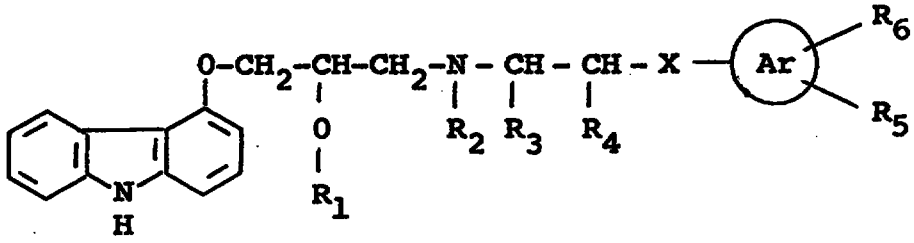
Carbazolyl-(4)-oxypropanolamine derivatives, processes for their preparation and medicaments containing these compounds

The invention concerns carbazolyl-(4)-oxypropanolamine derivatives, processes for their preparation and medicaments containing these compounds.

These compounds, as well as their pharmacologically acceptable salts, show, in the pharmacological test, vasodilating and β-receptor-blocking actions and are, therefore, suitable for the treatment and prophylaxis of circulatory and heart diseases, such as e.g. hypertension and angina pectoris.

From DE-PS 22 40 599, there are already known carbazole derivatives which block the activity of the β-receptors of the sympathetic system.

The invention concerns carbazolyl-(4)-oxypropanolamine derivatives of the formula I, their salts with physiologically acceptable acids, processes for their preparation and the use for the preparation of medicaments.



(I)

In formula I, there signify: R_1 hydrogen, a lower alkanoyl group or a benzoyl or naphthoyl group, R_2 hydrogen, a lower alkyl group or a benzyl, phenylethyl or phenylpropyl group, R_3 hydrogen or a lower alkyl group, R_4 hydrogen, a lower alkyl group, X a valency bond, a $-CH_2-$ group, an oxygen or a sulphur atom, Ar a phenyl, naphthyl, indanyl, tetrahydronaphthyl or pyridyl radical and R_5 and R_6, which can be the same or different, each signify hydrogen, halogen, a lower alkyl group, an aminocarbonyl group, a hydroxyl group, a lower alkoxy group, a benzyloxy group, a lower alkylmercapto group, a lower alkylsulphinyl group, a lower alkylsulphonyl group or together also represent a methylenedioxy group, whereby, for the case in which X represents an oxygen atom, R_4 and R_5 can together also signify the group $-CH_2-O-$.

The lower alkyl radicals of the substituents R_2, R_3, R_4, R_5 and R_6 contain 1 - 6, preferably 1 - 4 carbon atoms and can be straight-chained or branched. To be mentioned as preferred are the methyl, ethyl, isopropyl, t.-butyl and n-butyl radicals.

The lower alkanoyl groups are groups with 1 - 6 carbon atoms, especially the formyl, acetyl, propionyl and pivaloyl group.

By halogen one understands fluorine, chlorine and bromine.

A lower alkoxy, alkylmercapto, alkylsulphinyl or alkylsulphonyl radical can contain 1 - 6, preferably 1 - 4 carbon atoms. There are preferred the methoxy and the ethoxy group, the methylmercapto, the methylsulphinyl and the methylsulphonyl group.

As example of a radical in which R_4 and R_5 together form a $-CH_2-O-$ group, when X signifies oxygen, the 1,4-benzodioxanyl-(2)-methyl radical is to be mentioned.

The compounds according to the invention, as well as their pharmacologically acceptable salts, show, in comparison with the previously known substances with similar constitution and action, besides an outstanding β-receptor-blocking action, also good vasodilatory properties.

As evidence herefor, in the pharmacological test, as representative of the compounds according to the invention, the compound of Example 1, 1-[carbazolyl-(4)-oxy]-3-[2-(2-methoxyphenoxy)-ethylamino]-propan-2-ol, was compared with 4-(3-isopropylamino-2-hydroxy-propoxy)-carbazole hydrochloride of DE-PS 22 40 599.

As measure for the vasodilation, on the narcotised rabbit was determined the $DE_{30\ mm.Hg}$ value, i.e. the dosage of the pharmacologically active compound which weakened the CSE reflex (temporary increase of the blood pressure by occlusion of the neck pulse arteries for 2 minutes) by 20 mm.Hg. As measure for

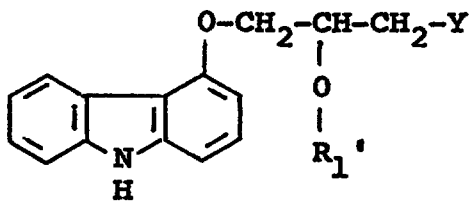
the β-receptor blockade, there served the DE_{250} determined in awake rabbits, i.e. the dosage of the β-blocker in the case of which the heart frequency after injection of isoprenaline only increased to 250 beats/min.

The evaluation of these experiments showed that for the chosen compound according to the invention, the quotient from the $DE_{30\ mm.Hg}$ and DE_{250} value lay at 1, i.e. β-receptor blockade and vasodilation lie at the same order of magnitude. For the comparative substance known from DE-PS 22 40 599, there was found a quotient of over 100, i.e. this compound showed practically only β-blocking properties; the vasodilation brought about by this substance is negligibly small.

