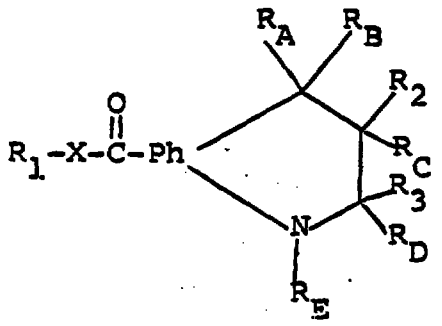
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QUINOLINE-3-CARBOXYLIC ACID DERIVATIVES, PROCESS FOR THEIR MANUFACTURE, PHARMACEUTICAL PREPARATIONS CONTAINING THEM AND THEIR USE.

Quinoline-3-carboxylic acid derivatives, process for their manufacture, pharmaceutical preparations containing them and their use.

The invention relates to novel quinoline-3-carboxylic acid derivatives of the formula (I)



(I),

in which X represents oxy or a direct bond, R_1 represents an aliphatic, cycloaliphatic, arcmatic, araliphatic, heterocyclic or heterccyclic-aliphatic radical or hydrogen, Ph represents an optionally additionally substituted 1,2-phenylene radical containing the group R_1-X-C(O)- and R_2 represents an optionally esterified or amidated carboxy group and in which either R_A and R_B together represent oxo, R_C and R_D together represent an additional bond and R_3 denotes hydroxy, hydrogen or an aliphatic radical, or R_C is hydrogen and R_3 and R_D together represent oxo and R_E in either case, represents

a radical R_5 which represents hydrogen or an aliphatic, cycloaliphatic, araliphatic or heterocyclic-aliphatic radical, or R_A represents an optionally etherified hydroxy group, R_3 denotes hydroxy, hydrogen or an aliphatic radical, and R_B together with R_C and also R_D together with R_E represent an additional bond in each case, or R_B and R_C together represent an additional bond, R_3 and R_D together represent oxo and R_E represents a radical R_5, with the proviso that in compounds of formula I, wherein R_2 denotes carboxy or lower alkoxycarbonyl, R_3 represents hydrogen or alkyl, R_A and R_B together represent oxo, R_C and R_D together represent an additional bond and R_E denotes hydrogen or R_A denotes hydroxy or lower alkoxy and R_B together with R_C and R_D together with R_E each represent an additional bond, respectively, the group R_1-X-C(=O)- is not carboxy,

and with the additional proviso that in the group of compounds of the formula I, wherein R_2 denotes optionally esterified or amidated carboxy, R_3 denotes hydrogen or alkyl, R_A and R_B together represent oxo, R_C and R_D together represent an additional bond and R_E denotes alkyl or alkenyl, the group R_1-X-C(=O)- is not acetyl, and

salts of salt-forming compounds of the formula (I), processes for their manufacture, pharmaceutical preparations containing compounds of the formula (I) or their salts, and the use of compounds of the formula (I) and their salts.

Aliphatic, cycloaliphatic, aromatic and araliphatic radicals are especially optionally substituted aliphatic, cycloaliphatic, aromatic or araliphatic hydrocarbon radicals, such as corresponding lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, phenyl or phenyl-lower alkyl. Substituents are, for example, hydroxy and/or lower alkoxy, and, in the case of radicals R_1, also lower alkylthio or phenylthio, lower alkanesulphinyl or benzenesulphinyl or

lower alkanesulphonyl or benzenesulphonyl, also lower alkanoyloxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, hydroxy-lower alkoxy-lower alkoxy or lower alkoxy-lower alkoxy-lower alkoxy, and, in the case of radicals R_5, also di-lower alkylamino or lower alkylene- or aza-, oxa- or thia-lower alkylene-amino having from 5 to 7 ring members. Heterocyclyl in heterocyclic or heterocyclic-aliphatic radicals is monocyclic heterocyclyl of aromatic character having a hetero atom, such as oxygen, sulphur or nitrogen, as ring member, such as furyl, thienyl or pyridyl. In heterocyclic-aliphatic radicals the aliphatic moiety is, for example, a corresponding aliphatic hydrocarbon radical, especially lower alkyl.

There come into consideration as additional substituents of Ph, for example, lower alkyl, lower alkoxy, hydroxy and/or halogen.

