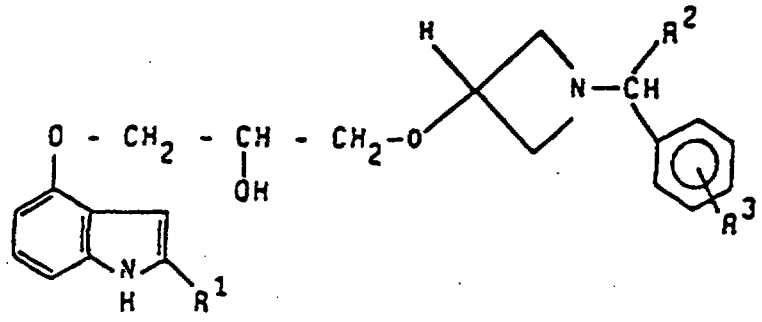
Description

The invention relates to new substituted indolylpropanols of the formula I



in which

R^1 is a cyano, carboxamide, alkoxycarbonyl, hydroxyl or acetyl group,

R^2 is pyridinyl, thienyl, phenyl or substituted phenyl, which is mono- or disubstituted by halogen, alkyl, cycloalkyl, alkoxy, difluoromethoxy, difluoromethylthio, trifluoromethoxy, trifluoromethylthio, trifluoroethoxy, alkoxyalkoxy, cycloalkylalkoxy, alkoxyalkyl, alkylthioalkoxy, alkylsulphinylalkoxy, alkylsulphonylalkoxy, alkoxyalkylthio, alkoxyalkylsulphinyl, alkoxyalkylsulphonyl, alkylthioalkyl, alkylsulphinylalkyl, alkylsulphonylalkyl and dialkylaminoalkoxy, and

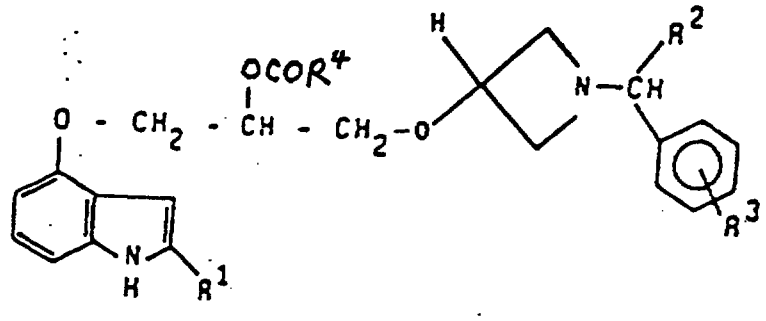
R^3 is hydrogen, alkoxy, halogen, difluoromethoxy, difluoromethylthio, trifluoromethoxy, trifluoromethylthio, trifluoroethoxy, alkoxyalkoxy, alkoxyalkyl, alkylthioalkoxy, alkylsulphinylalkoxy, alkylsulphonylalkoxy, alkoxyalkylthio, alkoxyalkylsulphinyl, alkoxyalkylsulphonyl, alkylthioalkyl, alkylsulphinylalkyl, alkylsulphonylalkyl or dialkylaminoalkoxy,

or a physiologically tolerated hydrolysable derivative thereof in which the hydroxyl group in the 2-position of the 3-aminopropoxy side chain is present in esterified form, and their tautomeric forms and their salts and acid addition salts, wherein, in all the abovementioned cases, alkyl of

alkyl groups or of alkyl moieties or alkylene moieties of groups in each case is straight-chain or branched alkyl or alkylene having 1 to 6 carbon atoms and cycloalkyl has 3 to 7 carbon atoms, and processes for their preparation and their use, and formulations comprising these compounds.

Physiologically hydrolysable derivatives are derivatives which are split under physiological conditions to give the corresponding compounds which contain a hydroxyl group in the 2-position of the propoxy side chain.