On the basis of a suitable selection of substances, it could be shown that the other compounds according to the invention also possess β-blocking and vasodilating properties of a comparable order of magnitude.

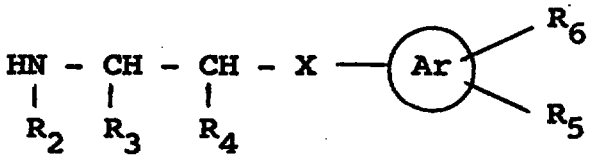
The preparation of the compounds according to the invention is characterised in that, in per se known manner, one

a) reacts a compound of the formula II



(II)

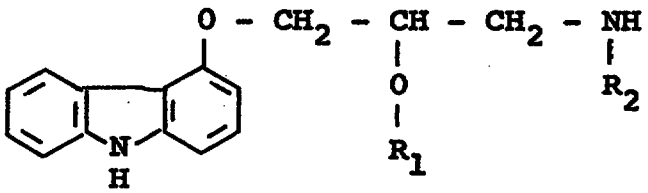
in which Y represents a reactive group and R_1' has the meaning given for R_1 or Y and R_1' together signify a valency bond, with a compound of the formula III



(III)

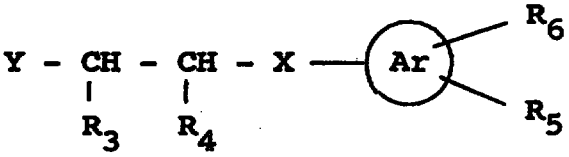
in which R_2, R_3, R_4, X, Ar, R_5 and R_6 have the given meaning; or

b) reacts a compound of the formula IV



(IV)

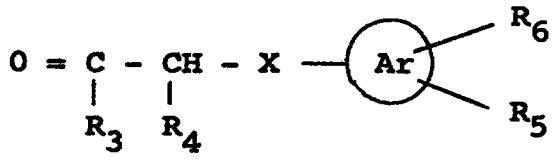
in which R_1 and R_2 have the given meaning, with a compound of the formula V



(V)

in which Y, R_3, R_4, X, Ar, R_5 and R_6 have the given meaning; or

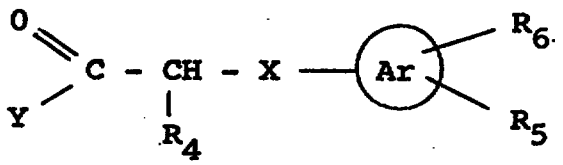
c) reduces a mixture of a compound of the formula IV and of a compound of the formula VI



(VI)

in which R_3, R_4, X, Ar, R_5 and R_6 have the given meaning; or

d) reacts a compound of the formula IV with a compound of the formula VII



(VII)

in which Y, R_4, X, Ar, R_5 and R_6 have the given meaning, and reduces the amide so obtained, whereupon, one optionally converts the compounds of formula I prepared according to the above processes into other compounds of formula I as well as, if desired, converts the compounds obtained of formula I into their pharmacologically acceptable salts.

Reactive groups Y of the compounds of formulae II, V and VII are especially acid residues, e.g. of hydrohalic acids or of sulphonic acids.

The processes a) and b) according to the invention are preferably carried out in an organic solvent inert under the reaction conditions, e.g.

toluene, dioxan, ethylene glycol dimethyl ether, isopropanol or dimethylformamide, optionally in the presence of an acid-binding agent. The reactions of the epoxides of formula II (Y and R' together a valency bond) with the amines of formula III can, however, also be accomplished after mixing the reaction components, by leaving to stand at room temperature or by heating. According to process c), an amine of formula IV is hydrogenated with a carbonyl compound of formula VI in a suitable inert solvent (e.g. methanol) in the presence of a catalyst (e.g. Raney nickel).

The reduction of the amides obtained according to process d) takes place by means of complex metal hydrides, e.g. lithium aluminium hydride. The esterification of compounds of formula I with R_1 = H can take place by reaction with an acid halide or acid anhydride, possibly in the presence of an acid-binding agent (e.g. pyridine, triethylamine), the removal of a benzyl protective group possibly present by catalytic hydrogenation with noble metal catalysts.

The starting compounds employed in the processes according to the invention are, as a rule, known from the literature. New compounds are generally obtained analogously to the processes described for the preparation of these known compounds. Thus, the amines of formula III are preferably prepared by reacting halo-

alkyl nitriles with corresponding phenols, naphthols or aryl compounds (e.g. chloroacetonitrile and phenol) and subsequent hydrogenation in the presence of ammonia.

The amines of formula IV can be obtained from the known 4-(2,3-epoxypropoxy)-carbazole (cf. DE-PS 2,240,599) by reaction with liquid ammonia.

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

The carbonyl compounds of formula VI and acid chlorides of formula VII are obtained from corresponding phenols, naphthols and aryl compounds via reactions with suitable haloalkyl compounds.

A subsequent conversion of a compound of formula I into another compound of formula I can take place, for example, by oxidation, e.g. conversion of an alkylmercapto group into an alkylsulphinyl or alkylsulphonyl group. Furthermore, hydroxyl groups can be etherified or esterified according to known methods or, vice versa, ester and ether groups can be converted into hydroxyl groups.