Esterified carboxy is, for example, carboxy esterified by an aliphatic or araliphatic alcohol, such as an optionally substituted lower alkanol or phenyl-lower alkanol, such as corresponding lower alkoxy- or phenyl-lower alkoxy-carbonyl. Substituted lower alkoxycarbonyl is, for example, hydroxy-, lower alkoxy- or di-lower alkylamino- or lower alkyleneamino-, aza-lower alkyleneamino-, oxa-lower alkyleneamino- or thia-lower alkyleneamino-lower alkoxycarbonyl. Substituents of phenyl-lower alkoxycarbonyl are, for example, lower alkyl, lower alkoxy and/or halogen.

In amidated carboxy, the amino group represents, for example, amino that is optionally mono-substituted by hydroxy or mono- or di-substituted by aliphatic radicals, such as amino, hydroxyamino, mono- or di-lower alkylamino or 5- to 7-membered lower alkylene- or aza-, oxa- or thia-lower alkylene-amino.

Etherified hydroxy R_A is, for example, lower alkoxy, lower alkenyloxy, lower alkoxy-lower alkoxy or di-lower alkylamino- or 5- to 7-membered lower alkylene- or aza-, oxo- or thia-lower alkylene-amino-lower alkoxy.

Hereinbefore and hereinafter, "lower" organic radicals and compounds are understood as being those that have up to and including 7, especially up to and including 4, carbon atoms.

Lower alkyl represents, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl or heptyl.

Lower alkenyl represents, for example, vinyl, 1-methyl-vinyl, 1-ethylvinyl, allyl or 2- or 3-methallyl.

Lower alkynyl represents, for example, ethynyl or prop-2-ynyl (propargyl).

Lower alkoxy and lower alkoxy in lower alkoxycarbonyl represent, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, hexyloxy or heptyloxy.

Lower alkylthio is, for example, methylthio, ethylthio, propylthio, butylthio, pentylthio, hexylthio or heptylthio.

Hydroxy-lower alkyl is, for example, 2- and/or 3-hydroxy-lower alkyl, for example 2-hydroxyethyl, 3-hydroxy-propyl or 2,3-dihydroxypropyl. Correspondingly, hydroxy-lower alkoxy and hydroxy-lower alkoxy in hydroxy-lower alkoxycarbonyl are especially 2- and/or 3-hydroxy-lower alkoxy, for example 2-hydroxyethoxy, 3-hydroxypropoxy or 2,3-dihydroxypropoxy, and hydroxy-lower alkoxy-lower alkoxy is especially ω-(ω-hydroxy-lower alkoxy)-lower alkoxy, for example 2-(2-hydroxyethoxy)-ethoxy.

Lower alkoxy-lower alkyl is, for example, 2- and/or 3-lower alkoxy-lower alkyl, for example 2-methoxyethyl, 2-ethoxyethyl or 3-methoxypropyl. Correspondingly, lower alkoxy-lower alkoxy and the same in lower alkoxy-lower

alkoxycarbonyl are especially 2- and/or 3-lower alkoxy-lower alkoxy, for example 2-methoxyethoxy, 2-ethoxyethoxy or 3-methoxypropoxy, and lower alkoxy-lower alkoxy-lower alkoxy is especially ω-(ω-lower alkoxy-lower alkoxy)-lower alkoxy, for example 2-(2-methoxyethoxy)-ethoxy.

Di-lower alkylamino-lower alkyl is, for example, 2- and/or 3-di-lower alkylamino-lower alkyl, for example 2-dimethylaminoethyl, 2-diethylaminoethyl or 3-dimethylamino-propyl. Correspondingly, di-lower alkylamino-lower alkoxy and the same in di-lower alkylamino-lower alkoxycarbonyl are especially 2- and/or 3-di-lower alkylamino-lower alkoxy, for example 2-dimethylaminoethoxy, 2-diethylaminoethoxy or 3-dimethylaminopropoxy.

Phenyl-lower alkyl is, for example, benzyl or 1- or 2-phenylethyl, and phenyl-lower alkoxy and the same in phenyl-lower alkoxycarbonyl are, for example, benzyloxy or 1- or 2-phenylethoxy.

Cycloalkyl is especially cycloalkyl having from 3 to 8, especially from 5 to 7, ring members, for example cyclopentyl, cyclohexyl or cycloheptyl, also cyclopropyl, cyclobutyl or cyclooctyl.

Furyl is, for example, 2-furyl, and, correspondingly, thienyl is, for example, 2-thienyl, while pyridyl may be 2-, 3- or 4-pyridyl.

Furyl-lower alkyl, thienyl-lower alkyl and pyridyl-lower alkyl have, as the alkyl moiety, especially methyl and are, for example, furfuryl, 2-thenyl or pyridylmethyl, such as 2- or 4-pyridylmethyl.

Mono- or di-lower alkylamino is, for example, methylamino, dimethlamino, ethylamino, diethylamino, propylamino or butylamino.