A group of such derivatives in esterified form of the compounds of the formula I comprises, for example, the compounds of the formula Ia



(Ia)

wherein R^1, R^2, R^3 and Y have the abovementioned meaning and

R^4 is alkyl having 1 to 12 carbon atoms, cycloalkyl having 3 to 7 carbon atoms, phenyl, phenylalkyl having 7 to 12 carbon atoms, phenyl or phenylalkyl having 7 to 12 carbon atoms which is monosubstituted in the phenyl ring by alkyl having 1 to 4 carbon atoms, phenyl or phenylalkyl having 7 to 12 carbon atoms which is mono- or disubstituted, by identical or different substituents, in the phenyl ring by halogen having an atomic number of 9 to 35, or phenyl or phenylalkyl having 7 to 12 carbon atoms which is mono- or di- or trisubstituted, by identical or different substituents, in the phenyl ring by alkoxy having 1 to 4 carbon atoms.

The compounds of the formula I in which the hydroxyl group in the 2-position of the propoxy side chain is present in non-esterified form are preferred.

For simplicity, the compounds according to the invention are defined in only one tautomeric form, represented by formula I. However, the invention extends to all the tautomeric forms of the compounds. In particular, the hydroxyindole form of the indole group substituted by hydroxyl in the 2-position is included.

Although pharmaceutically tolerated salts and acid addition salts of the new compounds of the formulae I and Ia and their tautomeric forms are preferred, all the salts lie within the scope of the invention. All the salts are useful for the preparation of the compounds, even if the specific salt is desired only as an intermediate product, such as, for example, if the salt is formed only for the purpose of purification or identification, or if it is used as an intermediate product in the preparation of a pharmaceutically tolerated salt, for example by ion exchange procedures.

The compounds of the general formula I and their salts contain asymmetric carbon atoms. The invention therefore also relates to the various optical isomers and the diastereoisomers, as well as to the salts and addition salts of these compounds with acids. The racemates can be separated into their optical antipodes by methods which are known per se.

Compounds in which the asymmetric carbon atom $C^{(1)*}$ in the propanolamine moiety of the formula I has the S configuration are preferred.

Compounds which are structurally related to the compounds of the present invention are described in European Patent Specification No. 25 111 and German Offenlegungsschrift 35 24 955. However, the compounds of the present invention are neither disclosed specifically nor suggested by these disclosures.

Unless stated otherwise, the alkyl groups according to the invention and alkyl moieties or alkylene moieties, according to the invention, of groups can be

straight-chain or branched, and in each case have 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, in particular 1 or 2 carbon atoms. Examples of such groups containing one or more alkyl or alkylene moieties are alkoxy, alkoxyalkoxy, alkoxyalkyl, alkylthioalkoxy, alkoxyalkylthio or dialkylalkoxy. Preferred alkyl or alkene moieties are methyl, ethyl, n-propyl, isopropyl, butyl or, correspondingly, methylene, ethylene, n- or isopropylene and butylene.

Cycloalkylalkoxy groups according to the invention, for example R^2, have 4 to 13 carbon atoms, in particular 4 to 9 carbon atoms.

The alkoxy radicals of the cycloalkylalkoxy groups have 1 to 6 carbon atoms, and methylene, ethylene and propylene are preferred as alkylene radicals of alkoxy radicals.

Cycloalkyl groups according to the invention, for example R^2, and cycloalkyl moieties according to the invention, such as cycloalkyl radicals of cycloalkylalkoxy groups, have 3 to 7 carbon atoms, in particular 3 to 6 carbon atoms. Cyclopropyl and cyclohexyl are particularly preferred.

Halogen radicals R^2 and R^3 are preferably F, Cl or Br, in particular F or Cl. Alkyl or the alkyl moiety of the alkoxy group of the substituents R^2 and R^3 are [sic] C_{1-6}-alkyl, preferably methyl, ethyl, n-propyl, isopropyl or butyl.

Preferred radicals R^3 are hydrogen, alkoxy and halogen, in particular hydrogen.

Preferred alkoxy groups of the alkoxycarbonyl group R^1 have 1 to 6, preferably 1 to 4, carbon atoms. Methoxy and ethoxy groups are particularly preferred. R^1 is preferably cyano.

Trifluoroethoxy radicals of R^2 or R^3 are preferably F_3CCH_2O radicals.

Pyridinyl is preferably pyridin-4-yl and thienyl is preferably thien-3-yl.

R^2 is preferably phenyl or substituted phenyl, but in particular phenyl. The phenyl group can carry one

or two of the substituents mentioned, which can be identical or different. If the phenyl groups are disubstituted, the substituents are preferably identical.