For the conversion of compounds of formula I into their pharmacologically acceptable salts, one reacts these, preferably in an organic solvent, with the equivalent amount of an inorganic or organic acid,

e.g. hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, acetic acid, citric acid, maleic acid, benzoic acid.

The compounds of formula I according to the invention can be separated from their racemic mixtures according to per se known methods via the diastereomeric salts, into the optically-active forms. For the racemates resolution there can be used e.g. tartaric acid, malic acid, camphoric acid, camphorsulphonic acid.

For the preparation of medicaments, the compounds of formula I are mixed in the 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, such as e.g. olive oil.

The compounds of formula I according to the invention and their salts can be administered enterally or parenterally in liquid or solid form. As injection medium, it is preferable to use water which contains the additives usual in the case of injection solutions, such as stabilising agents, solubilising agents or buffers. Such additives 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 sweetening materials.

The invention is explained in more detail by the following Examples:

Example 1.

1-[Carbazolyl-(4)-oxy]-3-[2-(2-methoxyphenyl)-ethylamino]-propan-2-ol.

6.0 g. 4-(2,3-Epoxypropoxy)-carbazole and 7.6 g. 2-(2-methoxyphenyl)-ethylamine are stirred for 20 hours at 70°C. One triturates with ether, filters off with suction and recrystallises from ethyl acetate, with the use of active charcoal and fullers' earth. Yield 6.0 g. (61% of theory) of colourless crystals; m.p. 135-136°C.

In analogous manner one obtains:

a) 1-[carbazolyl-(4)-oxy]-3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propan-2-ol.

42% of theory; m.p. 129-130°C.; acetate m.p.180-183°C. from 4-(2,3-epoxypropoxy)-carbazole and 2-(3,4-dimethoxyphenyl)-ethylamine.

b) 1-[carbazolyl-(4)-oxy]-3-[2-(2-pyridyl)-ethylamino]-propan-2-ol

32% of theory; m.p. 105-107°C., from 4-(2,3-epoxy-propoxy)-carbazole and 2-(2-pyridyl)-ethylamine.

c) 1-[carbazolyl-(4)-oxy]-3-[2-(4-pyridyl)-ethylamino]-propan-2-ol

24% of theory; m.p. 86-88°C., from 4-(2,3-epoxy-propoxy)-carbazole and 2-(4-pyridyl)-ethylamine.

d) 1-[carbazolyl-(4)-oxy]-3-(3-phenylpropylamino)-propan-2-ol

30% of theory; succinate m.p. 98-99°C., from 4-(2,3-epoxypropoxy)-carbazole and 3-phenylpropylamine.

e) 1-[carbazolyl-(4)-oxy]-3-[4-phenylbutyl-(2)-amino]-propan-2-ol

13% of theory; m.p. 124-125°C., from 4-(2,3-epoxy-propoxy)-carbazole and 4-phenylbutyl-(2)-amine.

Example 2.

1-[Carbazolyl-(4)-oxy]-3-[2-methoxyphenoxy)-ethylamino]-propan-2-ol.

22.6 g. 4-(2,3-Epoxypropoxy)-carbazole and 17.4 g. 2-(2-methoxyphenoxy)-ethylamine in 75 ml. ethylene glycol dimethyl ether are stirred for 25 hours at 50°C. One brings the mixture to dryness in a Rotavapor, triturates with ether and recrystallises from ethyl acetate, with the use of active charcoal. Yield 15.1 g. (39% of theory) of colourless crystals; m.p. 114-115°C.

In analogous manner one obtains:

a) 1-[carbazolyl-(4)-oxy]-3-(2-phenoxyethylamino)-propan-2-ol

32% of theory; m.p. 105-107°C., from 4-(2,3-epoxypropoxy)-carbazole and 2-phenoxyethylamine.

b) 1-[carbazolyl-(4)-oxy]-3-[1-phenoxypropyl-(2)-amino]-propan-2-ol

31% of theory; hydrochloride m.p. 116-119°C., from 4-(2,3-epoxypropoxy)-carbazole and 1-phenoxypropyl-(2)-amine.

c) 1-[carbazolyl-(4)-oxy]-3-[1,4-benzodioxanyl-(2)-methylamino]-propan-2-ol

28% of theory; m.p. 129-131°C., from 4-(2,3-epoxypropoxy)-carbazole and 2-(aminomethyl)-1,4-benzodioxan.

d) 1-[carbazolyl-(4)-oxy]-3-[2-(4-carbamoylphenoxy)-ethylamino]-propan-2-ol

13% of theory; m.p. 120-122°C., from 4-(2,3-epoxypropoxy)-carbazole and 2-(4-carbamoylphenoxy)-ethylamine.

Example 3.

1-[Carbazolyl-(4)-oxy]-3-[2-(2-ethoxyphenoxy)-ethylamino]-propan-2-ol.

