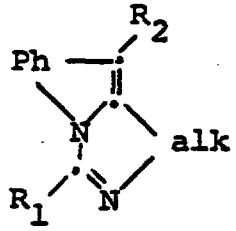
Novel amidines, processes for their manufacture, pharmaceutical preparations containing them, and their use.

The invention relates to novel amidines, especially N,N'-bridged carboxylic acid amidines of the general formula



(I),

in which

R_1 represents phenyl optionally substituted in the p-position by lower alkylthio having up to and including 7 carbon atoms, by lower alkanesulphinyl having up to and including 7 carbon atoms, by lower alkoxy having up to and including 7 carbon atoms or by halogen having an atomic number of up to and including 35, thienyl, or pyridyl optionally substituted by lower alkyl

having up to and including 7 carbon atoms,

R_2 represents carboxymethyl or, secondly, lower alkoxycarbonylmethyl having up to and including 8 carbon atoms,

Ph represents 1,2-phenylene optionally substituted in the p-position to the nitrogen atom by lower alkoxy having up to and including 7 carbon atoms or by halogen having an atomic number of up to and including 35, and

alk represents vinylene,

and salts thereof, with the proviso that if R_1 represents p-methylthiophenyl and Ph represents 1,2-phenylene substituted in the p-position to the nitrogen atom by fluorine, R_2 is other than carboxymethyl or ethoxycarbonylmethyl, and with the further proviso that if R_1 represents phenyl and Ph represents unsubstituted 1,2-phenylene or if R_1 represents p-chlorophenyl and Ph represents 1,2-phenylene substituted in the p-position to the nitrogen atom by methoxy, in each case R_2 is other than ethoxycarbonylmethyl, and to processes for their manufacture, to pharmaceutical preparations containing them and to their use as medicaments.

In the present description and claims, "lower" organic radicals and compounds are to be understood as those having up to and including 7, especially up to and including 4, carbon atoms.

The general definitions used hereinbefore and hereinafter have especially the following meanings within the scope of the present description:

Lower alkylthio is, for example, methyl-, ethyl-, n-propyl-, isopropyl-, n-butyl-, isobutyl-, sec.-butyl-, tert.-butyl, n-pentyl-, n-hexyl- or n-heptyl-thio, and lower alkanesulphinyl is, for example, methane-, ethane- or n-propane-sulphinyl.

Lower alkoxy is, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec.-butoxy or tert.-butoxy.

Halogen is, for example, halogen having an atomic number of up to and including 35, such as fluorine, chlorine or

bromine, and also iodine.

Lower alkyl is, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl, tert.-butyl, and also a pentyl, hexyl or heptyl radical.

Thienyl is, for example, 2- or 3-thienyl, and pyridyl is 2-, 3- or 4-pyridyl.

Lower alkoxycarbonyl is, for example, methoxy-, ethoxy- or n-propoxy-carbonyl, and also a butoxy-, pentyloxy-, hexyloxy- or heptyloxy-carbonyl radical.

Salts of compounds of the formula I according to the invention are preferably pharmaceutically acceptable salts, such as corresponding acid addition salts and/or, when R_2 is 1-carboxymethyl, internal salts or salts with bases. Suitable acid addition salts are, for example, salts with inorganic acids, such as mineral acids, or organic acids, such as sulphamic acids, for example cyclohexylsulphamic acid, optionally unsaturated dicarboxylic acids, or carboxylic acids optionally additionally substituted by hydroxy or additionally containing oxo and/or carboxy, or sulphonic acids. Mineral acids are, for example, sulphuric acid or hydrohalic acids, such as hydrobromic or hydrochloric acid. There come into consideration as optionally unsaturated dicarboxylic acids, for example, oxalic acid, malonic acid, fumaric acid or maleic acid, and there are used as carboxylic acids optionally additionally substituted by hydroxy or additionally containing oxo and/or carboxy, for example, tartaric acid, malic acid, pyruvic acid or citric acid. Sulphonic acids are, for example, benzenesulphonic, p-toluenesulphonic or methanesulphonic acid.

Suitable salts with bases are, for example, metal, such as alkali metal or alkaline earth metal, salts, for example sodium, potassium, magnesium or calcium salts, transition metal salts, such as zinc or copper salts, or salts with ammonia or salts of substituted organic amines, such as morpholine, thiomorpholine, piperidine and pyrrolidine, such as mono-, di- or tri-lower alkylamines or mono-, di- or tri-hydroxy-lower alkylamines, for example mono-,

di- or tri-ethanolamine and tris(hydroxymethyl)methylamine or diisopropanolamine. Mono-lower alkylamines are, for example, ethylamine or tert.-butylamine. Di-lower alkylamines are, for example, diethylamine or dipropylamine, and there come into consideration as tri-lower alkylamines, for example, triethylamine, tributylamine or dimethylpropylamine. Furthermore, salts can be formed with basic amino acids, such as lysine, arginine, histidine or ornithine, or with amines that are derived from monosaccharides, such as N-methyl-D-glucamine.

The compounds of the formula I have valuable pharmacological properties. In particular they exhibit a pronounced antinociceptive (analgesic) activity, which may be demonstrated, for example, by the acetic acid-writhing syndrome in rats in a dosage range of from approximately 1 to approximately 30 mg/kg p.o. and by the phenyl-p-benzoquinone-writhing test in mice in a dosage range of from approximately 1 to approximately 30 mg/kg p.o..

In addition, they have a marked anti-inflammatory and anti-arthritic activity, which may be demonstrated by suppression of kaolin paw oedema in normal rats in a dosage range of approximately 10 to 100 mg/kg p.o., and which, in addition, may be demonstrated by the suppression of carrageenin paw oedema in rats, analogously to the method described by Pasquale et al., Agents and Actions, 5, 256 (1976), in doses of from approximately 3 to approximately 300 mg/kg p.o..

Furthermore, in curative administration with administration, four times, of approximately 10 to 100 mg/kg p.o., the compounds of the formula I suppress kaolin paw oedema of rats having adjuvant-arthritis.

The compounds of the formula I are therefore excellently suitable as medicaments for the treatment of inflammatory disorders, especially those in the rheumatic and arthritic field, as antiphlogistics and/or as peripheral analgesics.

The invention relates, for example, to compounds of the formula I in which R_1 represents phenyl optionally substituted in the p-position by lower alkylthio having up to and including 4 carbon atoms, such as methylthio, by lower alkanesulphinyl having up to and including 4 carbon atoms, such as methanesulphinyl, by lower alkoxy having up to and including 4 carbon atoms, such as methoxy, or by halogen having an atomic number of up to and including 35, such as fluorine, thienyl, such as 2-thienyl, or pyridyl optionally substituted by lower alkyl having up to and including 4 carbon atoms, such as methyl, such as 2-picolinyl, R_2 represents carboxymethyl or, secondly, lower alkoxycarbonylmethyl having up to and including 5 carbon atoms, such as ethoxycarbonylmethyl, Ph represents 1,2-phenylene optionally substituted in the p-position to the nitrogen atom by lower alkoxy having up to and including 4 carbon atoms, such as methoxy, or by halogen having an atomic number of up to and including 35, such as fluorine, and alk represents vinylene, with the proviso that if R_1 represents p-methylthiophenyl and Ph represents 1,2-phenylene substituted in the p-position to the nitrogen atom by fluorine, R_2 is other than carboxymethyl or ethoxycarbonylmethyl, and with the further proviso that if R_1 represents phenyl and Ph represents unsubstituted 1,2-phenylene or if R_1 represents p-chlorophenyl and Ph represents 1,2-phenylene substituted in the p-position to the nitrogen atom by methoxy, in each case R_2 is other than ethoxycarbonylmethyl.

The invention relates preferably to compounds of the formula I in which R_1 represents unsubstituted phenyl, p-methoxyphenyl or p-methanesulphinylphenyl, R_2 in each case represents ethoxycarbonylmethyl, Ph in each case represents 1,2-phenylene substituted in the p-position to the nitrogen atom by fluorine and alk in each case represents vinylene, or in which R_1 represents unsubstituted 2-thienyl, unsubstituted phenyl, p-methanesulphinylphenyl or p-methoxyphenyl, R_2 in each case represents

carboxymethyl, Ph in each case represents 1,2-phenylene substituted in the p-position to the nitrogen atom by fluorine and alk in each case represents vinylene, or in which R_1 in each case represents unsubstituted 2-thienyl, R_2 represents carboxymethyl or ethoxycarbonylmethyl, Ph in each case represents unsubstituted 1,2-phenylene and alk in each case represents vinylene, or in which R_1 represents unsubstituted phenyl, R_2 represents carboxymethyl, Ph represents unsubstituted 1,2-phenylene, and alk represents vinylene, or in which R_1 represents 2-picolinyl or p-fluorophenyl, R_2 in each case represents carboxymethyl or ethoxycarbonylmethyl, Ph in each case represents 1,2-phenylene substituted in the p-position to the nitrogen atom by methoxy and alk in each case represents vinylene, and salts thereof.

The invention relates preferably to compounds of the formula I in which R_1 represents unsubstituted phenyl, p-methoxyphenyl or p-methanesulphinylphenyl, R_2 in each case represents ethoxycarbonylmethyl, Ph in each case represents 1,2-phenylene substituted in the p-position to the nitrogen atom by fluorine and alk in each case represents vinylene, or in which R_1 represents unsubstituted phenyl, p-methanesulphinylphenyl or p-methoxyphenyl, R_2 in each case represents carboxymethyl, Ph in each case represents 1,2-phenylene substituted in the p-position to the nitrogen atom by fluorine and alk in each case represents vinylene, or in which R_1 in each case represents unsubstituted thienyl, R_2 represents carboxymethyl or ethoxycarbonylmethyl, Ph in each case represents unsubstituted 1,2-phenylene and alk in each case represents vinylene, or in which R_1 represents unsubstituted phenyl, R_2 represents carboxymethyl, Ph represents unsubstituted 1,2-phenylene and alk represents vinylene, or in which R_1 represents 2-picolinyl or p-fluorophenyl, R_2 in each case represents carboxymethyl or ethoxycarbonylmethyl, Ph in each case represents 1,2-phenylene substituted in the p-position to the nitrogen atom by methoxy and alk in each

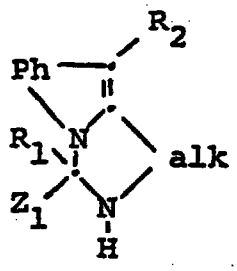
case represents vinylene, and salts thereof.

The invention relates especially to compounds of the formula I in which Ph represents unsubstituted 1,2-phenylene and R_1 represents phenyl and R_2 represents carboxymethyl or R_1 represents 2-thienyl and R_2 represents carboxy- or ethoxycarbonyl-methyl, or Ph represents 1,2-phenylene substituted in the p-position to the nitrogen atom by fluorine and R_1 represents phenyl, p-methanesulphinylphenyl or p-methoxyphenyl, and R_2 represents carboxy- or ethoxy-carbonyl-methyl, or Ph represents 1,2-phenylene substituted in the p-position to the nitrogen atom by methoxy and R_1 represents p-fluorophenyl or 2-picolinyl and R_2 represents carboxy- or ethoxycarbonyl-methyl, alk in each case representing vinylene, and salts thereof.

