylene radical or the group $>C=Q$, whereby Q stands for oxygen or sulphur; or the group $X_2=Y_2$, in which X_2 and Y_2 can be the same or different and each stands for a nitrogen atom or for a $=\overset{\cdot}{C}R_{12}$ group, whereby R_{12} represents hydrogen, an alkoxycarbonyl or C_{1-6} alkyl group, whereby for the case in which $X_2=Y_2$ represents a $-CH=N-$ group and R_1 an aralkyl or C_{1-6} alkyl group, this, because of the ability to tautomerise of the indazoles, can also be localised on the nitrogen atom standing for Y_2 , with the proviso that in each case Y_1 is connected with the radical $N-R_1$ of the general formula I, whereby for the case in which Q signifies an oxygen atom or $X_2=Y_2$ a $-CR_{12}=CR_{12}-$ group, either the two residues R_2 and R_3 cannot simultaneously be hydrogen or R_7 and R_8 must together form a $-CH_2-O-$ bridge, as well as of their pharmacologically compatible salts, characterised in that in per se known manner, one either

a) reacts a compound of the formula II



in which R_1 , R_2 , R_3 and A have the above-mentioned meaning, B represents a reactive group and R_4' has the above-given meaning for R_4 or, together with B, signifies a valency bond, with a compound of the formula III

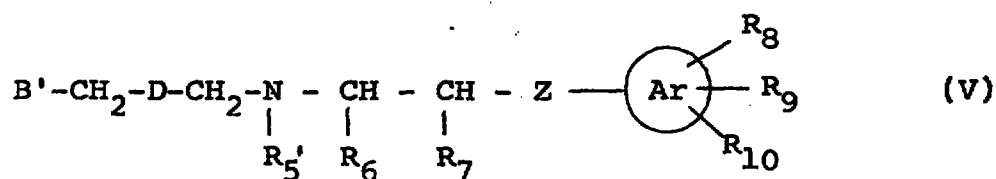


in which R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , Z and Ar have the above-given meaning; or

10 b) reacts a compound of the formula IV



in which R_1 , R_2 , R_3 and A have the given meaning, with a compound of the formula V





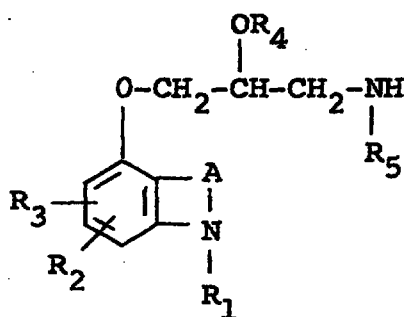
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in which R_6 , R_7 , R_8 , R_9 , R_{10} , Z and Ar have the above-given meaning, B' represents a reactive group, D stands for a $>CO$ or $>CH-OR_4$ group, whereby R_4 has the above-mentioned meaning for R_4 or, together with B', also signifies a valency bond and R_5 has the above-mentioned meaning for R_5 or, together with B', can also be a single bond, and, if D signifies the $>CO$ group, subsequently reduces; or

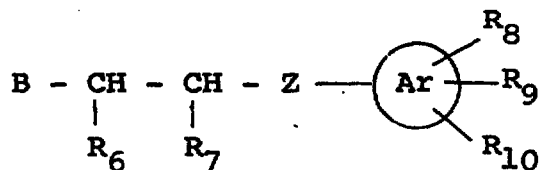
5 c) reacts a compound of the formula VI.

10



(VI),

in which R_1 , R_2 , R_3 , R_4 , R_5 and A have the above-given meaning, with a compound of the formula VII



(VII),

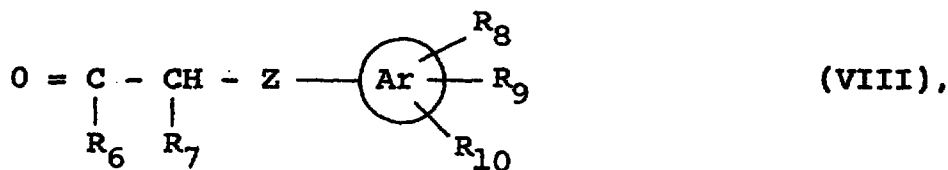
in which B, R_6 , R_7 , R_8 , R_9 , R_{10} , Z and Ar have the given meaning; or

d) hydrogenates a mixture of a compound of the formula VI with a compound of the formula VIII