6.0 g. 4-(2,3-Epoxypropoxy)-carbazole and 9.1 g. 2-(2-ethoxyphenoxy)-ethylamine are stirred for 20 hours at 70°C. After cooling, one stirs with ether, filters off with suction and recrystallises the residue from ethyl acetate, with the use of active charcoal and fullers' earth. Yield 4.4 g. (42% of theory) of

colourless crystals; m.p. 127.5-128.4°C.

In analogous manner one obtains:

a) 1-[carbazolyl-(4)-oxy]-3-[2-(4-fluorophenoxy)-ethylamino]-propan-2-ol

56% of theory; m.p. 145-146°C., from 4-(2,3-epoxy-propoxy)-carbazole and 2-(4-fluorophenoxy)-ethylamine.

b) 1-[carbazolyl-(4)-oxy]-3-[2-(4-tert.-butylphenoxy)-ethylamino]-propan-2-ol

51% of theory; m.p. 127-128°C., from 4-(2,3-epoxy-propoxy)-carbazole and 2-(4-tert.-butylphenoxy)-ethylamine.

c) 1-[carbazolyl-(4)-oxy]-3-[2-(2,3-dimethylphenoxy)-ethylamino]-propan-2-ol

51% of theory; m.p. 128-129°C., from 4-(2,3-epoxy-propoxy)-carbazole and 2-(2,3-dimethylphenoxy)-ethylamine.

d) 1-[carbazolyl-(4)-oxy]-3-{2-[indanyl-(5)-oxy]-ethylamino}-propan-2-ol.

54% of theory; m.p. 143-145°C., from 4-(2,3-epoxy-propoxy)-carbazole and 2-[indanyl-(5)-oxy]-ethylamine.

e) 1-[carbazolyl-(4)-oxy]-3-{2-[naphthyl-(1)-oxy]-ethylamino}-propan-2-ol

64% of theory; m.p. 116-119°C., from 4-(2,3-epoxy-propoxy)-carbazole and 2-[naphthyl-(1)-oxy]-ethylamine.

f) 1-[carbazolyl-(4)-oxy]-3-[2-(3,4-methylenedioxy-phenoxy)-ethylamino]-propan-2-ol

32% of theory; m.p. 142-143°C., from 4-(2,3-epoxypropoxy)-carbazole and 2-(3,4-methylenedioxyphenoxy)-ethylamine.

g) 1-[carbazolyl-(4)-oxy]-3-[2-(2,6-dimethoxyphenoxy)-ethylamino]-propan-2-ol

65% of theory; m.p. 136-138°C., from 4-(2,3-epoxypropoxy)-carbazole and 2-(2,6-dimethoxyphenoxy)-ethylamine.

h) 1-[carbazolyl-(4)-oxy]-3-[2-(2-methoxyphenoxy)-propylamino]-propan-2-ol

83% of theory; m.p. 137-157°C. (crude mixture of the diastereomers); from this, by two recrystallisations from ethyl acetate: 22% of theory; m.p. 173-175°C., from 4-(2,3-epoxypropoxy)-carbazole and 2-(2-methoxyphenoxy)-propylamine.

i) 1-[carbazolyl-(4)-oxy]-3-[2-(2-methylmercaptophenoxy)-ethylamino]-propan-2-ol

40% of theory; m.p. 83-85°C., from 4-(2,3-epoxypropoxy)-carbazole and 2-(2-methylmercaptophenoxy)-ethylamine.

k) 1-[carbazolyl-(4)-oxy]-3-[2-(2-benzyloxyphenoxy)-ethylamino]-propan-2-ol

56% of theory; m.p. 138-139°C., from 4-(2,3-epoxypropoxy)-carbazole and 2-(2-benzyloxyphenoxy)-ethylamine.

The starting amines employed in Examples 3c, 3d, 3f, 3g and 3i can be prepared via the corresponding

nitriles by reactions analogous to those in the literature.

2,3-Dimethylphenoxyacetonitrile

100 g. 2,3-Dimethylphenol, 57 ml. chloroacetonitrile, 110 g. potassium carbonate and 2.0 g. potassium iodide are stirred under reflux for 5 hours in 300 ml. methyl ethyl ketone. One filters off with suction, evaporates, distils the residue and obtains 88.0 g. of colourless oil; b.p.$_{13}$ 137-142°C.

One obtains analogously by the reactions of 5-indanole, 3,4-methylenedioxyphenol or 2-(methylmercapto)-phenol with chloroacetonitrile; indanyl-(5)-oxyacetonitrile; b.p.$_{14}$ 162-165°C. 3,4-methylenedioxyphenoxyacetonitrile; b.p.$_{12}$ 170-175°C. 2-methylmercaptophenoxyacetonitrile; m.p. 56-58°C.; b.p.$_{12}$ 173-176°C.

2-[indanyl-(5)-oxy]-ethylamine

109 g. Indanyl-(5)-oxyacetonitrile are hydrogenated in the presence of Raney nickel in 700 ml. ethanol and 180 ml. liquid ammonia at 110 ats. and 90°C. After distillation, one obtains 86 g. of colourless oil; b.p.$_{12}$ 154-156°C.

Analogously from 2,3-dimethylphenoxyacetonitrile or 3,4-methylenedioxyphenoxyacetonitrile, there are obtained by hydrogenation:
2-(2,3-dimethylphenoxy)-ethylamine; b.p.$_{12}$ 129-132°C.
2-(3,4-methylenedioxyphenoxy)-ethylamine; b.p.$_{13}$ 162-164°C.