The invention relates especially to processes for the manufacture of compounds of the formula I mentioned in the Examples and salts, especially pharmaceutically acceptable salts, thereof.

The invention relates especially to the compounds of the formula I mentioned in the Examples and to salts, especially pharmaceutically acceptable salts, thereof.

The compounds of the formula I and their salts can be manufactured according to methods known per se, for example by removing $H\text{-}Z_1$ from compounds of the general formula



(II),

in which Z_1 represents optionally functionally modified hydroxy or the mercapto group, or from salts thereof, with the introduction of an additional bond, and, if desired, converting a compound obtainable according to the invention into a different compound of the formula I or converting a free compound obtainable according to the invention into a salt, or converting a salt obtainable according to the process into the free compound or into a different salt.

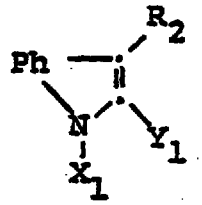
Functionally modified hydroxy is, for example, hydroxy etherified by a lower alkanol, such as methanol or ethanol, or by an optionally substituted aromatic alcohol, such as phenol, or hydroxy esterified by an inorganic acid, such as a mineral acid, for example a hydrohalic acid, such as hydrochloric acid, and represents, for example, lower alkoxy, such as methoxy, or optionally substituted aryloxy, such as phenoxy, or halogen, such as chlorine or bromine.

$H\text{-}Z_1$ is removed in customary manner, for example spontaneously, by thermal means, i.e. by heating, and/or in the presence of a catalytic agent. The thermal removal is usually carried out in a temperature range of from approximately 50° to approximately 200°C. As catalytic agents there are used, for example, basic or acidic catalysts, there being used as bases, for example, alkali metal hydroxides, amides or hydrides, such as potassium hydroxide, sodium amide or sodium hydride, metal oxides, such as aluminium oxide, or, especially, organic nitrogen bases, such as tertiary amines, for example pyridine, quinoline or N,N-dimethylaniline, and as acidic catalysts, for example, mineral acids or acidic salts or anhydrides thereof, such as sulphuric acid or phosphoric acids, hydrogen sulphates, such as alkali metal hydrogen sulphates, for example potassium hydrogen sulphate, phosphorus pentoxide, or mineral acid halides, such as phosphorus(III) or phosphorus(V) chloride or phosphorus oxychloride, or sulphuric acid halides, for example sulphuryl chloride.

The operation is, if necessary, carried out in the presence of an inert solvent or diluent, in a closed vessel and/or under an inert gas, for example nitrogen.

Inert solvents and diluents are optionally substituted hydrocarbons, such as optionally halogenated aliphatic or aromatic hydrocarbons, for example chloroform or chlorobenzene, ethers, such as aliphatic, cycloaliphatic or aromatic ethers, for example diethyl ether, dioxan, tetrahydrofuran, diphenyl ether or anisole, ketones, such as aliphatic ketones, for example acetone or methylethylketone, amides, such as dialkylamides, for example dimethylformamide, or sulphoxides, such as di-lower alkyl sulphoxides, for example dimethyl sulphoxide.

Starting materials of the formula II can be manufactured according to processes known per se, preferably in situ. It is thus possible, for example, to cyclise compounds of the formula



(IVa)

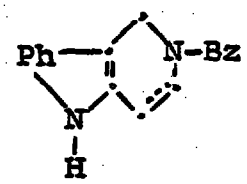
or salts thereof, in which X_1 represents hydrogen and Y_1 represents a group of the formula -alk-NH-C(=Z_1')(R_1) or X_1 represents -C(=Z_1')(R_1) and Y_1 represents a group of the formula -alk-NH_2 and Z_1' represents optionally functionally modified oxo, and, if desired, to convert a resulting free compound of the formula II into a different free compound or into a salt, or to convert a salt obtainable according to the process into the free compound or into a different salt. Thus, for example, free hydroxy can be converted in customary manner into halogen or, with a lower alkanecarboxylic acid, into esterified hydroxy.

Functionally modified oxo is, for example, thioxo, ketalised or thio-ketalised oxo, esterified dioxy, or imino. Ketalised oxo compounds are, for example, ketals with lower alkanols, such as methanol or ethanol, or lower alkanediols, such as ethylene glycol or propylene glycols, for example 1,3-dihydroxypropane, and thioketals are, for example, thioketals with lower alkanethiols, for example methanethiol or ethanethiol, or lower alkanedithiols, such as 1,2-ethanedithiol, or propanedithiols, for example propane-1,3-dithiol. Imino is, for example, imino optionally substituted by lower alkyl or phenyl, such as N-lower alkylimino, for example N-propylimino.

The cyclisation is carried out in known manner, for example in the presence of catalysts, such as acidic catalysts. These are, for example, mineral acids, such as sulphuric acid or polyphosphoric acid, mineral acid halides, such as sulphuryl chloride, or phosphorus halides, for example phosphorus pentachloride, or organic sulphonic acids, such as benzenesulphonic, p-toluenesulphonic or methanesulphonic acid. The cyclisation is, if necessary, carried out in one of the above-mentioned inert solvents or diluents, preferably while heating, for example in a temperature range of from approximately 20° to approximately 200°C, in a closed vessel and/or under an inert gas, for example nitrogen.

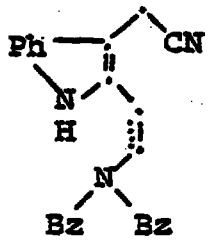
In an advantageous embodiment of the above-described process, compounds of the formula IVa are used as starting materials and the cyclisation to form compounds of the formula II and the removal of H-Z_1 from the compounds of the formula II are carried out in situ without isolation of the intermediates.

An especially advantageous embodiment of the above-described process carried out by way of the compounds of the formula II consists, for example, in quaternising, especially with benzyl bromide, compounds of the formula

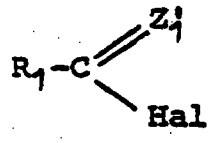


(IVd),

in which Bz represents an optionally substituted α-phenyl-lower alkyl radical, preferably benzyl, cleaving the bond at the quaternary nitrogen atom by means of cyanides, such as alkali metal cyanides, for example sodium cyanide, and, in a resulting compound of the formula IVe

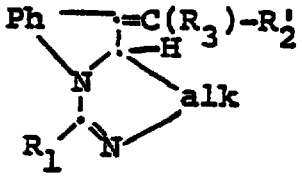


(IVe),

solvolysing the cyano group as desired, removing the benzyl groups by hydrogenolysis in the presence of a hydrogenation catalyst, for example palladium, and reacting the then free amino compound with a compound of the formula  in which Z_1' represents optionally functionally modified oxo and Hal represents halogen, and finally reacting by means of a cyclising agent, preferably a mineral acid halide, such as phosphorus oxychloride or phosphorus chloride, that is to say phosphorus(III) or phosphorus(V) chloride, to form a compound of the formula II, from which the

corresponding compound of the formula I is formed directly under the reaction conditions with condensation. This reaction is especially carried out in such a manner that corresponding 3,4-dihydropyrimido[1,6-a]indoleacetic acids or lower alkyl esters are formed. Accordingly, these dihydro derivatives must be dehydrogenated in the manner described below to form the desired compounds of the formula I.

The compounds of the formula I or salts thereof may furthermore be manufactured by isomerising compounds of the formula



(V),

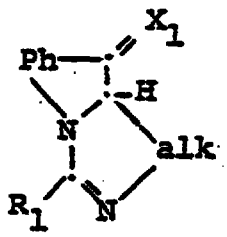
in which R_2' represents carboxy optionally esterified as indicated under R_2, and R_3 represents hydrogen, or salts thereof, and, if desired, converting a resulting free compound of the formula I into a different free compound or into a salt, or converting a salt obtainable according to the process into the free compound or into a different salt.

The isomerisation of compounds of the formula V to form compounds of the formula I is carried out in customary manner, if necessary by means of acids, such as mineral acids, for example sulphuric acid, bases, such as alkali metal hydroxides or carbonates, for example sodium hydroxide or potassium carbonate, or by means of organic amines, for example tertiary amines, such as pyridine, or by applying energy, such as at temperatures of above 100°C, optionally in the presence of a catalytic agent, such as a borate or phosphate, for example an alkali metal borate or phosphate and, if necessary, in a solvent or diluent, in a closed vessel and/or under an

inert gas, for example nitrogen.

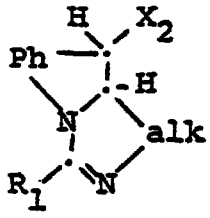
Inert solvents and diluents are optionally substituted hydrocarbons, such as optionally halogenated aliphatic or aromatic hydrocarbons, for example chloroform or chlorobenzene, ethers, such as aliphatic, cycloaliphatic or aromatic ethers, for example diethyl ether, dioxan, diphenyl ether or anisole, ketones, such as aliphatic ketones, for example acetone or methylethylketone, amides, such as dialkylamides, for example dimethylformamide, or sulphoxides, such as di-lower alkyl sulphoxides, for example dimethyl sulphoxide.

Starting materials of the formula V or salts thereof can be manufactured according to methods known per se, for example by reacting compounds of the formula



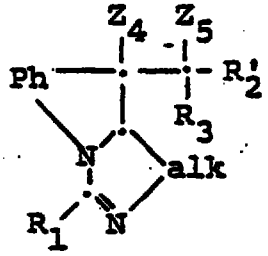
(VIa),

in which X_1 represents oxo or thioxo, with compounds of the formula $P(Z_2)_3=C(R_3)-R_2'$ or $X_1=P(Z_3)_2-CH(R_3)-R_2'$ respectively, which may be in the form of phosphonium ylides or in the form of phosphoranes, and in which X_1 represents oxo or thioxo, Z_2 represents alkyl and/or phenyl, Z_3 represents alkyl and/or phenyl, or alkoxy and/or phenoxy, and R_3 represents hydrogen. Starting materials of the formula V or salts thereof may likewise be manufactured, for example, by reacting compounds of the formula



(VIb),

in which X_2 represents a group of the formula $-C(R_3)=X_2'$ and X_2' represents optionally functionally modified oxo, with hydrogen cyanide or a salt, for example an alkali metal salt, thereof. After solvolysis, which optionally follows, a compound of the formula Z_4-Z_5 is removed from resulting intermediates of the formula



(VII),

in which Z_4 represents hydroxy or thio optionally present in salt form and Z_5 represents a radical of the formula $-\overset{\oplus}{P}(Z_2)_3$ or $-\overset{\oplus}{P}(Z_3)_2-\overset{\ominus}{O}$, or Z_4 represents hydrogen and Z_5 represents hydroxy or mercapto.

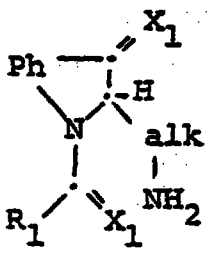
Alkoxy is, for example, lower alkoxy, such as methoxy, ethoxy, propoxy or butoxy. Optionally functionally modified oxo is oxo, thioxo, or imino optionally substituted by lower alkyl or phenyl.