Lower alkyleneamino or aza-, oxa- or thia-lower alkyleneamino and the same in correspondingly substituted lower alkyl or lower alkoxy radicals are, for example, pyrrolidin-1-yl, piperidino, morpholino, thiamorpholino, or N-lower alkylpiperazin-1-yl, such as N'-methylpiperazin-1-yl.

Lower alkanoyloxy is, for example, acetoxy, propionyloxy, butyryloxy or pivaloyloxy.

Halogen is especially halogen having an atomic number of up to and including 35, such as fluorine, chlorine or bromine.

Salt-forming compounds of the formula (I) are, for example, acidic compounds containing carboxy R_2, R_3 or R_1-X-C(=O)- and/or enolic hydroxy groups, for example hydroxy R_A, or basic compounds of the formula (I) containing basic groups, optionally in addition to a smaller number of acidic groups. Salts of the same are, for example, salts of acidic compounds with bases, especially pharmaceutically acceptable salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, also ammonium salts with ammonia or amines, such as lower alkyl- or hydroxy-lower alkyl-amines, for example trimethylamine, triethylamine or di- or tri-(2-hydroxyethyl)-amine, or acid addition salts, especially pharmaceutically acceptable acid addition salts, for example salts with inorganic acids, such as mineral acids, for example hydrohalic acid, sulphuric acid or phosphoric acid, addition salts or acid addition salts with suitable organic sulphonic or carboxylic acids, for example hydrochlorides, hydrobromides, sulphates, phosphates, malates, maleates, fumarates or tartrates.

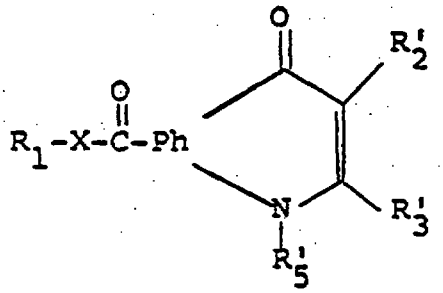
The invention relates, for example, to those compounds of the formula (I) in which X represents a direct bond and R_1, R_2, R_3, R_5, R_A, R_B, R_C, R_D, and R_E have the meanings given at the beginning, R_1 being different from hydrogen, or

in which X represents oxy, R_1 represents lower alkyl, or phenyl that is optionally substituted, for example as indicated, and R_2, R_3, R_5, R_A, R_B, R_C, R_D and R_E have the meanings given at the beginning, and their salts, processes for their manufacture, pharmaceutical preparations containing them and their use as the active ingredients of medicaments.

The invention relates especially to compounds of the formula (I) in which R_1 represents lower alkyl, lower alkenyl or cycloalkyl each of which is optionally substituted by hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, hydroxy-lower alkoxy-lower alkoxy, lower alkoxy-lower alkoxy-lower alkoxy, lower alkylthio, lower alkanesulphinyl or by lower alkanesulphonyl, phenyl or phenyl-lower alkyl each of which is optionally substituted in the phenyl moiety by lower alkyl, lower alkoxy and/or by halogen, furyl, thienyl or pyridyl, or furyl-lower alkyl, thienyl-lower alkyl or pyridyl-lower alkyl or hydrogen, Ph represents 1,2-phenylene that is optionally additionally substituted by lower alkyl, lower alkoxy, hydroxy and/or by halogen, and R_2 represents carboxy, lower alkoxycarbonyl, hydroxy-lower alkoxycarbonyl, lower alkoxy-lower alkoxy-carbonyl, di-lower alkylamino-lower alkoxy- or 5 to 7-membered lower alkyleneamino- or aza-, oxa- or thia-lower alkyleneamino-lower alkoxy-carbonyl or amidated carboxy containing, as amino group, amino, hydroxyamino, lower alkylamino, di-lower alkylamino or 5- to 7-membered lower alkylene- or aza-, oxa-, or thia-lower alkylene-amino, and in which <u>either</u> R_A and R_B together represent oxo, R_C and R_D together represent an additional bond and R_3 represents hydrogen, lower alkyl or hydroxy, R_C is hydrogen, R_3 and R_D together represent oxo, or