Substituted phenyl groups R^2 are preferably substituted in the 3- and/or 4-position, in particular monosubstituted in the 4-position, by the substituents mentioned. The radical R^3 is likewise preferably in the 3- or 4-position, in particular in the 4-position.

R^3 is preferably hydrogen. Compounds of the formula I or Ia in which R^3 is hydrogen and the other radicals have the meaning given, but R^2 in particular is phenyl, are particularly preferred.

Alkoxyalkoxy, alkoxyalkyl, alkylthioalkoxy, alkylsulphinylalkoxy, alkylsulphonylalkoxy, alkoxyalkylthio, alkoxyalkylsulphinyl, alkoxyalkylsulphonyl, alkylthioalkyl, alkylsulphinylalkyl, alkylsulphonylalkyl or dialkylaminoalkoxy substituents R^3 or such substituents of the phenyl group of the radical R^2 preferably have 2-6, in particular 2-4 or 3-6 or 3-4 or else 2 carbon atoms. Preferred alkyl or alkylene moieties in these radicals are methyl, ethyl, n-propyl, isopropyl or, correspondingly, methylene, ethylene and propylene. They are preferably terminally substituted. Particularly preferred radicals of this type are alkoxyethoxy, alkoxymethyl, alkylthioethoxy, alkylsulphinylethoxy, alkylsulphonylethoxy, alkoxyethylthio, alkoxyethylsulphinyl, alkoxyethylsulphonyl, alkylthiomethyl, alkylsulphinylmethyl, alkylsulphonylmethyl and 2-dimethylaminoethoxy.

Particularly preferred radicals R^3 and substituents of the phenyl nucleus of R^2 are difluoromethoxy and alkoxyalkoxy, preferably alkoxyethoxy, in particular methoxyethoxy, and alkoxyalkyl, preferably alkoxymethyl, in particular methoxymethyl. 2-Methoxyethoxy is particularly preferred.

A preferred compound is 4-(3-(1-diphenylmethylazetidin-3-oxy)-2-hydroxypropoxy)-1H-indole-2-carbonitrile, and salts and physiologically hydrolysable derivatives thereof, in particular with the S configuration on $C^{(1)*}$ in the propanolamine moiety.

The compounds of the formula I according to the invention, their physiologically tolerated salts and acid addition salts and physiologically hydrolysable derivatives thereof are therapeutic active compounds, have a high pharmacological action and are valuable medicaments. In particular, they display a positively inotropic, vasodilating and antiarrhythmic action and are suitable for the treatment of cardiac insufficiency, disturbances in cardiac rhythm and hypertension, coronary heart diseases and disturbances in peripheral and central arterial circulation.

The compounds of the present invention can be used on humans orally or parenterally in a dosage of 1-800 mg, preferably 10-200 mg, particularly preferably 20-100 mg per day, in particular in subdivided doses, for example three times daily. These dosages are advantageous for the treatment of the abovementioned diseases, in particular cardiac insufficiency and/or hypertension and arrhythmias.

The positively inotropic action of the compounds according to the invention has been determined on the papillary muscle of guinea-pigs (Naunyn-Schmiedeberg's Arch. Pharmacol. 304, 37, 1978). The concentration of the substance in the organ bath was in each case 10^{-4} mol/l. The maximum percentage increase in the contraction amplitude was determined in each case on three papillary muscles and was at least 50%.

According to the invention, pharmaceutical compositions are provided which comprise a compound of the formula I or the derivatives which can be hydrolysed under physiological conditions to give the compounds according to the invention, such as, for example, esters, or pharmaceutically tolerated salts thereof, together with a pharmaceutically tolerated diluent or carrier.