In an advantageous embodiment of the above-described process for the manufacture of compounds of the formula I, for example using compounds of the formula VII as starting materials, the manufacture of compounds of the formula V and the isomerisation according to the invention can be carried out <u>in situ</u>.

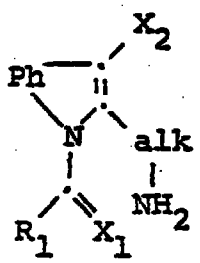
The removal of Z_4-Z_5 is carried out in customary manner, for example by the application of energy, for example a reaction temperature of from approximately 50° to approximately 200°C, or in the presence of a catalytic agent. Such agents are, for example, basic or acidic catalysts, there being used as bases, for example alkali metal hydroxides, amides, carbonates or hydrides, such as potassium hydroxide, sodium amide, potassium carbonate or sodium hydride, metal oxides, such as aluminium oxide, or organic nitrogen bases, such as tertiary amines, for example pyridine, quinoline or N,N-dimethylaniline, and as acidic catalysts, for example, mineral acids, such as sulphuric acid, hydrogen sulphates, such as alkali metal hydrogen sulphates, for example potassium hydrogen sulphate, polyphosphoric acid, mineral acid anhydrides, such as phosphorus pentoxide, or mineral acid halides, such as sulphuric acid halides, for example sulphuryl chloride.

The method for the formation of starting materials of the formula V is, if necessary, carried out in the presence of an inert solvent or diluent, in a closed vessel and/or under an inert gas, for example nitrogen.

Compounds of the formulae VIa or VIb may, for their part, be manufactured according to analogous processes that are known per se, for example by condensing compounds of the formula



(VId) or



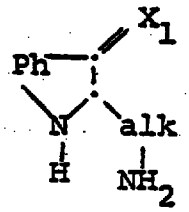
(VIe)

in the presence of a condensation agent. Suitable condensation agents are, for example, acids, such as mineral acids, for example sulphuric acid, polyphosphoric acid or a hydrohalic acid, for example hydrochloric acid, or phosphoric acid halides, such as phosphorus oxychloride or phosphorus trichloride.

Phosphoranes of the formula $P(Z_2)_3=C(R_3)-R_2'$ and their phosphonium ylides can be manufactured according to methods known per se, for example by reacting phosphines of the formula $P(Z_2)_3$ with quaternary ammonium bases of the formula $R_2'-CH(R_3)-\overset{\oplus}{N}(alk')_3B^{\ominus}$ in which alk' represents an alkyl radical, such as a lower alkyl radical, and $B^{\ominus}$ represents an anion, such as a halide or hydroxyl anion, and by subsequent reaction with strong bases, such as alkali metal organyls, for example butyllithium or phenyllithium. The corresponding quaternary ammonium bases are obtained likewise by reaction of phosphines $P(Z_2)_3$ with known compounds of the formula R_2-Hal in the presence of bases, such as alkali metal hydroxides, lower alkoxides, hydrides or amides, for example sodium hydroxide, sodium methoxide, potassium hydride or potassium amide.

Compounds of the formula $X_1=P(Z_3)_2-CH(R_3)-R_2'$ can be manufactured, for example, by reacting compounds of the formula $P(Z_3)_3$ in which Z_3 represents alkoxy or phenoxy, with compounds of the formula Hal-$CH(R_3)-R_2'$ in which Hal represents halogen.

Compounds of the formula VId are obtainable by acylation of compounds of the formula

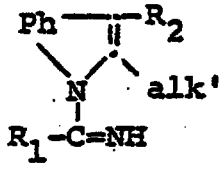


(VIg)

with compounds of the formula $R_1-C(=X_1)-X_4$ in which X_4 represents halogen or acyl.

Acyl is derived, for example, from a carboxylic acid, such as a lower alkanecarboxylic acid, and represents, for example, lower alkanoyl, such as acetyl, propionyl or pivaloyl.

The compounds of the formula I or salts thereof can furthermore be produced, for example, by cyclising a compound of the general formula



(VIII),

in which alk' represents a group of the formula $-CH=CH-Z_6$ or $-CH_2-CH=Z_6'$, and Z_6 represents optionally functionally modified hydroxy or amino, and Z_6' represents oxo or imino, or a salt thereof, and, if desired, converting a resulting free compound of the formula I into a different free compound or into a salt, or converting a salt obtainable according to the process into the free compound or into a different salt.

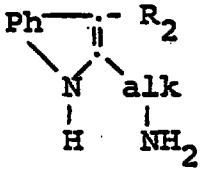
Functionally modified hydroxy is, for example, hydroxy etherified by lower alkanol, such as methanol or ethanol, or by an optionally substituted aromatic alcohol, such as phenol, or hydroxy esterified by a suitable anhydride, such as acetic anhydride, by an organic acid, such as a sulphonic acid, for example lower alkylsulphonic or optionally substituted arylsulphonic acid, such as methanesulphonic or p-toluenesulphonic acid, or by an inorganic acid, such as a mineral acid, for example a hydrohalic acid, such as hydrochloric acid, and represents,

for example, lower alkoxy, such as methoxy, or optionally substituted aryloxy, such as phenoxy, or lower alkanoyloxy, such as acetoxy, lower alkanesulphonyloxy or optionally substituted arylsulphonyloxy, such as methanesulphonyloxy or p-toluenesulphonyloxy, or halogen, such as chlorine or bromine.

The cyclisation is carried out in a manner known per se, for example in the presence of a condensation agent, such as an acidic condensation agent. Included among these are, for example, acids, such as mineral acids, for example sulphuric acid or polyphosphoric acid, and mineral acid halides, such as phosphoric acid halides, for example phosphorus oxychloride, phosphorus tribromide or phosphorus pentachloride. The reaction is, if necessary, carried out in a solvent or diluent, in a temperature range of from approximately 20° to approximately 200°C, in a closed vessel and/or under an inert gas, for example nitrogen.

Inert solvents and diluents are optionally substituted hydrocarbons, such as aliphatic or aromatic halogenated hydrocarbons, for example chloroform or chlorobenzene, optionally mixed ethers, such as aliphatic, cycloaliphatic or aromatic ethers, for example diethyl ether, dioxan, diphenyl ether or anisole, ketones, such as aliphatic ketones, such as acetone or methylethylketone, amides, such as dialkylamides, for example dimethylformamide, or sulphoxides, such as lower alkyl sulphoxides, for example dimethyl sulphoxide.

The starting materials of the formula VIII can be manufactured according to methods known per se, for example by substituting the primary amino group in compounds of the formula



(IX)

by means of alkali metal nitrites in the presence of acids, by hydroxy, optionally reactively esterifying this group, acylating the indole nitrogen with a compound of the formula R_1-COOH or with a functionally modified derivative thereof, and then forming the corresponding amidine with ammonia.

The acylation of the indole nitrogen is carried out according to methods known per se, for example by reaction with optionally functionally modified carboxy derivatives, such as acids, acid anhydrides or activated esters. Anhydridised carboxy in this process is anhydridised, for example, by inorganic acids, such as a hydrohalic acid, by hydrazoic acid, by hydrocyanic acid or by organic acids, such as lower alkanoic acids optionally substituted by halogen, for example acetic acid. Included among these are, for example, acid halides, for example acid chlorides, corresponding acid azides, acid nitriles or acyloxycarbonyl.

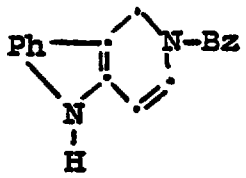
The acylation with a compound of the formula R_1-COOH or an optionally functionally modified derivative thereof is carried out in customary manner. When using an anhydride, especially an acid halide, as starting material, the acylation is preferably carried out in the presence of a strong base, for example an alkali metal hydride, for example sodium hydride, an alkali metal amide, for example sodium amide, or an alkali metal alcoholate, for example potassium methoxide.

The acylation, like the subsequent reaction with ammonia, is carried out, for example, in an inert solvent, such as an alkylated amide, for example N,N-dimethylformamide, an optionally halogenated hydrocarbon, for example chloroform or chlorobenzene, or a nitrile, for example acetonitrile, or in a mixture thereof, if necessary at reduced or elevated temperature and/or in an inert gas atmosphere.

The compounds of the formula IX may, for their part, be produced according to processes known per se, for

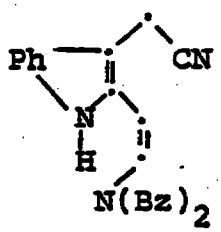
example analogously to Fischer's indole synthesis, by treating phenyl hydrazones or correspondingly 1,3-substituted 4-piperidones with acids, such as with ethanolic hydrochloric acid, or by acylation and condensation of correspondingly substituted α-hydroxyketones with optionally substituted anilines.

The compounds of the formula IX may furthermore, in a preferred embodiment, be manufactured, for example, by quaternising starting compounds of the formula



(IVd),

in which Bz represents an optionally substituted α-phenyl-lower alkyl radical, preferably benzyl, especially with benzyl bromide, and cleaving the bond at the resulting quaternary nitrogen by means of a nucleophile, preferably by cyanides, and in a compound of the formula

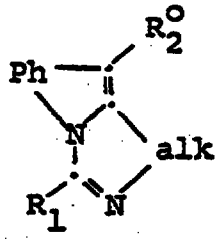


(IVe)

obtainable as intermediate, solvolysing the cyano group as desired and removing the benzyl groups, for example by hydrogenolysis in the presence of a hydrogenation catalyst, for example palladium.

The compounds of the general formula I or salts thereof can furthermore be manufactured, for example, by,

in a compound of the formula



(X),

in which R_2^o represents a radical that can be converted into the group R_2, or in salts thereof, converting R_2^o into the group R_2 by solvolysis or oxidation and, if desired, converting a resulting free compound of the formula I into a different free compound or into a salt, or converting a salt obtainable according to the process into the free compound or into a different salt.

Thus, R_2^o is, for example, a group of the formula $-CH(R_3)-R_2''$ in which R_3 represents hydrogen and R_2'' represents functionally modified carboxy other than R_2' and R_2' is identical to the carboxy or lower alkoxycarbonyl moiety of R_2 as hereinbefore defined,

or is a group of the formula $-C(=O)-\overset{\oplus\ominus}{N_2}B^{\ominus}$, in which $B^{\ominus}$ represents the anion of a mineral acid, for example chloride, bromide, or tetrafluoroborate, or represents methyl optionally oxidised to the formyl stage.

Functionally modified carboxy radicals and functionally modified carboxy radicals other than R_2' are, for example, corresponding esterified or amidated carboxy, optionally functionally modified ortho-ester groups, such as trihalo-, halo-di-lower alkoxy- or tri-lower alkoxymethyl groups, anhydridised carboxy, such as cyano, a group of the formula =C=O, cyano-, azido- or halo-carbonyl, acyloxycarbonyl, lower alkanoylcarbonyl, such as, for example, acetoxycarbonyl, or derivatives of carboxy of the formula R_1' or R_2'', in which oxo is optionally replaced

by thio or optionally substituted imino, such as optionally esterified thiocarboxy, such as lower alkylthiocarboxy, for example ethylthiocarboxy, amidated thiocarboxy, imino-esters, such as imide- or amide-halide groupings, for example iminochloromethyl or aminodichloromethyl, imino ether groupings, such as lower alkylimino ether or lower alkyleneimino ether groupings, for example methoxyiminomethylene or ethoxyiminomethylene, or amidino groups, such as amidino or lower alkylamidino, for example methylamidino.