and R_E represents hydrogen, lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, di-lower alkylamino-lower alkyl, 5- to 7-membered lower alkyleneamino- or aza-, oxa- or thia-lower alkyleneamino-lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl having from 3 to 8, especially from 5 to 7, ring members, phenyl-lower alkyl, furyl-lower alkyl, thienyl-lower alkyl or pyridyl-lower alkyl, each of which is optionally substituted by lower alkyl, lower alkoxy and/or by halogen, or R_A represents hydroxy or lower alkoxy, R_3 represents hydrogen, lower alkyl or hydroxy, R_B together with R_C and also R_D together with R_E represent an additional bond in each case, or R_B and R_C together represent an additional bond and R_3 and R_D together represent oxo, and R_E represents hydrogen, lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, di-lower alkylamino-lower alkyl, 5- to 7-membered lower alkyleneamino- or aza-, oxa- or thia-lower alkyleneamino-lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl having from 3 to 8, especially from 5 to 7, ring members, phenyl-lower alkyl, furyl-lower alkyl, thienyl-lower alkyl or pyridyl-lower alkyl, each of which is optionally substituted by lower alkyl, lower alkoxy and/or by halogen, and salts of the above-defined compounds having salt-forming properties.

The invention relates on the one hand especially to compounds of the formula (Ia)



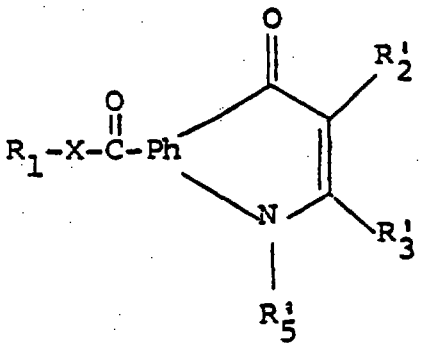
(Ia),

in which R_1 represents lower alkyl having up to 7 carbon atoms, for example propyl, isopropyl, butyl, isobutyl, tert-butyl, sec-butyl or pentyl; lower alkoxy-, lower alkylthio-, lower alkanesulphinyl- or lower alkanesulphonyl-

lower alkyl each having up to 4 carbon atoms in the alkyl moiety, for example methanesulphinyl- or methanesulphonyl-methyl; phenylthio-, benzenesulphinyl- or benzenesulphonyl-lower alkyl having up to 4 carbon atoms in the alkyl moiety, for example benzenesulphonylmethyl; lower alkenyl having up to 4 carbon atoms, for example allyl; 3- to 8-membered cycloalkyl, for example cyclopentyl, cyclohexyl or cycloheptyl; phenyl or phenyl-lower alkyl having up to 4 carbon atoms in the alkyl moiety, for example corresponding benzyl or 1- or 2-phenylethyl, each of which is optionally substituted by lower alkyl having up to 4 carbon atoms, for example methyl, lower alkoxy having up to 4 carbon atoms, for example methoxy, and/or by halogen having an atomic number of up to and including 35, for example chlorine or bromine; furyl, thienyl or pyridyl, for example 2-furyl, 2-thienyl or 2-, 3- or 4-pyridyl, or furyl-, thienyl- or pyridyl-lower alkyl having up to 4 carbon atoms in the alkyl moiety, for example furfuryl, 2-thenyl, or 2- or 4-picolyl, and X represents a direct bond or R_1 represents hydrogen or lower alkyl having up to 7 carbon atoms and X represents oxy, and in which Ph represents 1,2-phenylene that contains the group R_1-X-C(=O)- and that is optionally additionally substituted by lower alkyl having up to 4 carbon atoms, for example methyl, lower alkoxy having up to 4 carbon atoms, for example methoxy, hydroxy or by halogen having an atomic number of up to and including 35, for example chlorine, R_2' represents carboxy, lower alkoxycarbonyl having up to 5 carbon atoms, for example methoxy- or ethoxy-carbonyl, hydroxy-lower alkoxycarbonyl having up to 5 carbon atoms, for example 2-hydroxyethoxycarbonyl, lower alkoxy-lower alkoxy-carbonyl having up to 4 carbon atoms in the alkoxy moieties, for example 2-methoxy- or 2-ethoxy-ethoxycarbonyl, di-lower alkylamino-lower alkoxycarbonyl having up to 4 carbon atoms in the alkyl moiety and up to 4 carbon atoms in the alkoxy moiety, for example 2-dimethylaminoethoxy- or 2-diethyl-aminoethoxy-carbonyl, carbamoyl, N-hydroxycarbamoyl or N-lower