2-(2-methylmercaptophenoxy)-ethylamine

26.7 g. (2-Methylmercaptophenoxy)-acetonitrile are reduced with 8.5 g. lithium aluminium hydride in 1.3 litres ether (4 hours reflux). After the usual working up and distillation, there are obtained 21.0 g. of colourless oil; $b.p._{0.1}$ 117-120°C.

Analogously, by the reduction of 2,6-dimethoxy-phenoxyacetonitrile:

2-(2,6-dimethoxyphenoxy)-ethylamine; $b.p._{12}$ 160-162°C.

Example 4.

1-[Carbazolyl-(4)-oxy]-3-[2-(2-methylphenoxy)-ethyl-amino]-propan-2-ol.

6.0 g. 4-(2,3-Epoxypropoxy)-carbazole and 7.6 g. 2-(2-methylphenoxy)-ethylamine are stirred for 20 hours at 70°C. One dissolves in methylene chloride and separates the mixture by chromatography on a silica gel column (500 ml.) with the elution agents methylene chloride, methylene chloride-ethyl acetate (9:1 and 7:3), ethyl acetate and ethyl acetate-methanol (9:1). The sequence of the elution: tertiary amine, secondary amine and primary starting amine. After trituration with ether and recrystallisation from ethyl acetate, with the use of active charcoal and fullers' earth, there are obtained 5.2 g. (53% of theory) of colourless crystals; m.p. 125-126°C.

In analogous manner one obtains:

a) 1-[carbazolyl-(4)-oxy]-3-[2-(3-methylphenoxy)-ethylamino]-propan-2-ol

43% of theory; m.p. 129-130°C., from 4-(2,3-epoxy-propoxy)-carbazole and 2-(3-methylphenoxy)-ethylamine.

b) 1-[carbazolyl-(4)-oxy]-3-[2-(2-chlorophenoxy)-ethylamino]-propan-2-ol

26% of theory; m.p. 111-112°C., from 4-(2,3-epoxy-propoxy)-carbazole and 2-(2-chlorophenoxy)-ethylamine.

c) 1-[carbazolyl-(4)-oxy]-3-[2-(3-methoxyphenoxy)-ethylamino]-propan-2-ol

22% of theory; m.p. 111-113°C., from 4-(2,3-epoxy-propoxy)-carbazole and 2-(3-methoxyphenoxy)-ethylamine.

d) 1-[carbazolyl-(4)-oxy]-3-[2-(4-methoxyphenoxy)-ethylamino]-propan-2-ol

48% of theory; m.p. 106-108°C., from 4-(2,3-epoxy-propoxy)-carbazole and 2-(4-methoxyphenoxy)-ethylamine.

e) 1-[carbazolyl-(4)-oxy]-3-[2-(2-methoxyphenyl-mercapto)-ethylamino]-propan-2-ol

15% of theory; m.p. 108-109°C., from 4-(2,3-epoxy-propoxy)-carbazole and 2-(2-methylphenylmercapto)-ethylamine.

f) 1-[carbazolyl-(4)-oxy]-3-[1-(2-methoxyphenoxy)-propyl-2-amino]-propan-2-ol

85% of theory; m.p. 112-125°C. (crude mixture of the diastereomers), from which, by recrystallisation from ethanol, ethyl acetate and toluene-isopropanol, colourless crystals, m.p. 140-141°C. and from the

mother liquor a further product m.p. 121.5-122.5°C., from 4-(2,3-epoxypropoxy)-carbazole and 1-(2-methoxyphenoxy)-propyl-2-amine.

g) 1-[carbazolyl-(4)-oxy]-3-[2-methylsulphinylphenoxy)-ethylamino]-propan-2-ol

25% of theory; oxalate decomposes above 126°C., from 4-(2,3-epoxypropoxy)-carbazole and 2-(2-methylsulphinylphenoxy)-ethylamine.

The compound is also obtained by the oxidation of 1-[carbazolyl-(4)-oxy]-3-[2-(2-methylmercaptophenoxy)-ethylamino]-propan-2-ol (cf. Example 3i) with the equivalent amount of hydrogen peroxide in acetic acid at room temperature.

The starting amines in Examples 4e, 4f and 4g can be prepared by reactions analogous to those in the literature as follows:

2-(2-methoxyphenylmercapto)-ethylamine

by the reaction of o-(2-chloroethylthio)-anisole in liquid ammonia (8 hours at 120°C.); oil; $b.p._{0.05}$ 118-122°C.; hydrochloride m.p. 163-167°C.;

1-(2-methoxyphenoxy)-propyl-2-amine

by the hydrogenation of 2-methoxyphenoxyacetone in ammonia-ethanol (120 ats.; 90°C.); oil; $b.p._{13}$ 144-146°C.; oxalate m.p. 199-200°C. (decomp.);

2-(2-methylsulphinylphenoxy)-ethylamine

by the oxidation of 2-(2-methylmercapto)-ethylamine with 1 equivalent of perhydrol (30%) in acetic acid

at room temperature; oil; oxalate m.p. 174-175°C.