Esterified carboxy R_2'' is, for example, lower alkoxycarbonyl which may be mono-substituted by optionally substituted aryl, such as phenyl or pyridyl, or mono- or poly-substituted by hydroxy, halogen or lower alkoxy: such as lower alkoxycarbonyl substituted by hydroxy, lower alkoxy and/or halogen, for example mono- or di-hydroxy-lower alkoxy-, halo- or lower alkoxy-lower alkoxycarbonyl, or phenyl-lower alkoxycarbonyl substituted by lower alkyl, lower alkoxy and/or halogen.

Amidated carboxy R_2'' is, for example, carbamoyl which may be mono-substituted by hydroxy or amino, mono- or di-substituted by lower alkyl or hydroxy-lower alkyl or phenyl-lower alkyl, or di-substituted by 4- to 7-membered lower alkylene or 3-oxa-, 3-thia- or 3-aza-lower alkylene. Examples that may be mentioned are: carbamoyl, N-hydroxy-, N-amino-, N-mono- or N,N-di-lower alkyl- or N-mono- or N,N-di-hydroxy-lower alkyl-carbamoyl. Carbamoyl N-di-substituted by 4- to 7-membered lower alkylene is, for example, pyrrolidin-1-yl- or piperidino-carbonyl or morpholino-, thiomorpholino-, piperazin-1-yl- or N-lower alkyl-, such as N-methyl-piperazin-1-yl-carbonyl.

Methyl oxidised to the formyl stage, or functionally modified groups thereof are, for example, optionally reactively esterified or etherified hydroxymethyl or optionally functionally modified formyl, such as hydroxymethyl, mono- or di-halomethyl, lower alkoxymethyl, formyl or formimino.

Functionally modified carboxy compounds, such as esterified or amidated carboxy, optionally functionally modified ortho-esters, anhydridised carboxy or acyloxycarbonyl, can be solvolysed directly or in several solvolysis steps to form free or esterified carboxy R_2'. Esterified carboxy other than R_2' can be converted into esterified carboxy R_2' by customary transesterification.

The solvolysis of R_2'' is effected in known manner, for example by hydrolysis with water or by alcoholysis, for example of cyano or optionally substituted carbamoyl, to form esterified carboxy R_2' with a corresponding alcohol. The transesterification is also effected by alcoholysis with the desired alcohol. In each case the operation is carried out, if necessary, in the presence of a catalyst, in a solvent or diluent, in a closed vessel, in a temperature range of from approximately 0° to approximately $150^\circ C$, and/or under an inert gas, for example nitrogen.

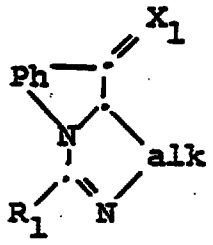
Catalysts are, for example, basic condensation agents, such as alkali metal or alkaline earth metal hydroxides, for example sodium, potassium or calcium hydroxide, or tertiary organic amines, such as pyridine or trialkylamines, for example triethylamine, or acidic hydrolysing agents, such as mineral acids, for example hydrohalic acids, such as hydrochloric acid, or organic carboxylic or sulphonic acids, such as lower alkanecarboxylic acids or optionally substituted benzenesulphonic acids, for example acetic acid or p-toluenesulphonic acid.

Methyl optionally oxidised to the formyl stage, such as methyl, hydroxymethyl or formyl, or functionally modified derivatives thereof, such as halomethyl, for example chloromethyl, mercaptomethyl, thioformyl or optionally substituted formimino, may be oxidised directly or by way of several oxidation steps, optionally by way of hydroxymethyl or formyl, to form carboxy. Etherified hydroxymethyl, preferably lower alkoxymethyl, for example ethoxymethyl, is oxidised, in the presence of an oxidising agent, to form lower alkoxycarbonyl. The

reaction of formyl to form carbamoyl is carried out, for example, by means of an amino compound in the presence of an oxidising agent, such as a transition metal oxide, for example manganese dioxide, and, if necessary, in the presence of a nucleophile, especially a cyanide.

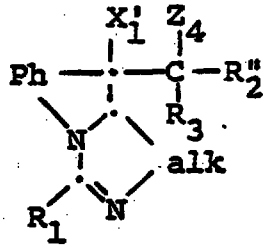
Oxidation of R_2'' is carried out in customary manner, for example using customary oxidising agents. These are, for example, optionally catalytically activated oxygen, alkali metal salts of chromates or manganates, such as sodium chromate or potassium permanganate, or transition metal oxides, such as manganese dioxide or chromium trioxide. The oxidation is carried out, if necessary, in an inert solvent, in a closed vessel and/or while cooling or heating, for example at approximately 0° to approximately $150^\circ C$.

The starting materials of the formula X can be manufactured according to analogous processes, for example by reacting compounds of the formula



(VIa),

in which X_1 represents oxo or thioxo, with compounds of the formula $P(Z_2)_3-R_2^o$, which may be in the form either of phosphonium ylides or of phosphoranes, or $X_1=P(Z_3)_2-R_2^o$, in which Z_2 represents alkyl and/or phenyl and Z_3 represents alkyl and/or phenyl, or alkoxy, such as lower alkoxy, and/or phenoxy, and R_2'' represents functionally modified carboxy other than R_2', a group of the formula $-C(=O)\overset{\oplus}{N}_2\overset{\ominus}{B}$ or methyl optionally oxidised to the formyl stage, removing from intermediates of the formula

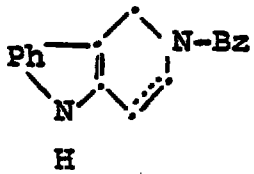


(VIh),

which may be obtained in this manner, in which X_1' represents $-O^{\ominus}$ or $-S^{\ominus}$ and Z_4 represents a radical of the formula $-\overset{\oplus}{P}(Z_2)_3$ or $-\overset{\oplus}{P}(X_1')(Z_3)_2$, respectively, a compound of the formula $X_1=P(Z_2)_3$ or $X_1=P(X_1')(Z_3)_2$, respectively, and isomerising a compound obtained in this manner to form a compound of the formula X.

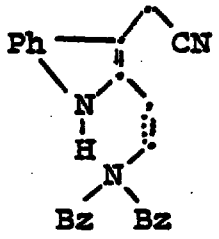
The reaction is usually carried out in an inert solvent, for example an optionally halogenated hydrocarbon, such as an aromatic compound, for example benzene or toluene, an ether, such as tetrahydrofuran or dioxan, or an amide, for example dimethylformamide, in a temperature range of from approximately 20° to approximately 150°C and/or optionally in the presence of a catalyst, such as a base, for example an alkali metal alcoholate, such as potassium tert.-butoxide.

Especially, the starting materials of the formula X in which R_2^o is a radical that can be converted by solvolysis or oxidation into R_2 are obtained, and starting, for example, from compounds of the formula



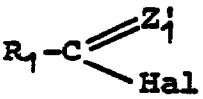
(IVd)

in which Bz represents an optionally substituted α-phenyl-lower alkyl radical, preferably benzyl, the tertiary nitrogen atom is quaternised, especially with benzyl chloride, the bond at the quaternary nitrogen atom is cleaved by means of a strong base, such as by a cyanide, for example sodium cyanide, and in a resulting compound of the formula



(IVe)

the cyano group is converted into R_2^o, for example by solvolysis to carboxy or lower alkoxycarbonyl and then reduction to hydroxymethyl or lower alkoxymethyl, respectively, and the Bz groups are removed by hydrogenolysis in the presence of a hydrogenation catalyst. The compound obtained in this manner is then reacted with a compound of the formula



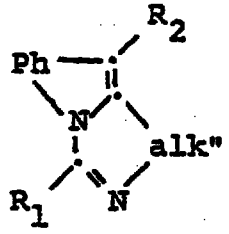
, in which Z_1' represents optionally functionally modified oxo and Hal represents halogen, and cyclisation to form corresponding compounds of the formula X is carried out in the presence of a customary cyclising agent, such as a mineral acid halide, for example phosphorus oxychloride.

In a preferred embodiment of this process variant, using corresponding starting materials of the formulae IVd, IVe and R_1-C(=Z_1')-Hal, there are formed first of all, without isolation of the intermediates, those compounds of the formula X in which alk represents 1,2-ethylene and R_1, R_2^o and Ph have the meanings indicated.

Especially, corresponding compounds of the formula X in which alk represents 1,2-ethylene and R_2^o represents cyanomethyl or optionally substituted carbamoylmethyl formed therefrom, are first dehydrogenated analogously to the dehydrogenation described hereinafter and then solvolysed as desired to form the desired compounds of the formula I.

Accordingly, using suitable starting materials of the formulae IVd, IVe and R_1-C(=Z_1)-Hal, there are formed, with isolation of the intermediates, those 3,4-dihydro compounds of the formula X in which R_2^o represents lower alkoxycarbonylmethyl and alk represents 1,2-ethylene. In the next reaction step the lower alkoxycarbonyl group is reduced to form 2-hydroxyethyl R_2^o, for example using complex hydrides, such as lithium aluminium hydride, and the hydroxy group is etherified with a desired lower alkanol. The compounds that are obtainable in corresponding manner are then dehydrogenated in the manner described hereinafter. 2-Lower alkoxyethyl R_2^o, 2-hydroxyethyl formed therefrom and formylmethyl R_2^o are finally oxidised in the desired manner to form R_2, as indicated above.

The compounds of the formula I are manufactured preferably by dehydrogenating corresponding compounds of the formula



(XI) ,

in which alk" represents ethylene, with the removal of hydrogen and the simultaneous formation of an additional bond, and, if desired, converting a compound obtainable according to the invention into a different compound of the formula I or converting a free compound of the formula I obtainable according to the invention into a salt or a salt obtainable according to the process into the free compound of the formula I or into a different salt.

The dehydrogenation is carried out in a manner known per se, especially at elevated temperature, for example in a temperature range of from room temperature to approximately 300°C, especially from approximately 100° to approximately 300°C, and using a dehydrogenating agent. As such agents there come into consideration, for example, dehydrogenation catalysts, for example sub-group elements, preferably of the sub-group VIII, such as palladium or platinum, or salts thereof, such as ruthenium-triphenyl-phosphide-chloride, the catalysts optionally being supported on a suitable carrier, such as carbon, aluminium oxide or silicon dioxide. Other dehydrogenating agents are, for example, quinones, such as p-benzoquinones, for example tetrachloro-p-benzoquinone or 2,3-dichloro-5,6-dicyano-p-benzoquinone, or anthraquinones, for example phenanthrene-9,10-quinone. Preferred dehydrogenation catalysts are suitable selenium derivatives, especially selenium dioxide or diphenylselenium bis(acetate), and also diphenylselenium oxide. In an advantageous embodiment of the dehydrogenation described above, this process is carried out at elevated temperature when using selenium dioxide as catalyst, and when using diphenyl-selenium bis(trifluoroacetate) the dehydrogenation is effected at room temperature.