alkyl- or N,N-di-lower alkyl-carbamoyl having up to 4 carbon atoms in the alkyl moiety, for example N-methyl-, N-ethyl- or N,N-dimethyl-carbamoyl, R'_3 represents hydrogen, lower alkyl having up to 4 carbon atoms, for example methyl, or hydroxy, and R'_5 represents lower alkyl or lower alkenyl having up to 4 carbon atoms, for example methyl, ethyl or allyl; phenyl-, furyl-, thienyl- or pyridyl-lower alkyl that have up to 4 carbon atoms in the alkyl moiety and each of which is optionally substituted by lower alkyl having up to 4 carbon atoms, for example methyl, lower alkoxy having up to 4 carbon atoms, for example methoxy, and/or by halogen having an atomic number of up to and including 35, for example chlorine, for example corresponding benzyl, 1- or 2-phenylethyl, furfuryl, 2-thenyl or 2- or 4-picolyl; lower alkoxy-lower alkyl having up to 4 carbon atoms in the alkoxy moiety and up to 4 carbon atoms in the alkyl moiety, for example 2-methoxy- or 2-ethoxy-ethyl; or di-lower alkylamino-lower alkyl in which lower alkyl has up to 4 carbon atoms or lower alkylene or aza-, oxa- or thia-lower alkylene having from 5 to 7 ring members, for example 2-dimethylamino- or 2-diethylamino-ethyl, and tautomers thereof in which a hydroxy group R'_3 is in the tautomeric oxo form, and salts of salt-forming compounds of the formula (Ia) or their tautomers.

The invention relates on the other hand especially to compounds of the formula



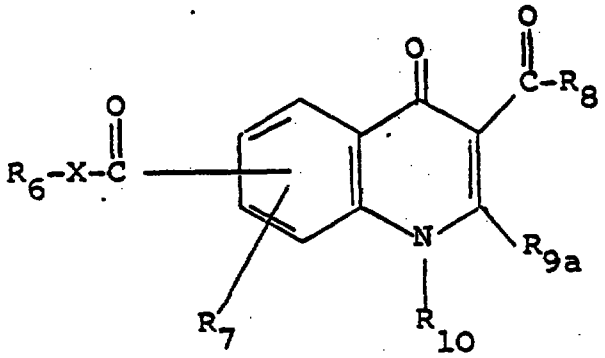
(Ia),

in which R_1 represents lower alkyl having up to 7 carbon atoms, for example propyl, isopropyl, butyl, isobutyl,

tert-butyl, sec-butyl or pentyl, lower alkoxy-, lower alkylthio-, lower alkanesulphinyl- or lower alkanesulphonyl-lower alkyl each having up to 4 carbon atoms in the alkyl moiety, for example methanesulphinyl- or methanesulphonyl-methyl, lower alkenyl having up to 4 carbon atoms, for example allyl, or 3- to 8-membered cycloalkyl, for example cyclopentyl, cyclohexyl or cycloheptyl, and X represents a direct bond, or R_1 represents hydrogen, lower alkyl having up to 7 carbon atoms, for example propyl, isopropyl, butyl, isobutyl, tert-butyl, sec-butyl or pentyl, lower alkoxy-, lower alkylthio-, lower alkanesulphinyl- or lower alkanesulphonyl-lower alkyl each having up to 4 carbon atoms in the alkyl moiety, for example methanesulphinyl- or methanesulphonyl-methyl, lower alkenyl having up to 4 carbon atoms, for example allyl, 3- to 8-membered cycloalkyl, for example cyclopentyl, cyclohexyl or cycloheptyl, ω-hydroxy-lower alkyl having from 2 to 4 carbon atoms, such as 2-hydroxy-ethyl, lower alkanoyloxymethyl having up to and including 7 carbon atoms in the alkanoyl moiety, such as acetoxy- or pivaloyloxy-methyl, or ω-(ω-hydroxy-lower alkoxy)-lower alkyl, ω-(ω-lower alkoxy-lower alkoxy)-lower alkyl, ω-[ω-(ω-hydroxy-lower alkoxy)-lower alkoxy]-lower alkyl or ω-[ω-(ω-lower alkoxy-lower alkoxy)-lower alkoxy]-lower alkyl each having from 1 to 4 carbon atoms in the alkyl moiety and from 2 to 4 carbon atoms in the alkylene moiety, such as 2-(2-hydroxyethoxy)-ethyl, 2-(2-methoxyethoxy)-ethyl, 2-[2-(2-hydroxyethoxy)-ethoxy]-ethyl or 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl, and X represents oxy, and in which Ph represents 1,2-phenylene that contains the group R_1-X-CO- and is optionally additionally substituted by lower alkyl having up to 4 carbon atoms, for example methyl, lower alkoxy having up to 4 carbon atoms, for example methoxy, hydroxy or by halogen having an atomic number of up to and including 35, for example chlorine, R_2' represents carboxy, lower alkoxycarbonyl having up to 5 carbon atoms, for example methoxy- or ethoxy-carbonyl, hydroxy-lower alkoxycarbonyl having up to 5 carbon atoms,