Example 5.

1-[Carbazolyl-(4)-oxy]-3-[N-benzyl-2-(2-methoxy-phenoxy)-ethylamino]-propan-2-ol.

15.1 g. 4-(2,3-Epoxypropoxy)-carbazole and 16.2 g. N-[2-(2-methoxyphenoxy)-ethyl]-benzylamine in 50 ml. ethylene glycol dimethyl ether are heated under reflux for 24 hours. One brings to dryness, purifies over a silica gel column with the elution agents methylene chloride, methylene chloride-ethyl acetate (9:1 and 7:3), ethyl acetate and triturates the residue of the main fraction with ether. Yield: 25.0 g. (80% of theory) of colourless crystals; m.p. 97-99°C.

In analogous manner one obtains:

a) 1-[carbazolyl-(4)-oxy]-3-[N-methyl-2-(2-methoxy-phenoxy)-ethylamino]-propan-2-ol

22% of theory; colourless oil; hydrochloride m.p. 109°C. (slight gassing), from 4-(2,3-epoxypropoxy)-carbazole and N-methyl-2-(2-methoxyphenoxy)-ethylamine.

b) 1-[carbazolyl-(4)-oxy]-3-[N-butyl-2-(2-methoxy-phenoxy)-ethylamino]-propan-2-ol

84% of theory; colourless oil; hydrochloride m.p. 169-170°C., from 4-(2,3-epoxypropoxy)-carbazole and N-[2-(2-methoxyphenoxy)-ethyl]-butylamine.

c) 1-[carbazolyl-(4)-oxy]-3-[N-benzyl-2-(5-carbamoyl-2-pyridyloxy)-ethylamino]-propan-2-ol

80% of theory; m.p. 165-167°C., from 4-(2,3-epoxy-propoxy)-carbazole and N-[2-(5-carbamoyl-2-pyridyloxy)-ethyl]-benzylamine.

Example 6.

1-[Carbazolyl-(4)-oxy]-2-formyloxy-3-[N-benzyl-2-(2-methoxyphenoxy)-ethylamino]-propane hydrochloride.

One allows a formic acid-acetic acid anhydride mixture prepared from 3 ml. formic acid and 6 ml. acetic anhydride to act for 2½ days at room temperature on 7.9 g. 1-[carbazolyl-(4)-oxy]-3-[N-benzyl-2-(2-methoxyphenoxy)-ethylamino]-propan-2-ol, pours into ice water, neutralises with sodium hydrogen carbonate solution, extracts with methylene chloride and precipitates the hydrochloride from an ethereal solution of the extraction residue. Yield 8.1 g. (91% of theory) of colourless crystals, sinter above 85°C., bubble formation above 120°C.

Example 7.

1-[Carbazolyl-(4)-oxy]-2-pivaloyloxy-3-[N-benzyl-2-(2-methoxyphenoxy)-ethylamino]-propane hydrochloride.

1.9 ml. pivalic acid chloride is introduced into a solution of 7.0 g. 1-[carbazolyl-(4)-oxy]-3-[N-benzyl-2-(2-methoxyphenoxy)-ethylamino]-propan-2-ol in 35 ml. pyridine. After standing overnight, one pours into water, takes up methylene chloride, purifies chromatographically over a silica gel column and precipitates the hydrochloride from an ethereal solution of the

base. Yield 6.6 g. (7% of theory) of colourless crystals, sinter above 102°C., m.p. 120°C. (slight gassing).

In analogous manner, one obtains by benzoylation:

1-[carbazolyl-(4)-oxy]-2-benzoyloxy-3-[N-benzyl-2-(2-methoxyphenoxy)-ethylamino]-propane hydrochloride. 70% of theory; m.p. 113°C. (slight gassing).

Example 8.

1-[Carbazolyl-(4)-oxy]-2-formyloxy-3-[2-(2-methoxy-phenoxy)-ethylamino]-propane hydrochloride.

2.2 g. 1-[Carbazolyl-(4)-oxy]-2-formyloxy-3-[N-benzyl-2-(2-methoxyphenoxy)-ethylamino]-propane hydrochloride are hydrogenated in 40 ml. abs. tetrahydrofuran in the presence of 0.3 g. 10% palladium-charcoal at normal pressure. The residue obtained after suction filtration and evaporation becomes crystalline in the case of working up with ether. Yield 1.3 g. (70% of theory) of colourless crystals; m.p. 62°C. (with bubble formation).