The reaction is carried out in an inert, optionally high-boiling, solvent, such as an ether, for example diphenyl ether, if necessary under pressure, in a closed vessel and/or under an inert gas, for example nitrogen.

The starting materials of the formula XI in which alk" represents 1,2-ethylene are manufactured analogously to the procedure described at the beginning starting from corresponding compounds of formulae II, V, VIII or X wherein alk is ethylene and alk' is 2-Z_6-ethyl. For example, compounds of the formula IVd are alkylated exhaustively, for example with benzyl halides, and the bond at the quaternary nitrogen

atom is cleaved with alkali metal cyanides. In the resulting compounds of the formula IVe, the cyano group can be solvolysed as desired in customary manner, conversion into lower alkoxycarbonyl being preferred. After removing the benzyl groups by hydrogenolysis, reaction is effected with compounds of the formula R_1-C(=Z_1')-Hal, there being formed under the reaction conditions, with the aid of cyclising agents, such as phosphorus oxychloride, corresponding compounds of the formula II which lead directly to corresponding compounds of the formula XI in which alk" represents 1,2-ethylene and R_2 preferably represents lower alkoxycarbonylmethyl.

If it is desired to manufacture free acid derivatives after the subsequent dehydrogenation, resulting lower alkyl esters are advantageously hydrolysed.

A compound of the formula I obtainable according to the invention can be converted into a different compound of the formula I in a manner known per se.

If the group R_2 contains free carboxy, this can be converted according to esterification methods known per se into correspondingly esterified carboxy, for example by reacting optionally reactive modified carboxy or a salt thereof by alcoholysis with a desired alcohol, for example a reactive derivative thereof or an olefin derived therefrom, or by alkylation with diazo-lower alkane.

Suitable reactive functional carboxy derivatives are, for example, anhydrides, there being used as anhydrides especially mixed anhydrides, for example those with inorganic acids, such as hydrohalic acids, for example hydrochloric acid, or hydrazoic or hydrocyanic acids, or with organic carboxylic acids, such as lower alkanoic acids, for example acetic acid.

Reactive derivatives of an alcohol are, for example, carboxylic, phosphorous, sulphurous or carbonic acid

esters, for example lower alkanecarboxylic acid esters, tri-lower alkylphosphite, di-lower alkylsulphite or pyrocarbonate, or mineral or sulphonic acid esters, for example chloride, bromide or sulphuric acid esters, benzenesulphonic, toluenesulphonic or methanesulphonic acid esters, of the alcohol concerned.

The esterification of free carboxy is carried out in the presence of a condensation agent. There come into consideration as agents that split off water by catalysis in the esterification with alcohols, for example, acids, for example protonic acids, such as hydrochloric, hydrobromic, sulphuric, phosphoric, boric, benzenesulphonic and/or toluenesulphonic acid, or Lewis acids, such as boron trifluoride etherate. Customary water-binding condensation agents are, for example, carbodiimides substituted by hydrocarbon radicals, for example N,N'-diethylcarbodiimide, N,N'-dicyclohexylcarbodiimide or N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide. Condensation agents for the esterification with reactive esters are, for example, basic condensation agents, such as inorganic bases, for example alkali metal or alkaline earth metal hydroxides or carbonates, such as sodium, potassium or calcium hydroxide or carbonate, or organic nitrogen bases, for example tertiary organic amines, such as triethylamine or pyridine. The esterification is advantageously carried out in an excess of the alcohol used. It is preferably carried out in an anhydrous medium, if necessary in the presence of an inert solvent, such as in halogenated hydrocarbons, for example chloroform or chlorobenzene, or in ethers, for example tetrahydrofuran or dioxan.

The reaction with an olefin can be carried out, for example, in the presence of an acidic catalyst, for example a Lewis acid, for example boron trifluoride, a sulphonic acid, for example p-toluenesulphonic acid, or, especially, a basic catalyst, for example sodium or potassium hydroxide, advantageously in an inert solvent,

such as an ether, for example diethyl ether or tetrahydrofuran.

Furthermore, free carboxy or reactive functional carboxy derivatives can be converted into a desired amidated form by solvolysis with ammonia or a primary or secondary amine, it being possible also for hydroxylamines or hydrazines to be used, the solvolysis being carried out in customary manner with dehydration, optionally in the presence of a condensation agent. There are used as condensation agents preferably bases, for example inorganic bases, such as alkali metal hydroxides, for example sodium or potassium hydroxide, organic nitrogen bases, such as tert.-amines, for example pyridine, tributylamine or N-dimethylaniline, or tetrahalosilanes, such as tetrachlorosilane.

Further, compounds of the formula I obtainable according to the invention in which R_2 contains esterified carboxy as substituent, can be transesterified in customary manner, for example by reaction with a corresponding alcohol or a metal salt thereof, such as an alkali metal salt, for example the sodium or potassium salt, if necessary in the presence of a catalyst, for example a strong base, such as an alkali metal hydroxide, amide or alcoholate, for example potassium hydroxide, sodium amide or sodium methoxide, or a strong acid, such as a mineral acid, for example sulphuric acid, phosphoric acid or hydrochloric acid, or an organic sulphonic acid, for example an aromatic sulphonic acid, such as p-toluenesulphonic acid.

Esterified carboxy can furthermore be converted into the free carboxy group according to known processes, for example by hydrolysis in the presence of a catalyst. There come into consideration as catalysts preferably bases, for example alkali metal hydroxides, such as sodium or potassium hydroxide. Esterified carboxy may furthermore be converted into carboxy in customary manner, for example by solvolysis, optionally in the presence of

a catalyst, for example an acidic or basic agent, or into amidated carboxy by ammonolysis or aminolysis with ammonia or with a primary or secondary amine. There are used as bases, for example, alkali metal hydroxides, such as sodium or potassium hydroxides, and as acids, for example, mineral acids, such as sulphuric acid, phosphoric acid or hydrochloric acid. Likewise, in compounds of the formula I obtainable according to the invention in which the group R_2 contains an amidated carboxy substituent, it is possible according to methods known per se to cleave the amide bond and thus convert the carbamoyl into free carboxy. This operation is carried out in the presence of a catalyst, for example a base, such as an alkali metal or alkaline earth metal hydroxide or carbonate, for example sodium, potassium or calcium hydroxide or carbonate, or an acid, such as a mineral acid, for example hydrochloric acid, sulphuric acid or phosphoric acid.

If the group R_2 of the formula I contains an esterified carboxy group, this can be converted into an amidated carboxy group, for example by customary solvolysis, advantageously by an excess of ammonia or an amine containing at least one hydrogen atom, optionally in the presence of a catalyst. There are used as catalysts, for example, acids, such as mineral acids, for example hydrochloric, sulphuric or phosphoric acid, or bases, such as alkali metal hydroxides, for example sodium or potassium hydroxide.

If the group R_2 of the formula I contains as substituent amidated carboxy, this can be converted into esterified carboxy, for example by customary solvolysis with an alcohol in the presence of a catalyst. The catalysts used are, for example, acidic catalysts, such as mineral acids, for example phosphoric acid, hydrochloric acid or sulphuric acid.

If the substituent R_1 of the formula I is substituted by lower alkylthio, this can be oxidised in

customary manner to form corresponding lower alkanesulphinyl or lower alkanesulphonyl. There come into consideration as suitable oxidising agents for the oxidation to the sulphoxide stage, for example, inorganic peracids, such as peracids of mineral acids, for example periodic acid or persulphuric acid, organic peracids, such as suitable percarboxylic or persulphonic acids, for example performic, peracetic, trifluoroperacetic, perbenzoic or p-toluenepersulphonic acid, or mixtures of hydrogen peroxide and acids, for example a mixture of hydrogen peroxide with acetic acid.

Frequently, the oxidation is carried out in the presence of suitable catalysts, and there should be mentioned as catalysts suitable acids, such as optionally substituted carboxylic acids, for example acetic or trifluoroacetic acid, or transition metal oxides, such as oxides of elements of sub-group VII, for example vanadium, molybdenum or tungsten oxide. The oxidation is carried out under mild conditions, for example at temperatures of approximately -50° to approximately +100°C.

The oxidation to the sulphone stage can also be carried out in corresponding manner, using dinitrogen tetroxide as catalyst in the presence of oxygen at low temperatures, as can also the direct oxidation of the lower alkylthio to lower alkanesulphonyl, except that usually the oxidising agent is used in excess.

Compounds of the formula I in which R_1 represents an aromatic radical substituted by lower alkylsulphinyl or lower alkylsulphonyl can be reduced according to methods known per se to the corresponding lower alkylthio compounds, and, starting from lower alkanesulphonyl derivatives, also to lower alkanesulphinyl. A suitable reducing agent is, for example, catalytically activated hydrogen, there being used noble metals or oxides, such as palladium, platinum or rhodium or their oxides, optionally supported on a suitable carrier, such as active carbon or barium sulphate. There also come into

consideration reducing metal cations, such as tin(II), lead(II), copper(I), manganese(II), titanium(II), vanadium(II), molybdenum(III) or tungsten(III) compounds, hydrogen halides, such as hydrogen chloride, hydrogen bromide or hydrogen iodide, hydrides, such as complex metal hydrides, for example lithium aluminium hydride, sodium borohydride and tributyltin hydride, phosphorus compounds, such as phosphorus halides, for example phosphorus trichloride, phosphorus tribromide, phosphorus pentachloride or phosphorus oxychloride, phosphines, such as triphenylphosphine, or phosphorus pentasulphide-pyridine, or sulphur compounds, such as mercaptans, thio acids, such as thiophosphoric acids or dithiocarboxylic acids, dithionite or sulphur/oxygen complexes, such as an iodine/pyridine/sulphur dioxide complex.

Resulting salts can be converted into the free compounds in a manner known per se, for example by treatment with an acidic reagent, such as a mineral acid, or a base, for example an alkali hydroxide solution.

Depending upon the starting materials and methods chosen, the novel compounds may be in the form of one of the possible isomers or mixtures thereof, for example, depending on the number of asymmetrical carbon atoms, in the form of pure optical isomers, such as antipodes, or in the form of mixtures of isomers, such as racemates, mixtures of diastereoisomers or mixtures of racemates.

Resulting mixtures of diastereoisomers and mixtures of racemates can be separated on the basis of the physico-chemical differences between the constituents, in known manner, into the pure isomers, diastereoisomers or racemates, for example by chromatography and/or fractional crystallisation.

Resulting racemates can furthermore be resolved into the optical antipodes by known methods, for example by recrystallisation from an optically active solvent, with the aid of micro-organisms or by reacting an acidic end

product with an optically active base that forms salts with the racemic acid, and separating the salts obtained in this manner, for example on the basis of their different solubilities, into the diastereoisomers, from which the antipodes can be freed by the action of suitable agents. Advantageously, the more active of the two antipodes is isolated.

The compounds, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for the crystallisation.

As a result of the close relationship between the novel compounds in free form and in the form of their salts, hereinbefore and hereinafter the free compounds or their salts shall be understood to mean optionally also the corresponding salts or free compounds, respectively, where appropriate with regard to meaning and purpose.