for example 2-hydroxyethoxycarbonyl, lower alkoxy-lower alkoxycarbonyl having up to 4 carbon atoms in the alkoxy moieties, for example 2-methoxy- or 2-ethoxy-ethoxycarbonyl, carbamoyl, N-hydroxycarbamoyl or N-lower alkyl- or N,N-di-lower alkyl-carbamoyl having up to 4 carbon atoms in the alkyl moiety, for example N-methyl-, N-ethyl or N,N-dimethyl-carbamoyl, R_3' represents hydroxy, and R_5' represents hydrogen, lower alkyl having up to and including 4 carbon atoms, for example ethyl, lower alkenyl having up to and including 4 carbon atoms, such as allyl, or lower alkynyl having up to and including 4 carbon atoms, such as propargyl, and tautomers thereof in which a hydroxy group R_3' is in the tautomeric oxo form, and salts of salt-forming compounds of the formula (Ia) or their tautomers.

The invention relates more especially to compounds of the formula (II)



(II),

in which

X represents a direct bond and R_6 represents hydrogen or lower alkyl having up to 7 carbon atoms, for example propyl, isopropyl or especially butyl, also isobutyl, sec-butyl or pentyl, or X represents oxy and R_6 represents hydrogen, lower alkyl having up to 7 carbon atoms, for example propyl, isopropyl or especially butyl, also isobutyl, sec-butyl or pentyl, ω-hydroxy-lower alkyl having from 2 to 4 carbon atoms, such as 2-hydroxyethyl, lower alkanoyloxymethyl having up to and including 7 carbon atoms in the alkanoyl moiety, such as acetoxy- or pivaloyloxy-methyl, or ω-(ω-hydroxy-lower alkoxy)-lower alkyl, ω-(ω-lower alkoxy-lower alkoxy)-lower alkyl, ω-[ω-(ω-hydroxy-lower alkoxy)-lower

alkoxy]-lower alkyl or ω-[ω-(ω-lower alkoxy-lower alkoxy)-lower alkoxy]-lower alkyl each having from 1 to 4 carbon atoms in the alkyl moiety and from 2 to 4 carbon atoms in the alkylene moiety, such as 2-(2-hydroxyethoxy)-ethyl, 2-(2-methoxyethoxy)-ethyl, 2-[2-(2-hydroxyethoxy)-ethoxy]-ethyl or 2-[2-(2-methoxyethoxy)-ethoxy]-ethyl, R_7 represents hydrogen or especially lower alkyl having up to and including 4 carbon atoms, for example methyl, or also lower alkoxy having up to and including 4 carbon atoms, for example methoxy, halogen having an atomic number of up to and including 35, for example chlorine, or hydroxy, R_8 represents hydroxy or lower alkoxy having up to 4 carbon atoms, for example methoxy or ethoxy, R_{9a} represents hydrogen or especially hydroxy, and R_{10} represents lower alkyl, lower alkenyl or lower alkynyl each having up to and including 4 carbon atoms, for example ethyl, allyl or propargyl, it also being possible for 2-hydroxy-4-oxo-1,4-dihydroquinoline compounds of the formula (II) to be in the tautomeric 2-oxo-4-hydroxy-1,2-dihydro- or 2,4-dioxo-1,2,3,4-tetrahydro-quinoline form, and very especially to those in which the radical of the formula R_6-X-C(=O)- is in the 6-position and a radical R_7 that is not hydrogen is in the 5- or 7-position of the quinoline ring system, and salts of salt-forming compounds of the formula (II) or of their tautomers.

Of particular importance in accordance with the invention are compounds of the formula (II) in which X represents oxy, the group R_6-O-C(=O)- is bonded in the 6-position, R_6 is hydrogen, lower alkyl having up to 7 carbon atoms, for example butyl, isobutyl, or sec-butyl, lower alkanoyloxymethyl having up to and including 7 carbon atoms in the alkanoyl moiety, such as acetoxy- or pivaloyloxy-methyl, or ω-(ω-hydroxy-lower alkoxy)-lower alkyl, ω-(ω-lower alkoxy-lower alkoxy)-lower alkyl, ω-[ω-(ω-hydroxy-lower alkoxy)-lower alkoxy]-lower alkyl or ω-[ω-(ω-lower alkoxy-lower alkoxy)-lower alkoxy]-lower alkyl each having from 1 to 4 carbon atoms in the