In analogous manner one obtains:

a) 1-[carbazolyl-(4)-oxy]-2-pivaloyloxy-3-[2-(2-methoxyphenoxy)-ethylamino]-propane hydrochloride 85% of theory; m.p. 199-210°C. (slight gassing); by hydrogenolysis of 1-[carbazolyl-(4)-oxy]-2-pivaloyloxy-3-[N-benzyl-2-(2-methoxyphenoxy)-ethyl-amino]-propane hydrochloride.

b) 1-[carbazolyl-(4)-oxy]-2-benzoyloxy-3-[2-(2-methoxyphenoxy)-ethylamino]-propane hydrochloride

84% of theory; m.p. 102°C. (with gassing); by hydrogenolysis of 1-[carbazolyl-(4)-oxy]-2-benzoyloxy-3-[N-benzyl-2-(2-methoxyphenoxy)-ethylamino]-propane hydrochloride.

c) 1-[carbazolyl-(4)-oxy]-3-[2-(5-carbamoyl-2-pyridyloxy)-ethylamino]-propan-2-ol

m.p. 176-178°C.; by hydrogenolysis of 1-[carbazolyl-(4)-oxy]-3-[N-benzyl-2-(5-carbamoyl-2-pyridyloxy)-ethylamino]-propan-2-ol.

d) 1-[carbazolyl-(4)-oxy]-3-[2-(2-hydroxyphenoxy)-ethylamino]-propan-2-ol

77% of theory; hydrochloride m.p. 214-215°C.; by hydrogenolysis of 1-(carbazolyl-(4)-oxy]-3-[2-(2-benzyloxyphenoxy)-ethylamino]-propan-2-ol.

Example 9.

1-[Carbazolyl-(4)-oxy]-3-[2-(5-fluoro-2-methoxyphenoxy)-ethylamino]-propan-2-ol.

7.0 g. 1-Amino-3-[carbazolyl-(4)-oxy]-propan-2-ol, 9.2 g. p-toluenesulphonic acid [2-(5-fluoro-2-methoxy-phenoxy)-ethyl ester] and 3.8 ml. triethylamine are stirred in 20 ml. dimethylformamide for 20 hours at 70°C. One pours into a dilute aqueous solution of sodium hydroxide, extracts with methylene chloride, dries and purifies chromatographically as described in Example 4. After recrystallisation from ethyl

acetate with the use of active charcoal and fullers' earth, there are obtained 2.7 g. (23% of theory) of colourless crystals; m.p. 146-147°C.

The starting materials can be prepared as follows:

1-amino-3-[carbazolyl-(4)-oxy]-propan-2-ol

40 g. 4-(2,3-Epoxypropoxy)-carbazole are stirred with 500 ml. liquid ammonia in 2 litres methanol for 24 hours at 50°C. (autoclave). After evaporating and recrystallising from ethanol: 31 g. of colourless crystals; m.p. 141-143°C.

p-Toluenesulphonic acid [2-(5-fluoro-2-methoxyphenoxy)-ethyl ester]

40.4 g. 5-Fluoro-2-methoxyphenol, 24.6 ml. 2-chloroethanol and 20.7 g. potassium hydroxide are stirred in 100 ml. DMF for 2 hours at 70°C. One pours into water, extracts with methylene chloride, distils the extract residue in a high vacuum and obtains 11.3 g. 2-(5-fluoro-2-methoxyphenoxy)-ethanol, colourless oil, which solidifies upon standing; m.p. 43-45°C. The further reaction with p-toluenesulphonic acid chloride gives the tosylate; m.p. 66-68°C. (from ethanol).

Example 10.

1-[Carbazolyl-(4)-oxy]-3-[1-(2-methoxyphenoxy)-propyl-2-amino]-propan-2-ol.

One hydrogenates a mixture of 8.1 g. 1-amino-3-[carbazolyl-(4)-oxy]-propan-2-ol and 6.0 g. (2-methoxyphenoxy)-acetone in 250 ml. methanol in the presence of 1.0 g. 10% palladium charcoal (5 ats, 38°C.) and purifies the crude product obtained chromatographically as described in Example 4. After triturating the residue of the main fraction, there are obtained 5.5 g. (41% of theory) of colourless crystals, m.p. 113-117°C., of crude diastereomeric mixture. By recrystallisation from ethyl acetate and from ethanol, there is obtained therefrom a product with constant m.p. 140-141°C.

Example 11.

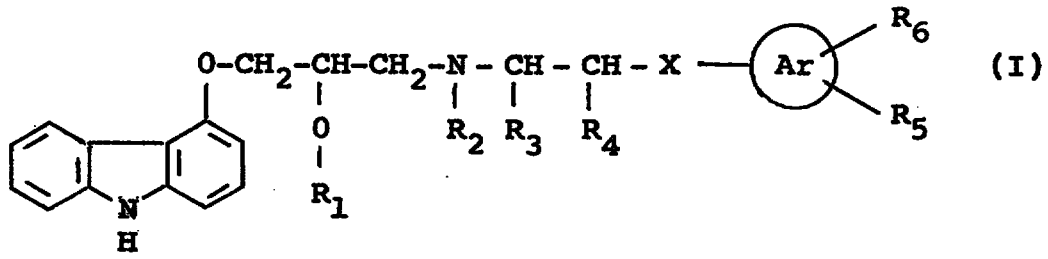
1-[Carbazolyl-(4)-oxy]-3-[3-(2-methoxyphenyl)-propyl-amino]-propan-2-ol.