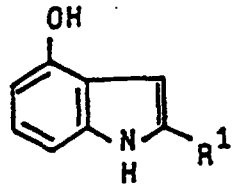
The compounds according to the invention can be mixed with customary pharmaceutically tolerated diluents or carriers and, if appropriate, with other auxiliaries and administered, for example, orally or parenterally. They can be administered orally in the form of tablets,

coated tablets, syrups, suspensions and liquids, or parenterally in the form of solutions or suspensions. Preparations for oral administration can comprise one or more additives, such as sweeteners, aromatizing agents, dyestuffs and preservatives. Tablets can comprise the active compound mixed with customary pharmaceutically tolerated auxiliaries, for example inert diluents, such as calcium carbonate, sodium carbonate, lactose and talc, granulating agents and agents which promote disintegration of the tablets on oral administration, such as starch or alginic acid, binders, such as starch or gelatin, and lubricants, such as magnesium stearate, stearic acid and talc.

Suitable carrier substances are, for example, milk sugar (lactose), gelatin, maize starch, stearic acid, ethanol, propylene glycol, ethers of tetrahydrofurfuryl alcohol and water.

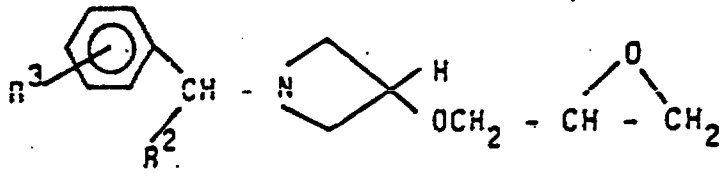
The tablets can be coated by known procedures, in order to delay disintegration and absorption in the gastrointestinal tract, whereby the activity of the active compound can extend over a longer time span. The active compound can likewise be mixed in suspensions with auxiliaries which are customary for preparation of such compositions, for example suspending agents, such as methylcellulose, tragacanth or sodium alginate, wetting agents, such as lecithin, polyoxyethylene stearate and polyoxyethylenesorbitan monooleate, and preservatives, such as ethyl parahydroxybenzoate. Capsules can comprise the active compound as the only constituent or mixed with a solid diluent, such as calcium carbonate, calcium phosphate or kaolin. The injectable preparations are likewise formulated in a manner known per se. The pharmaceutical preparations can comprise the active compound in an amount of 0.1 to 90%, in particular 1 to 90%, the remainder being a carrier substance or additive. Solid preparations, such as tablets and capsules, are preferred in respect of preparation and administration. The preparations preferably comprise the active compound in an amount of 5-50 mg.

The compounds of the formula I can be prepared by reaction of the known indole derivatives of the formula IX



(IX)

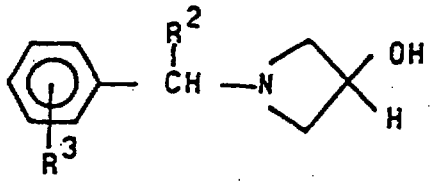
with compounds of the formula X



(X)

wherein R^1, R^2 and R^3 have the abovementioned meaning. The reactions can be carried out in aqueous dioxane or in other suitable solvents in the presence of alkali, preferably sodium hydroxide solution. The reaction temperature can be between room temperature and the boiling point of the mixture. It is preferably between 50 and 70°C.

The compounds of the formula X, in which R^2 and R^3 have the abovementioned meaning, can be prepared by reaction of known compounds, or compounds which can be prepared by known processes, of the formula XI, in which R^2 and R^3 have the abovementioned meaning,

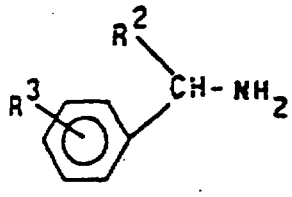


(XI)

with epichlorohydrin in a suitable solvent, such as, for example, dimethylsulphoxide, in the presence of alkali, preferably sodium hydroxide solution, at temperatures

between 0°C and 50°C, preferably room temperature.

The compounds of the general formula XI can be prepared by reaction of benzhydrylamines of the general formula XII



(XII)

in which R^2 and R^3 have the meaning given, with epichlorohydrin in a suitable solvent, such as methanol, preferably at room temperature up to the boiling point of the mixture, in particular at 70°C.

The compounds of the formula XII can be prepared by processes known per se or by processes analogous to the processes described here or analogous to processes known per se (literature: Beilstein, fourth supplement 12, system number 1734 and Najer et al., Bl. 1959, 352-355).