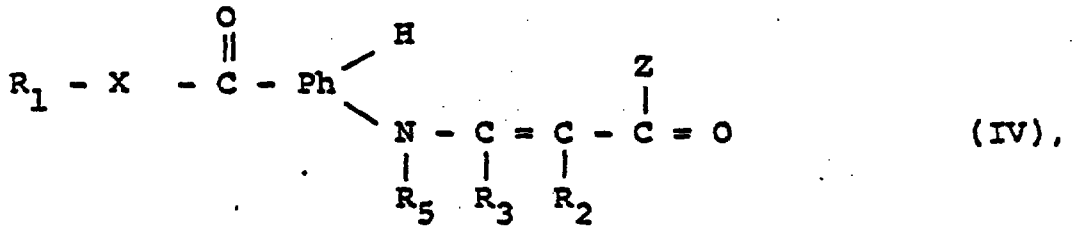
alkyl moiety and from 2 to 4 carbon atoms in the alkylene moiety, such as 2-(2-hydroxyethoxy)-ethyl, 2-(2-methoxy-ethoxy)-ethyl, 2-[2-(2-hydroxyethoxy)-ethoxy]-ethyl or 2-[2-(2-methoxyethoxy)-ethoxy]-ethyl, R_7 represents hydrogen, R_8 represents hydroxy or lower alkoxy having up to and including 4 carbon atoms, for example methoxy or ethoxy, R_{9a} represents hydroxy, and R_{10} represents lower alkenyl having up to and including 4 carbon atoms, for example allyl, or X represents a direct bond, R_6 represents hydrogen or lower alkyl having up to and including 7 carbon atoms, such as propyl, R_7 represents lower alkyl having up to and including 4 carbon atoms, such as methyl, the group R_6-C(=O)- taking up the 6-position and the lower alkyl group R_7 the 7-position, R_8 represents hydroxy or lower alkoxy having up to and including 4 carbon atoms, such as methoxy or ethoxy, R_{9a} represents hydroxy and R_{10} represents lower alkyl having up to and including 4 carbon atoms, such as propyl, or the 2-oxo-4-hydroxy-1,2-dihydroquinoline or 2,4-dioxo-1,2,3,4-tetrahydroquinoline tautomer thereof in free form or in salt form.

The invention relates most especially to compounds of the formula (II) in which X represents a direct bond and R_6 represents lower alkyl having up to 7 carbon atoms, for example propyl, or X represents oxy and R_6 represents hydrogen or lower alkyl having up to and including 4 carbon atoms, such as methyl, and in which R_7 represents hydrogen or especially lower alkyl having up to and including 4 carbon atoms, such as methyl, the group R_6-X-C(=O)- preferably taking up the 6-position and lower alkyl R_7 preferably the 7-position, R_8 represents hydroxy or lower alkoxy having up to 4 carbon atoms, such as ethoxy, R_{9a} represents hydroxy and R_{10} represents lower alkyl or lower alkenyl having up to 4 carbon atoms, such as methyl, ethyl, propyl or allyl, and their 2-oxo-4-hydroxy-1,2-

dihydroquinoline or 2,4-dioxo-1,2,3,4-tetrahydroquinoline tautomers, and, if appropriate, salts, especially pharmaceutically acceptable salts, of salt-forming compounds of the type mentioned.

The invention relates especially to the specific compounds of the formula (I) mentioned in the Examples.

The compounds of the formula (I) can be manufactured according to methods known per se, for example by subjecting a compound of the formula (IV)



(IV),

in which Z is a removable radical, or a tautomer and/or salt thereof, to intramolecular cyclisation and, if desired, converting the resulting compound into a different compound of the formula (I) and/or converting a resulting free compound into a salt or a resulting salt into the free compound or into a different salt.

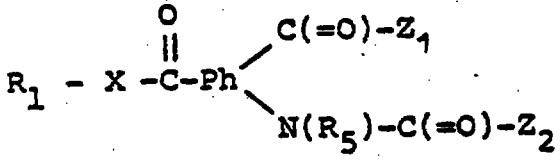
The removable radical Z is, for example, an optionally etherified or esterified hydroxy group. Etherified hydroxy groups are, for example, hydroxy groups etherified by aliphatic, araliphatic or aromatic alcohols, such as lower alkoxy, for example methoxy or ethoxy, or optionally substituted phenoxy, such as phenoxy containing lower alkyl, lower alkoxy or especially halogen and/or nitro, for example phenoxy, 4-chlorophenoxy, 4-nitrophenoxy, 2,4-dinitrophenoxy and 3,5-dichlorophenoxy. Esterified hydroxy groups are, for example, hydroxy groups esterified by organic carboxylic acids, such as lower alkanoic acids,