The invention relates also to those embodiments of the process according to which compounds obtainable as intermediates at any stage of the process are used as starting materials and the remaining steps are carried out or a starting material is used in the form of a salt or, especially, is formed under the reaction conditions.

In the process of the present invention it is preferable to use those starting materials which result in the compounds described at the beginning as being especially valuable. The present invention relates also to novel starting materials and to processes for their manufacture.

The pharmaceutical preparations according to the invention, which contain compounds of the formula I or pharmaceutically acceptable salts thereof, are for enteral, such as oral or rectal, and parenteral administration and also for topical application to (a) warm blooded animal(s) and contain the pharmacological active ingredient alone or together with a pharmaceutically

acceptable carrier. The dosage of the active ingredient depends on the species of warm-blooded animal, age and individual condition, and on the method of administration. In normal cases, the estimated approximate daily dose in the case of oral administration to a warm-blooded animal weighing approximately 75 kg is about 30 - 300 mg, advantageously divided into several equal partial doses.

The novel pharmaceutical preparations contain, for example, from approximately 10 % to approximately 80 %, preferably from approximately 20 % to approximately 60 %, of active ingredient. Pharmaceutical preparations according to the invention for enteral or parenteral administration are, for example, those in dosage unit forms, such as dragées, tablets, capsules or suppositories, and also ampoules. These are manufactured in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. For example, pharmaceutical preparations for oral use can be obtained by combining the active ingredient with solid carriers, optionally granulating a resulting mixture and processing the mixture or granulate, if desired or necessary after the addition of suitable adjuncts, to form tablets or dragée cores.

Suitable carriers are especially fillers, such as sugar, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium biphosphate, also binders, such as starch pastes using, for example, maize, wheat, rice or potato starch, gelatine, tragacanth, methylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, cross-linked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Adjuncts are especially flow-regulating agents and lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or poly-

ethylene glycol. Dragée cores are provided with suitable coatings that are optionally resistant to gastric juices, there being used, inter alia, concentrated sugar solutions which may contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions in suitable organic solvents or solvent mixtures or, for the production of coatings that are resistant to gastric juices, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments can be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Further pharmaceutical preparations for oral administration are dry-filled capsules consisting of gelatine and also soft, sealed capsules consisting of gelatine and a plasticiser, such as glycerine or sorbitol. The dry-filled capsules may contain the active ingredient in the form of a granulate, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and optionally stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, it being possible also to add stabilisers.

As rectally administrable pharmaceutical preparations there come into consideration, for example, suppositories which consist of a combination of the active ingredient with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols and higher alkanols. It is also possible to use gelatine rectal capsules which contain a combination of the active ingredient with a base material; as base materials there come into consideration, for example, liquid triglycerides, polyethylene glycols and paraffin hydrocarbons.

Especially suitable for parenteral administration are aqueous solutions of an active ingredient in water-soluble form, for example a water-soluble salt, also suspensions of the active ingredient, such as corresponding oily injection suspensions, there being used suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, or aqueous injection suspensions that contain substances which increase the viscosity, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, optionally, also stabilisers.

There come into consideration as pharmaceutical preparations for topical use especially creams, ointments, pastes, foams, tinctures and solutions that contain from approximately 0.5 % to approximately 20 % of active ingredient.

Creams are oil-in-water emulsions that contain more than 50 % of water. As oily base there are used especially fatty alcohols, for example lauryl, cetyl or stearyl alcohol, fatty acids, for example palmitic or stearic acid, liquid to solid waxes, for example isopropyl myristate, wool wax or beeswax, and/or hydrocarbons, for example petroleum jelly (petrolatum) or paraffin oil. As emulsifiers there come into consideration surface-active substances having predominantly hydrophilic properties, such as corresponding non-ionic emulsifiers, for example fatty acid esters of polyalcohols, or ethylene oxide adducts thereof, such as polyglycerine fatty acid esters or polyoxyethylene sorbitan fatty acid esters (Tweens)(RTM), also polyoxyethylene fatty alcohol ethers or polyoxyethylene fatty acid esters, or corresponding ionic emulsifiers, such as alkali metal salts of fatty alcohol sulphates, for example sodium lauryl sulphate, sodium cetyl sulphate or sodium stearyl sulphate, which are customarily used in the presence of fatty alcohols, for example cetyl alcohol or stearyl alcohol. Additives to the aqueous phase are, inter alia, agents that reduce the

drying out of the creams, for example polyalcohols, such as glycerine, sorbitol, propylene glycol and/or polyethylene glycols, also preservatives, perfumes etc..

Ointments are water-in-oil emulsions that contain up to 70 %, but preferably from approximately 20 % to approximately 50 %, of water or aqueous phases. As fatty phase there come into consideration especially hydrocarbons, for example petroleum jelly, paraffin oil and/or hard paraffins, which, in order to improve the water-binding capacity, preferably contain suitable hydroxy compounds, such as fatty alcohols or esters thereof, for example cetyl alcohol or wool wax alcohols, or wool wax. Emulsifiers are corresponding lipophilic substances, such as sorbitan fatty acid esters (Spans)(RTM), for example sorbitan oleate and/or sorbitan isostearate. Additives to the aqueous phase are, inter alia, humectants, such as polyalcohols, for example glycerine, propylene glycol, sorbitol and/or polyethylene glycol, and also preservatives, perfumes etc..

Fatty ointments are anhydrous and contain as base especially hydrocarbons, for example paraffin, petroleum jelly and/or liquid paraffins, and also natural or partially synthetic fats, for example coconut fatty acid triglyceride, or preferably hardened oils, for example hydrogenated ground nut oil or castor oil, and also fatty acid partial esters of glycerine, for example glycerine mono- and di-stearate, and also, for example, the fatty alcohols, which increase the water-absorbing capacity, emulsifiers and/or additives mentioned in connection with the ointments.

Pastes are creams and ointments containing powder ingredients that absorb secretions, such as metal oxides, for example titanium oxide or zinc oxide, also talc and/or aluminium silicates, the purpose of which is to bind any moisture or secretions present.

Foams are administered from pressurised containers and are liquid oil-in-water emulsions in aerosol form,

halogenated hydrocarbons, such as chlorofluoro-lower alkanes, for example dichlorodifluoromethane and dichlorotetrafluoroethane, being used as propellants. For the oily phase there are used, inter alia, hydrocarbons, for example paraffin oil, fatty alcohols, for example cetyl alcohol, fatty acid esters, for example isopropyl myristate, and/or other waxes. As emulsifiers there are used, inter alia, mixtures of those emulsifiers having predominantly hydrophilic properties, such as polyoxyethylene sorbitan fatty acid esters (Tweens), and those having predominantly lipophilic properties, such as sorbitan fatty acid esters (Spans). In addition, there may be used customary additives, such as preservatives etc..

Tinctures and solutions generally have an aqueous ethanolic base to which there are added, inter alia, polyalcohols, for example glycerine, glycols, and/or polyethylene glycol, as humectants for reducing evaporation, and fat-restoring substances, such as fatty acid esters with lower polyethylene glycols, that is to say lipophilic substances that are soluble in the aqueous mixture, to replace the fatty substances that are taken from the skin by the ethanol, and, if necessary, other adjuncts and additives.

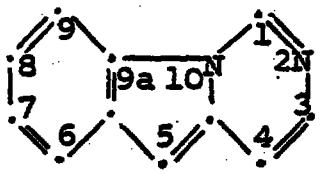
The pharmaceutical preparations for topical application are manufactured in a manner known per se, for example by dissolving or suspending the active ingredient in the base or, if necessary, in a part thereof. When processing the active ingredient in the form of a solution, it is usually dissolved in one of the two phases before emulsification; when processing the active ingredient in the form of a suspension, it is mixed with a part of the base after emulsification and then added to the remainder of the formulation.

The present invention relates also to the use of compounds of the formula I and salts of such compounds

having salt-forming properties, preferably for the treatment of inflammation, especially inflammatory disorders of the rheumatic type, especially chronic arthritis.

The following Examples illustrate the invention described above but are not intended to limit the scope of the invention in any way. Temperatures are given in degrees Centigrade.

There is no consistent characterisation in the literature of the linking points in the pyrimido-indole ring system,



forming the basis of the compounds of the formula I.

Thus, the older literature sources characterise the linking points in the ring system by [3,4-a], whereas recently the characterisation [1,6-a] has been used.

From considerations of principle, the following nomenclature is used hereinafter for the above ring structure: pyrimido[1,6-a]indole.

Example 1

While stirring, 38 g of 7-fluoro-1-phenyl-3,4-dihydro-pyrimido[1,6-a]indole-5-acetic acid ethyl ester in 200 ml of diphenyl ether are heated at 260° for 50 minutes in the presence of 10 g of palladium-carbon (10 %). The diphenyl ether is removed under reduced pressure and the residue obtained after concentration by evaporation is taken up in diethyl ether, filtered off from the catalyst and concentrated until crystallisation begins. The crystals are stirred with hexane and a small quantity of diethyl ether and filtered with suction. 7-fluoro-1-phenylpyrimido[1,6-a]indole-5-acetic acid ethyl ester having a melting point of 91 - 93° is obtained.

The starting material can be prepared, for example, as follows:

a) 131 g (0.45 mol) of 3-benzyl-6-fluorotetrahydro-γ-carboline are dissolved, while stirring, in 1300 ml of acetonitrile at 40°, and 94 g (0.55 mol) of benzyl bromide are added over a period of 10 minutes. After a short time the benzylammonium derivative begins to crystallise out. Stirring is continued at room temperature for approximately 15 hours followed by cooling in an ice bath and the crystallisate is filtered with suction.

b) 464 g (1 mol) of the N,N-dibenzyl-6-fluorotetrahydro-γ-carbolinium bromide so obtained are dissolved in 4250 ml of methanol while heating at 65° and, while stirring, a solution of 196 g (4 mol) of sodium cyanide in 500 ml of water is added over a period of 5 minutes. The solution is boiled under reflux for 3 hours. On cooling and after inoculation, 2-(dibenzylaminoethyl)-3-cyanomethyl-5-fluoroindole crystallises to form colourless crystals.

c) 220 g (0.537 mol) of the nitrile prepared as described in b) are dissolved in 300 ml of absolute ethanol and, at -5°, the solution is saturated with dry

hydrogen chloride. The solution is then stirred at 20° for 5½ days. The precipitated crystals are allowed to settle and the supernatant liquid is decanted off; the sediment is dissolved in 2000 ml of ice water and the solution is stirred at 20° for approximately 3 hours. While cooling with ice, the solution is then rendered alkaline with concentrated ammonia solution and extracted by stirring with 1500 ml of toluene ice water. The separated toluene phase is washed with water, dried over sodium sulphate and filtered through 1000 g of aluminium oxide (act. stage 3) and then washed with toluene. After distilling off the toluene there remains a light-brown oil which is subjected to hydrogenation as described in d) without further purification.