Esterification of the hydroxyl group in the 3-amino-propoxy side chain, which may be necessary, can be carried out by methods analogous to those known for preparation of analogous esters of 3-amino-2-hydroxy-propoxyaryl compounds, if necessary under selective conditions, if other reactive groups are present.

The starting materials used are known or can be prepared by processes known per se or by processes analogous to the processes described here or analogous to processes known per se.

The compounds of the general formula I can be either bases or acids or can be amphoteric and can therefore be isolated from the reaction mixtures in the form of their salts or acid addition salts. As bases, they can be converted into salts with suitable inorganic or organic acids by known processes, or as acids they form salts with bases.

Physiologically tolerated salts or acid addition salts are preferred. Inorganic acids which are suitable

for these are, for example, sulphuric acid or hydrogen halide acids, for example hydrochloric acid, and organic acids which are suitable for these are, for example, fumaric acid, maleic acid, nitric acid and tartaric acid. For the preparation, an alcoholic solution of a suitable acid is added to the hot alcoholic solution of the base, and the salt is obtained after addition of ether. Preferred salts are the alkali metal, alkaline earth metal and ammonium salts of the compounds of the formula I, which are obtained with the corresponding bases, in particular sodium hydroxide or potassium hydroxide.

The compounds of the formula I according to the invention have a chirality centre of carbon atom 2 of the propoxy side chain and, independently of the substituents, can have further asymmetric carbon atoms and can therefore be present as racemates and diastereoisomers. Diastereoisomers can be separated into their racemic modifications in a known manner on the basis of the physicochemical differences of their constituents. Racemates can be separated by known methods, for example by recrystallization in optically active solvents, by microorganisms or by reaction with an optically active acid or base which forms a salt with the racemic compound, separation of the diastereoisomers by fractional crystallization and liberation of the enantiomers by suitable agents. Particularly suitable optically active acids are, for example, the d and l forms of tartaric acid, ditolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid or pyrrolidonecarboxylic acid. Suitable optically active bases are alpha-phenylethylamine, menthylamine, ephedrine, brucine and quinine. The more active of the antipodes is advantageously isolated. According to the invention, however, it is also possible to obtain the pure enantiomers by asymmetric synthesis.

The following examples serve to illustrate the invention.

Preparation Example

1-(Diphenylmethyl)-3-(2,3-epoxypropoxy)-azetidine

37.5 g of diphenylmethyl-azetidin-3-ol are dissolved in a mixture of 250 ml of dimethylsulphoxide and 150 ml of 5% strength sodium hydroxide solution at room temperature, 65 ml of epichlorohydrin are added and the mixture is left to stand at room temperature for 3 days. The reaction mixture is extracted with 300 ml of methylene chloride and the organic phase is dried over sodium sulphate and evaporated. The crude product is distilled in vacuo.

Yield: 29.0 g

1-(Diphenylmethyl)-3-(2,3-epoxypropoxy)-azetidine

Boiling point 174-176°C/0.2 mbar

Example 1

4-(3-(1-Diphenylmethyl-azetidin-3-oxy)-2-hydroxypropoxy)-1H-indole-2-carboxamide

8.8 g of 4-hydroxy-1H-indole-2-carboxamide are dissolved in 250 ml of 0.8 per cent strength sodium hydroxide solution, and a solution of 16.3 g of 1-(diphenylmethyl)-3-(2,3-epoxypropoxy)-azetidine in 250 ml of dioxane is added. The mixture is left to stand at room temperature for 4 hours and then heated at 60°C for a further 20 hours. The reaction mixture is then stirred into 1 l of ice-water and extracted twice with 500 ml of methylene chloride each time. The organic phase is dried with potassium carbonate and the solvent is distilled off in vacuo. The residue is triturated twice with 100 ml of diisopropyl ether each time and filtered off with suction.