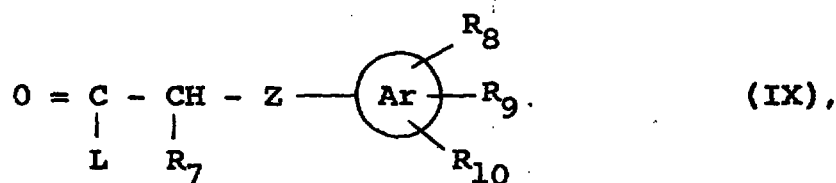
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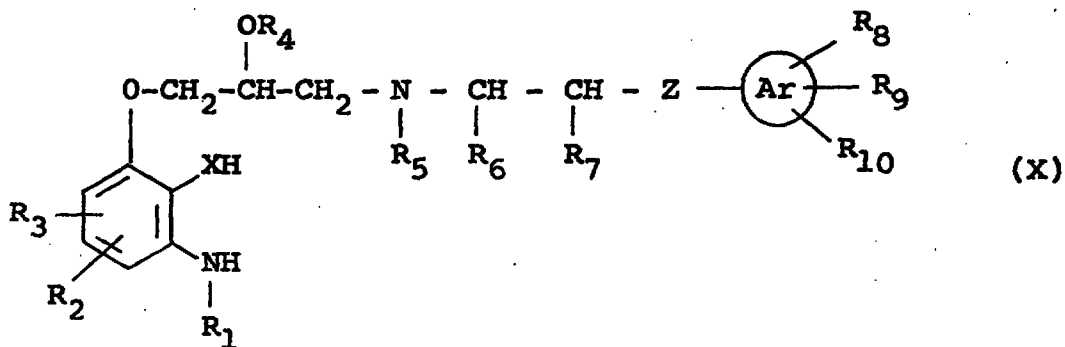
in which R_6 , R_7 , R_8 , R_9 , R_{10} , Z and Ar have the given meaning; or

- e) reacts a compound of the formula VI with a compound
5 of the formula IX



in which R_7 , R_8 , R_9 , R_{10} , Z and Ar have the given meaning and L represents a reactive residue, and subsequently reduces the amide obtained; or

- 10 f) a compound of the formula X



in which R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , Z and Ar have the given meaning and X represents X_1 or HX_2 , for the case in which A signifies the group $\text{X}_1 - \text{Y}_1$, reacts and cyclises a compound in which $\text{X} = \text{X}_1$ with a compound of the general formula XIa



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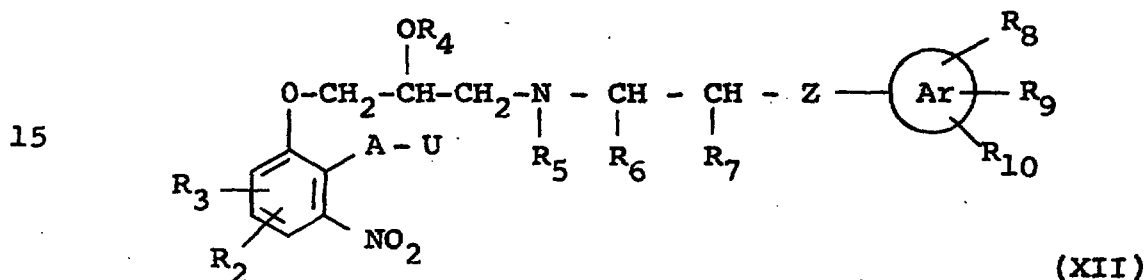
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in which Y_1 has the above-given meaning, L_1 signifies a hydrogen atom, the hydroxyl group or a reactive residue T and L_2 a hydrogen atom or a reactive residue T, or for the case in which A signifies the group $X_2 = Y_2$, reacts and cyclises a compound in which X represents HX_2 with a compound of the general formula XIb



10 in which L_1 and Y_2 have the above-given meaning, L_2' represents a hydrogen atom or a reactive residue T and L_3 a hydrogen atom or, together with L_2' , an oxygen atom; or
g) reduces and cyclises a compound of the formula XII



in which $R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, Z, A$ and Ar have the given meaning and U represents a group which can be split off, and possibly subsequently



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in a compound obtained of the general formula I,
converts one of the residues R_1 , R_2 , R_3 , R_4 , R_5 , R_8 ,
 R_9 , R_{10} or R_{12} according to conventional methods into
another residue R_1 , R_2 , R_3 , R_4 , R_5 , R_8 , R_9 , R_{10} or R_{12}
5 defined in the claim and, if desired, converts the
compounds obtained into their pharmacologically
compatible salts.

3. Medicaments containing an active material of
the general formula I, as well as per se known
10 pharmacologically compatible carrier and adjuvant
materials.

4. Aminopropanols according to claim 1 or their
salts for use as medicaments for the treatment of
heart and circulatory diseases.