d) 181.3 g of the 2-dibenzylamino-5-fluoroindole-3-acetic acid ethyl ester obtained as described in c) are dissolved in 1500 ml of absolute alcohol and are hydrogenated at normal pressure at 20 - 35° with the addition of 18 g of Pd/C (5 %). After 12500 ml of H_2 have been absorbed, a further 18 g of catalyst are added and hydrogenation is continued until the absorption of H_2, totalling 17300 ml, has ceased. After filtering off from the catalyst and subsequently washing with methylene chloride, the solution is concentrated to dryness by evaporation and the residue is dissolved in 250 ml of ether. After inoculation, the 2-aminoethyl-5-fluoro-indole-3-acetic acid ethyl ester crystallises in the form of colourless crystals.

e) 61.7 g (0.223 mol) of the 2-aminoethyl-5-fluoro-indole-3-acetic acid ethyl ester prepared as described in d) are dissolved in 600 ml of methylene chloride and the solution is covered with a layer of 150 ml of 2N sodium hydroxide solution. While stirring vigorously at 0 - 5°, a solution of 43 g (0.245 mol) of benzoyl chloride is added over a period of 2½ hours and then

extracted by stirring for a further 1 hour. The methylene chloride phase is then separated off, washed with water, dried over $MgSO_4$ and concentrated to dryness by evaporation. The residue crystallises when taken up in ether. 2-(2-benzoylaminoethyl)-5-fluoroindole-3-acetic acid ethyl ester is obtained.

f) 37 g (0.154 mol) of 2-(2-benzoylaminoethyl)-5-fluoro-indole-3-acetic acid ethyl ester in 160 ml of phosphorus oxychloride are boiled under reflux for 3 hours. The excess phosphorus oxychloride is distilled off in vacuo at 60° and the residue is stirred with 650 ml of ice water. The aqueous solution is cleared by filtering through diatomaceous earth, rendered alkaline with concentrated ammonia solution and extracted with 400 ml of ether. The ether phase is dried over sodium sulphate and concentrated to dryness. The residue is dissolved in 150 ml of acetone and 16 ml of an approximately 4N solution of hydrogen chloride in ether are added. After inoculation, the hydrochloride of 7-fluoro-1-phenyl-3,4-dihydropyrimido[1,6-a]indole-5-acetic acid ethyl ester crystallises to form yellowish crystals which can be recrystallised from 2N hydrochloric acid. After recrystallisation from ether, the base freed from the salt melts at 56 - 58°.

Example 2

In a manner analogous to that described in Example 1 there is obtained using 2-aminoethyl-5-fluoroindole-3-acetic acid ethyl ester and p-methanesulphinylbenzoyl chloride as starting materials and via 7-fluoro-1-(p-methanesulphinylphenyl)-3,4-dihydropyrimido[1,6-a]indole-5-acetic acid ethyl ester (melting point of the hydrochloride = 208 - 210°), 7-fluoro-1-(p-methanesulphinyl-phenyl)-pyrimido[1,6-a]indole-5-acetic acid ethyl ester having a melting point of 133 - 135°.

Example 3

In a manner analogous to that described in Example 1 there is obtained using 2-aminoethylindole-3-acetic acid ethyl ester and 2-thenoyl chloride as starting materials and via 1-(2-thienyl)-3,4-dihydropyrimido[1,6-a]indole-5-acetic acid ethyl ester (melting point of the hydrochloride = 153 - 157°), 1-(2-thienyl)-pyrimido[1,6-a]indole-5-acetic acid ethyl ester having a melting point of 94 - 95°.

Example 4

In a manner analogous to that described in Example 1, there is obtained using 2-aminoethyl-5-methoxyindole-3-acetic acid ethyl ester and 2-picolyl chloride as starting materials and via 7-methoxy-1-(2-picolinyl)-3,4-dihydro-pyrimido[1,6-a]indole-5-acetic acid ethyl ester, 7-methoxy-1-(2-picolinyl)-pyrimido[1,6-a]indole-5-acetic acid ethyl ester having a melting point of 103 - 104°.

Example 5

12.2 g of 1-phenylpyrimido[1,6-a]indole-5-acetic acid ethyl ester (melting point 59 - 62°), manufactured from 2-aminoethylindole-3-acetic acid ethyl ester and benzoyl chloride via 1-phenyl-3,4-dihydropyrimido[1,6-a]indole-5-acetic acid ethyl ester (melting point 83 - 84°), are stirred at room temperature for 3 hours with 30 ml of ethanol and 40 ml of 2N sodium hydroxide solution. The mixture is acidified to pH 3 with concentrated hydrochloric acid and, while stirring, 30 ml of propylene oxide are added. After a short time 1-phenylpyrimido-[1,6-a]indole-5-acetic acid crystallises out. This is filtered off and recrystallised from 90 % ethanol. Melting point 198 - 204° (decomposition).

Example 6

In a manner analogous to that described in Example 5 there is obtained, using 7-fluoro-1-(p-methanesulphinyl-phenyl)-pyrimido[1,6-a]indole-5-acetic acid ethyl ester as starting material, 7-fluoro-(p-methanesulphinylphenyl)-pyrimido[1,6-a]indole-5-acetic acid having a melting point of 218 - 224° (decomposition).

Example 7

In a manner analogous to that described in Example 5 there is obtained using 7-fluoro-1-phenylpyrimido[1,6-a]-indole-5-acetic acid ethyl ester as starting material, 7-fluoro-1-phenylpyrimido[1,6-a]indole-5-acetic acid having a melting point of 217 - 220°.

Example 8

In a manner analogous to that described in Example 5 there is obtained using 1-(2-thienyl)-pyrimido[1,6-a]-indole-5-acetic acid ethyl ester as starting material, 1-(2-thienyl)-pyrimido[1,6-a]indole-5-acetic acid having a melting point of 196 - 200° (decomposition).

Example 9

In a manner analogous to that described in Example 5 there is obtained using 7-methoxy-1-(2-picolinyl)-pyrimido-[1,6-a]indole-5-acetic acid ethyl ester as starting material, 7-methoxy-1-(2-picolinyl)-pyrimido[1,6-a]indole-5-acetic acid having a melting point of 201 - 206°.

Example 10

In a manner analogous to that described in Examples 1 and 5 there are also obtained:

7-fluoro-1-(p-methoxyphenyl)-pyrimido[1,6-a]indole-5-acetic acid having a melting point of 220 - 225° and the ethyl ester thereof,

7-methoxy-1-(p-fluorophenyl)-pyrimido[1,6-a]indole-5-acetic acid and the ethyl ester thereof, and

7-fluoro-1-(2-thienyl)-pyrimido[1,6-a]indole-5-acetic acid having a melting point of 233 - 236° and the ethyl ester and salts thereof.

Example 11

While stirring, 3 g of 7-fluoro-1-phenyl-3,4-dihydro-pyrimido[1,6-a]indole-5-acetic acid ethyl ester are boiled for 1.5 hours with 1 g of selenium dioxide in 50 ml of chlorobenzene and 5 ml of glacial acetic acid. The mixture is concentrated to dryness by evaporation and the residue is taken up in 20 ml of ethyl acetate, filtered off from the selenium and the solution is washed neutral with sodium bicarbonate solution and concentrated to dryness by evaporation. The residue is taken up in ether and chromatographed over 80 g of silica gel. The 7-fluoro-1-phenylpyrimido[1,6-a]indole-5-acetic acid ethyl ester is eluted with hexane/ethyl acetate (4:1) and crystallises from ether/hexane. Melting point 91 - 93°.

Example 12

A solution of 0.01 mol of diphenylselenium bis(trifluoroacetate) [manufactured according to J. Amer. Chem. Soc., 103, 4642 (1981)], is added dropwise over a period of 0.5 hours to a solution of 3.38 g of 1-(2-thienyl)-3,4-dihydropyrimido[1,6-a]indole-5-acetic acid ethyl ester in 20 ml of dimethoxyethane. The mixture is left to stand at room temperature for a further 3 hours, concentrated to dryness by evaporation and the residue is taken up in ether, washed with sodium bicarbonate solution and chromatographed over 80 g of silica gel. 1-(2-thienyl)-pyrimido[1,6-a]indole-5-acetic acid ethyl ester is eluted with hexane/ethyl acetate (4:1) and crystallises from ether/hexane to form yellow crystals. Melting point 94 - 95°.

Example 13

Tablets containing 25 mg of the active ingredient, for example 7-fluoro-1-(p-methylthiophenyl)-pyrimido[1,6-a]-indole-5-acetic acid or a salt, for example the hydrochloride, thereof, can be manufactured as follows:

Constituents (for 1000 tablets)

active ingredient	25.0 g
lactose	100.7 g
wheat starch	7.5 g
polyethylene glycol 6000	5.0 g
talc	5.0 g
magnesium stearate	1.8 g
demineralised water	q.s.

Preparation

All the solid ingredients are first forced through a sieve having a mesh width of 0.6 mm. Then the active ingredient, the lactose, the talc, the magnesium stearate and half the starch are mixed together. The other half of the starch is suspended in 40 ml of water and this suspension is added to a boiling solution of the polyethylene glycol in 100 ml of water. The resulting starch paste is added to the main quantity and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35°, forced through a sieve having a mesh width of 1.2 mm and pressed to form tablets of approximately 6 mm diameter that are concave on both sides.

In analogous manner it is possible to manufacture tablets each containing 25 mg of a different compound of the formula I selected from those mentioned in Examples 1 to 12, it being possible for the compounds also to be in the form of acid addition salts, such as hydrochlorides, and in the case of compounds in which R_2 is 1-carboxymethyl to be also in the form of salts with bases, such as sodium, potassium or zinc salts.

Example 14

Chewable tablets containing 30 mg of active ingredient, for example 7-fluoro-1-(p-methylthiophenyl)-pyrimido[1,6-a]indole-5-acetic acid or a salt, for example the hydrochloride, thereof, can be manufactured, for example, as follows:

Composition (for 1000 tablets)

active ingredient	30.0 g
mannitol	267.0 g
lactose	179.5 g
talc	20.0 g
glycine	12.5 g
stearic acid	10.0 g
saccharin	1.0 g
5 % gelatine solution	q.s.

Manufacture

All the solid ingredients are first forced through a sieve having a mesh width of 0.25 mm. The mannitol and the lactose are mixed, granulated with the addition of gelatine solution, forced through a sieve having a mesh width of 2 mm, dried at 50° and again forced through a sieve having a mesh width of 1.7 mm. The active ingredient, the glycine and the saccharin are carefully mixed together, the mannitol, the lactose granulate, the stearic acid and the talc are added and the whole is mixed thoroughly and pressed to form tablets of approximately 10 mm diameter that are concave on both sides and have a breaking groove on the upper side. In analogous manner it is also possible to manufacture chewable tablets each containing 30 mg of a different compound of the formula I selected from those mentioned in Examples 1 to 12, it being possible for the compounds to be also in the form of acid addition salts, such as hydrochlorides, and in the case of compounds in which R_2 is 1-carboxymethyl to be also in the form of salts with bases, such as sodium, potassium and zinc salts.