Yield: 7.1 g

4-(3-(1-diphenylmethyl-azetidin-3-oxy)-2-hydroxypropoxy)-1H-indole-2-carboxamide

Melting point 186°C

Example 2

4-(3-(1-Diphenylmethyl-azetidin-3-oxy)-2-hydroxypropoxy)-1H-indole-2-carbonitrile

10.0 g of 4-(3-(1-diphenylmethyl-azetidin-3-oxy)-2-hydroxypropoxy)-1H-indole-2-carboxamide are dissolved

in a mixture of 112 ml of dioxane and 10 g of pyridine, and 10 ml of trifluoroacetic anhydride in 10 ml of dioxane are added at 10°C. After the mixture has stood at room temperature for two hours, it is stirred into ice-water. It is extracted with methylene chloride and washed first with dilute NaOH and then with water, and the organic phase is dried over sodium sulphate and concentrated. The residue is purified by column chromatography on silica gel (mobile phase: chloroform). Yield: 9.3 g (41%) of 4-(3-(1-diphenylmethyl-azetidin-3-oxy)-2-hydroxypropoxy)-1H-indole-2-carbonitrile
Melting point: 83-85°C

Example 3

Preparation of ampoules

Ampoules which comprise the constituents mentioned below can be prepared in a known manner. The active compound is dissolved in water and 1,2-propanediol and glass ampoules are filled with the mixture under nitrogen.

4-(3-(1-diphenylmethyl-azetidin-3-oxy)-2-hydroxypropoxy)-1H-indole-2-carbonitrile	2 mg
1,2-propanediol	0.8 ml
distilled water to	2.0 ml

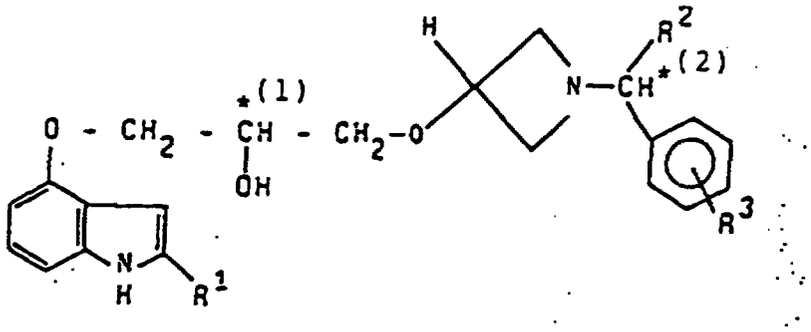
Example 4

Preparation of tablets and capsules

Tablets and capsules which comprise the constituents mentioned below are prepared by known procedures. These are suitable for the treatment of the abovementioned diseases, in particular cardiac insufficiency, in dosage amounts of in each case one tablet or capsule three times daily.

Constituents	Weight (mg	
	Tablet	Capsule
4-(3-(1-Diphenylmethyl-azetidin-3-oxy)-2-hydroxypropoxy)-1H-indole-2-carbonitrile	30	10
Tragacanth	10	
Lactose	247.5	300
Maize starch	25	
Talc	15	
Magnesium stearate	2.5	

The compounds of the formula I according to the invention shown in the following Table can be obtained analogously to the above Examples 1 and 2 (Examples 1-11):



"rac" denotes racemic. Unless indicated otherwise by R^4, the 2-hydroxyl group of the propoxyamino side chain is in the non-esterified form.

"---" denotes that no asymmetric carbon atom is present.

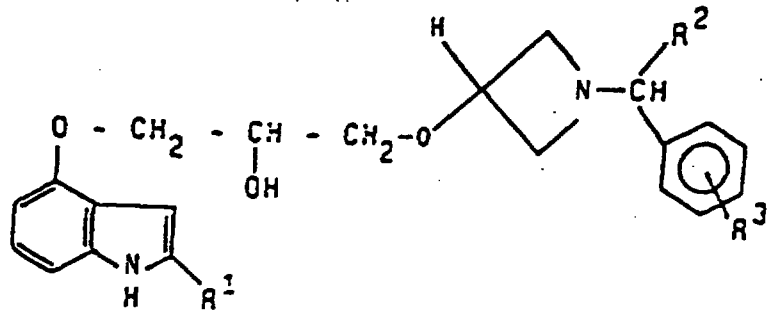
Example	R^1	R^2	R^3	Configuration C*(1)	Configuration C*(2)	Melting point °C
3	CN	Phenyl	3-OCH_3	rac	rac	
4	CN	Phenyl	2-Cl	rac	rac	
5	CN	4-Cl-phenyl	4-Cl	rac	---	
6	CN	Phenyl	4-Cl	rac	rac	
7	CN	Phenyl	4-OCH_3	rac	rac	
8	$CONH_2$	Phenyl	H	rac	---	186
9	CN	4-F-phenyl	4-F	rac	---	78-80
10	CN	Phenyl	H	S	---	79
11	CN	Phenyl	O-$(CH_2)_2OCH_3$	rac	rac	