A solution of 4.4 g. 3-(2-methoxyphenyl)-propionic acid chloride in 50 ml. methylene chloride is added dropwise, with stirring, to a solution of 6.0 g. 1-amino-3-[carbazolyl-(4)-oxy]-propan-2-ol and 3.3 ml. triethylamine in 50 ml. methylene chloride at room temperature. After standing overnight, one shakes out with water, dries the organic phase, evaporates, stirs the residue with ether and obtains 8.2 g. (84% of theory) 1-[carbazolyl-(4)-oxy]-3-[3-(2-methoxy-phenyl)-propionylamino]-propan-2-ol; m.p. 142-144°C. 7.7 g. of this intermediate product are reduced with 1.5 g. lithium aluminium hydride in 100 ml. abs.

tetrahydrofuran (20 hours reflux). The oil obtained after usual working up is purified chromatographically over a silica gel column (cf. Example 4). By re-crystallisation from toluene, with the use of active charcoal and fullers' earth, there are obtained 2.1 g. (28% of theory) of colourless crystals; m.p. 102-104°C.

Patent Claims

1. Carbazolyl-(4)-oxypropanolamine derivatives of the formula I

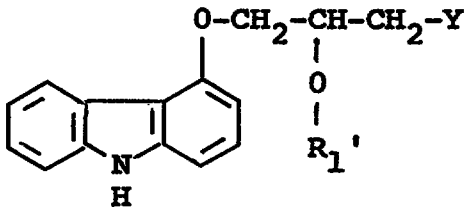


(I)

in which R_1 signifies hydrogen, a lower alkanoyl group or a benzoyl or naphthoyl group, R_2 hydrogen, a lower alkyl group or a benzyl, phenylethyl or phenylpropyl group, R_3 hydrogen or a lower alkyl group, R_4 hydrogen or a lower alkyl group, X is a valency bond, a $-CH_2-$ group, an oxygen or sulphur atom, Ar a phenyl, naphthyl, indenyl, tetrahydronaphthyl or a pyridyl radical and R_5 and R_6, which can be the same or different, each hydrogen, halogen, a lower alkyl group, an aminocarbonyl group, a hydroxyl group, a lower alkoxy group, a benzyloxy group, a lower alkylmercapto group, a lower alkylsulphinyl group, a lower alkylsulphonyl group or also together a methylenedioxy group, whereby, for the case in which X represents an oxygen atom, R_4 and R_5 together can also signify the group $-CH_2-O-$, as well as their physiologically acceptable salts.

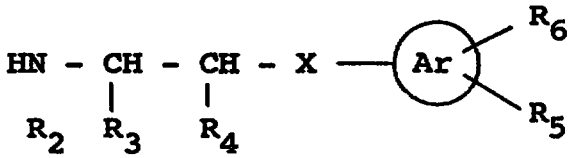
2. Process for the preparation of carbazolyl-(4)-oxypropanolamine derivatives according to claim 1 with the there-given meanings for R_1, R_2, R_3, R_4, X, Ar, R_5 and R_6, as well as of their physiologically acceptable salts, characterised in that, in per se known manner, one either

a) reacts a compound of the formula II



(II),

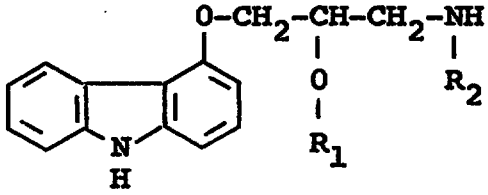
in which Y represents a reactive group and R_1' has the meaning given for R_1 or Y and R_1' together represent a valency bond, with a compound of the formula III



(III),

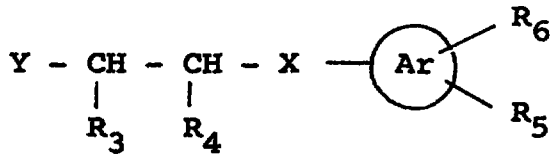
in which R_2, R_3, R_4, X, Ar, R_5 and R_6 have the given meaning; or

b) reacts a compound of the formula IV



(IV),

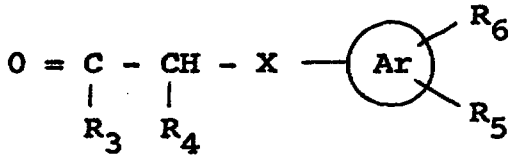
in which R_1 and R_2 have the given meaning, with a compound of the formula V



(V),

in which Y, R_3, R_4, X, Ar, R_5 and R_6 have the given meaning; or

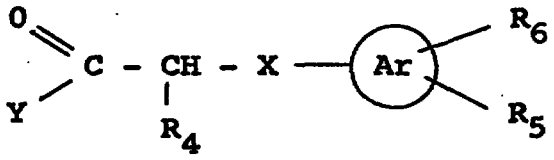
c) reduces a mixture of a compound of the formula IV and of a compound of the formula VI



(VI),

in which R_3, R_4, X, Ar, R_5 and R_6 have the given meaning; or

d) reacts a compound of the formula IV with a compound of the formula VII



(VII),

in which Y, R_4, X, Ar, R_5 and R_6 have the given meaning, and reduces the so obtained amide,

whereafter one possibly converts the compounds of general formula I prepared according to the above process into other compounds of formula I, as well as,

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if desired, converts the compounds obtained of formula I into their pharmacologically acceptable salts.

3. Use of compounds of formula I and of their pharmacologically acceptable salts for the preparation of medicaments with vasodilatory and/or β-receptor-blocking action.

4. Medicaments containing an active material of formula I, as well as per se known pharmacologically compatible carrier materials.