Example 15

Tablets containing 100 mg of active ingredient, for example 7-fluoro-1-(p-methylthiophenyl)-pyrimido[1,6-a]-indole-5-acetic acid ethyl ester, can be manufactured in the following manner:

Composition (for 1000 tablets)

active ingredient	100.0 g
lactose	248.5 g
maize starch	17.5 g
polyethylene glycol 6000	5.0 g
talc	15.0 g
magnesium stearate	4.0 g
demineralised water	q.s.

Manufacture

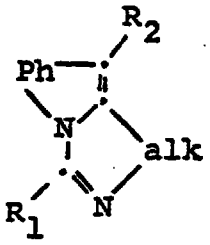
The solid ingredients are first forced through a sieve having a mesh width of 0.6 mm. Then the active ingredient, lactose, talc, magnesium stearate and half the starch are intimately mixed. The other half of the starch is suspended in 65 ml of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 ml of water. The resulting paste is added to the pulverulent substances and the whole is mixed and granulated, if necessary with the addition of water. The granulate is dried overnight at 35°, forced through a sieve having a mesh width of 1.2 mm and pressed to form tablets of approximately 10 mm diameter that are concave on both sides and have a breaking notch on the upper side.

In analogous manner it is possible to manufacture tablets containing 100 mg of a different compound of the formula I according to Examples 1 to 12, it being

possible for compounds to be also in the form of acid addition salts, such as hydrochlorides, and in the case of compounds in which R_2 is 1-carboxymethyl to be also in the form of salts with bases, such as sodium, potassium or zinc salts.

CLAIMS:-

1. A N,N'-bridged carboxylic acid amidine of the general formula



(I),

in which

R_1 represents phenyl optionally substituted in the p-position by lower alkylthio having up to and including 7 carbon atoms, by lower alkanesulphinyl having up to and including 7 carbon atoms, by lower alkoxy having up to and including 7 carbon atoms or by halogen having an atomic number of up to and including 35, thienyl, or pyridyl optionally substituted by lower alkyl having up to and including 7 carbon atoms,

R_2 represents carboxymethyl or, secondly, lower alkoxycarbonylmethyl having up to and including 8 carbon atoms,

Ph represents 1,2-phenylene optionally substituted in the p-position to the nitrogen atom by lower alkoxy having up to and including 7 carbon atoms or by halogen having an atomic number of up to and including 35, and

alk represents vinylene,

and salts thereof, with the proviso that if R_1 represents p-methylthiophenyl and Ph represents 1,2-phenylene substituted in the p-position to the nitrogen atom by fluorine, R_2 is other than carboxymethyl or ethoxycarbonylmethyl, and with the further proviso that if R_1 represents phenyl and Ph represents unsubstituted 1,2-phenylene or if R_1 represents p-chlorophenyl and Ph represents 1,2-phenylene substituted in the p-position to the nitrogen atom by methoxy, in each case R_2 is other than ethoxycarbonylmethyl.

2. A compound of the formula I according to claim 1 in which R_1 represents unsubstituted phenyl, p-methoxyphenyl or p-methanesulphinylphenyl, R_2 in each case represents ethoxycarbonylmethyl, Ph in each case represents 1,2-phenylene substituted in the p-position to the nitrogen atom by fluorine and alk in each case represents vinylene, or in which R_1 represents unsubstituted 2-thienyl, unsubstituted phenyl, p-methanesulphinylphenyl or p-methoxyphenyl, R_2 in each case represents carboxymethyl, Ph in each case represents 1,2-phenylene substituted in the p-position to the nitrogen atom by fluorine and alk in each case represents vinylene, or in which R_1 in each case represents unsubstituted 2-thienyl, R_2 represents carboxymethyl or ethoxycarbonylmethyl, Ph in each case represents unsubstituted 1,2-phenylene and alk in each case represents vinylene, or in which R_1 represents unsubstituted phenyl, R_2 represents carboxymethyl, Ph represents unsubstituted 1,2-phenylene and alk represents vinylene, or in which R_1 represents 2-picolinyl or p-fluorophenyl, R_2 in each case represents carboxymethyl or ethoxycarbonylmethyl, Ph in each case represents 1,2-phenylene substituted in the p-position to the nitrogen atom by methoxy and alk in each case represents vinylene, and salts thereof.

3. A compound of the formula I according to claim 1 in which Ph represents unsubstituted 1,2-phenylene and R_1 represents phenyl and R_2 represents carboxymethyl or R_1 represents 2-thienyl and R_2 represents carboxy- or ethoxycarbonyl-methyl, or Ph represents 1,2-phenylene substituted in the p-position to the nitrogen atom by fluorine and R_1 represents phenyl, p-methanesulphinyl-phenyl or p-methoxyphenyl and R_2 represents carboxy- or ethoxycarbonyl-methyl, or Ph represents 1,2-phenylene substituted in the p-position to the nitrogen atom by methoxy and R_1 represents p-fluorophenyl or 2-picolinyl and R_2 represents carboxy- or ethoxy-carbonyl-methyl, alk in each case representing vinylene, and salts thereof.

4. 7-fluoro-1-phenyl-pyrimido[1,6-a]indole-5-acetic acid ethyl ester or a salt thereof.

5. 7-fluoro-1-(2-thienyl)-pyrimido[1,6-a]indole-5-acetic acid ethyl ester or a salt thereof.

6. 1-(2-thienyl)-pyrimido[1,6-a]indole-5-acetic acid ethyl ester or a salt thereof.

7. 7-methoxy-1-(2-picolinyl)-pyrimido[1,6-a]indole-5-acetic acid ethyl ester or a salt thereof.

8. 1-phenylpyrimido[1,6-a]indole-5-acetic acid or a salt thereof.

9. 7-fluoro-1-(p-methanesulfinylphenyl)-pyrimido[1,6-a]indole-5-acetic acid ethyl ester.

10. 7-fluoro-1-(p-methanesulphinylphenyl)-pyrimido[1,6-a]-indole-5-acetic acid or a salt thereof.

11. 7-fluoro-1-phenyl-pyrimido[1,6-a]indole-5-acetic acid or a salt thereof.

12. 1-(2-thienyl)-pyrimido[1,6-a]indole-5-acetic acid or a salt thereof.

13. 7-methoxy-1-(2-picolinyl)-pyrimido[1,6-a]indole-5-

* C L M S *

acetic acid or a salt thereof.

14. 7-fluoro-1-(p-methoxyphenyl)-pyrimido[1,6-a]indole-5-acetic acid or a salt thereof.

15. 7-fluoro-1-(p-methoxyphenyl)-pyrimido[1,6-a]indole-5-acetic acid ethyl ester or a salt thereof.

16. 7-methoxy-1-(p-fluorophenyl)-pyrimido[1,6-a]indole-5-acetic acid or a salt thereof.

17. 7-methoxy-1-(p-fluorophenyl)-pyrimido[1,6-a]indole-5-acetic acid ethyl ester or a salt thereof.

18. 7-fluoro-1-(2-thienyl)-pyrimido[1,6-a]indole-5-acetic acid or a salt thereof.

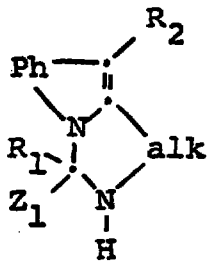
19. A pharmaceutical composition containing at least one compound according to any one of claims 2 and 18 in the free form or in the form of a pharmaceutically acceptable salt together with customary pharmaceutical adjuncts and/or carriers.

20. A pharmaceutical composition containing at least one compound according to any one of claims 1 and 3 to 17 in the free form or in the form of a pharmaceutically acceptable salt together with customary pharmaceutical adjuncts and/or carriers.

21. A compound as claimed in any one of claims 1 to 18 for use as an analgesic or anti-inflammatory agent.

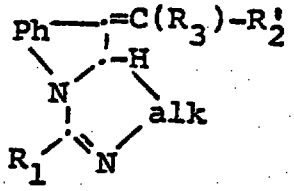
22. Process for the manufacture of compounds of the general formula I as defined in claim 1, comprises removing the group $H-Z_1$

from compounds of the general formula



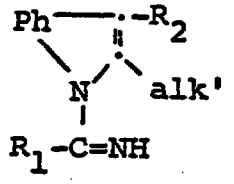
(II),

in which R_1, R_2, Ph and alk are as defined in claim 1 and Z_1 represents optionally functionally modified hydroxy or the mercapto group, or from salts thereof, with the introduction of an additional bond, or compounds of the formula



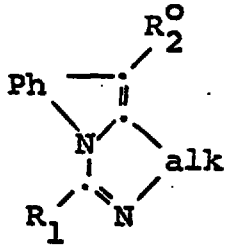
(V),

in which R_2' represents carboxy optionally esterified as indicated under R_2, and R_3 represents hydrogen, or salts thereof, are isomerised, or a compound of the general formula



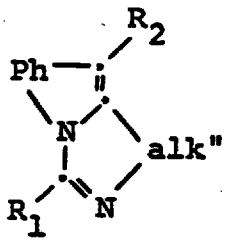
(VIII),

in which alk' represents a group of the formula $-CH=CH-Z_6$ or $-CH_2-CH=Z_6'$, in which Z_6 represents optionally functionally modified hydroxy or amino and Z_6' represents oxo or imino, or a salt thereof, is cyclised, or in a compound of the formula



(X),

in which R_2^o represents a radical that can be converted into the group R_2, or in salts thereof, R_2^o is converted into the group R_2 by solvolysis or oxidation, or compounds of the formula

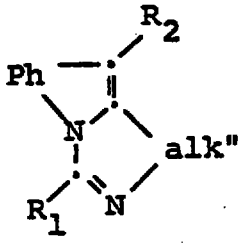


(XI) ,

in which alk" represents ethylene are dehydrogenated with the removal of hydrogen and the simultaneous formation of an additional bond, and, if desired, a compound obtainable according to the invention is converted into a different compound of the formula I or a free compound of the formula I obtainable according to the invention is converted into a salt or a salt obtainable according to the process is converted into the free compound of the formula I or into a different salt.

23. Process according to claim 22, wherein a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining steps are carried out or a starting material is used in the form of a salt or is formed under the reaction conditions.

24. Process according to claim 22, wherein a compound of the formula



(XI) ,

in which alk" represents ethylene is dehydrogenated with the removal of hydrogen and the simultaneous formation of an

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additional bond, or, for the manufacture of compounds of the formula I, wherein R_2 represents carboxymethyl, a compound of the formula I, wherein R_2 represents lower alkoxycarbonylmethyl having up to and including 5 carbon atoms, is hydrolysed, or, for the manufacture of compounds of the formula I, wherein R_2 represents lower alkoxycarbonylmethyl, a compound of the formula I, wherein R_2 represents carboxy methyl, or a salt thereof is esterified, and, if desired, a compound obtainable according to the invention is converted into a different compound of the formula I or a free compound of the formula I obtainable according to the invention is converted into a salt or a salt obtainable according to the process is converted into the free compound of the formula I or into a different salt.

25. A process of producing a compound of formula I substantially as described with reference to any of Examples 1 to 12.

26. The compounds of formula I obtainable by the process according to any one of claims 22 to 25.

27. The novel compounds of formula I substantially as described with reference to any of Examples 1 to 12.

28. A pharmaceutical composition according to claim 19 or 20 substantially as described with reference to any of Examples 13 to 15.