* C L M S *

Patent claims

for the contracting states: AT, BE, CH, DE, FR, GB, IT, Li, NL, SE

1. Substituted indolylpropanols of the formula I



in which

R^1 is a cyano, carboxamide, alkoxycarbonyl, hydroxyl or acetyl group,

R^2 is pyridinyl, thienyl, phenyl or substituted phenyl, which is mono- or disubstituted by halogen, alkyl, cycloalkyl, alkoxy, difluoromethoxy, difluoromethylthio, trifluoromethoxy, trifluoromethylthio, trifluoroethoxy, alkoxyalkoxy, cycloalkylalkoxy, alkoxyalkyl, alkylthioalkoxy, alkylsulphinylalkoxy, alkylsulphonylalkoxy, alkoxyalkylthio, alkoxyalkylsulphinyl, alkoxyalkylsulphonyl, alkylthioalkyl, alkylsulphinylalkyl, alkylsulphonylalkyl and dialkylaminoalkoxy, and

R^3 is hydrogen, alkoxy, halogen, difluoromethoxy, difluoromethylthio, trifluoromethoxy, trifluoromethylthio, trifluoroethoxy, alkoxyalkoxy, alkoxyalkyl, alkylthioalkoxy, alkylsulphinylalkoxy, alkylsulphonylalkoxy, alkoxyalkylthio, alkoxyalkylsulphinyl, alkoxyalkylsulphonyl, alkylthioalkyl, alkylsulphinylalkyl, alkylsulphonylalkyl or dialkylaminoalkoxy,

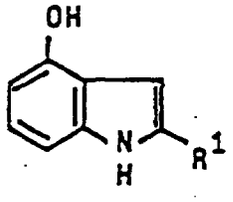
or a physiologically tolerated hydrolysable derivative thereof in which the hydroxyl group in the 2-position of the 3-aminopropoxy side chain is present in esterified form, and their tautomeric forms and their salts and acid addition salts,

wherein, in all the abovementioned cases, alkyl of alkyl groups or of alkyl moieties or alkylene moieties of groups in each case is straight-chain or branched alkyl or alkylene having 1 to 6 carbon atoms and cycloalkyl has 3 to 7 carbon atoms.

2. 4-(3-(1-Diphenylmethyl-azetidin-3-oxy)-2-hydroxy-propoxy)-1H-indole-2-carbonitrile.

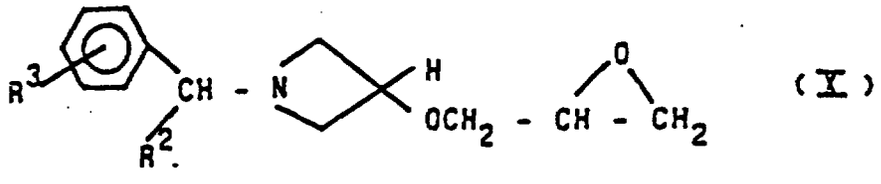
3. Process for the preparation of compounds of the formula I according to Claim 1, in which R^1 is a cyano or nitrile group, characterized in that corresponding compounds of the formula I in which R^1 is a carboxamido group are dehydrated.

4. Process for the preparation of compounds of the formula I according to Claim 1, characterized in that indole derivatives of the formula IX



(IX)

in which R^1 has the abovementioned meaning, are reacted with compounds of the formula X



(X)

in which R^2 and R^3 have the meaning given, and, if appropriate, the resulting compounds are esterified and converted into salts.

5. Pharmaceutical preparation, characterized in that it comprises one or more of the compounds according to Claim 1 or physiologically tolerated salts thereof and if appropriate customary carrier substances and/or diluents.

6. Compound according to Claim 1 as a pharmaceutical

active compound, in particular for the treatment of cardiac insufficiency, disturbances in cardiac rhythm and hypertension, coronary heart diseases and disturbances in peripheral and central arterial circulation.