or by monofunctional carbonic acid derivatives, such as carbonic acid monoesters or monohalides, but especially by mineral acids, such as hydrohalic acids, for example formyloxy, acetoxy, chlorocarbonyloxy, lower alkoxycarbonyloxy, such as ethoxycarbonyloxy, or especially halogen atoms, such as chlorine, bromine or iodine, also sulphonyloxy groups, such as sulphonyloxy groups derived from organic sulphonic acid or halosulphonic acids, for example fluorosulphonyloxy, chlorosulphonyloxy, methanesulphonyloxy, benzenesulphonyloxy, p-toluenesulphonyloxy or p-bromosulphonyloxy. Tautomers of compounds of the formula (IV) are especially those in which a hydroxy group R_3 is in the tautomeric oxo form. Salts of compounds of the formula (IV) are especially salts with bases, such as alkali metal salts, of compounds of the formula (IV) in which Z is hydroxy and/or R_2 is carboxy, or acid addition salts of basic compounds of the formula (IV).

The intramolecular condensation can be carried out in customary manner, preferably by heating, for example to from approximately 150°C to approximately 250°C, in the presence of a suitable condensation agent and, if necessary, of a solvent that is inert under the reaction conditions, and, if necessary, under an inert gas, such as nitrogen, and/or in a closed vessel. Solvents that are inert under the reaction conditions are, for example, higher-boiling hydrocarbons, such as toluene or xylene, ethers, such as diphenyl ether, or tertiary carboxylic acid amides, such as dimethylformamide or N-methylpyrrolidone. Suitable condensation agents are, for example, acidic agents, such as protonic acids, for example mineral acids, inter alia sulphuric acid, phosphoric acid or polyphosphoric acid, or acidic mineral acid esters, such as mono- or di-lower alkyl phosphates or phosphites, inter alia triethyl phosphate, triethyl phosphite or tetraethyl pyrophosphate, also Lewis acids, such as, for example, aluminium chloride, aluminium bromide, zinc chloride, boron trifluoride or antimony pentachloride.

The starting materials of the formula (IV), insofar as they are novel, can be obtained according to methods known per se, for example starting from corresponding aniline compounds of the formula R_1-X-C(=O)-Ph(NHR_5)-H (V). Thus, starting materials of the formula (IV) in which Z represents an etherified hydroxy group, can be obtained, for example, by condensing the above-mentioned aniline compound in customary manner with a lower alkoxy-R_3-methylenemalonic acid ester. From the resulting esters of the formula (IV) there can be manufactured in customary manner, for example by hydrolysis, the corresponding acids, and from those, in customary manner, other functional derivatives of the same.

Compounds of the formula (I), in which R_3 represents hydroxy, or tautomers of the same, can also be manufactured by subjecting a compound of the formula (VI)



(VI),

in which one of radicals Z_1 and Z_2 represents a group of the formula CH_2-R_2 and the other represents an optionally reactively etherified or esterified hydroxy group, or a tautomer and/or salt thereof, to intramolecular cyclisation, and, if desired, converting the resulting compound into a different compound of the formula (I) and/or converting a resulting free compound into a salt or a resulting salt into the free compound or into a different salt.

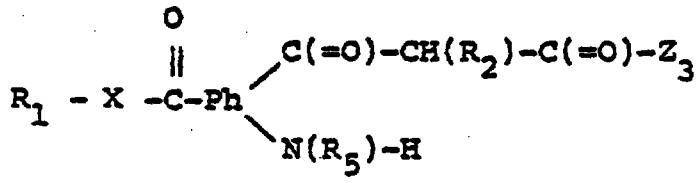
Etherified hydroxy groups are, for example, hydroxy groups etherified by an aliphatic alcohol, such as by a lower alkanol, for example by methanol or ethanol, or by an optionally substituted aromatic alcohol, for example phenol. Esterified hydroxy groups are, for example, hydroxy groups esterified by a mineral acid, such as a hydrohalic acid, for example by hydrochloric, hydrobromic or hydriodic acid, or, less favourably, by a halosulphonic acid or an organic sulphonic acid, for example methane-, ethane-, benzene-, p-toluene-, or fluoro-sulphonic acid.

The intramolecular cyclisation is carried out in customary manner, preferably in a substantially anhydrous solvent, advantageously in the presence of a dehydrating agent and, if necessary, in the presence of a basic condensation agent, if necessary at elevated temperature, for example at approximately from 50 to 150°C, under an inert gas, such as nitrogen, and/or in a closed vessel. Suitable solvents are especially lower alkanols, such as methanol, ethanol or butanol, lower alkylene glycols, such as ethylene glycol, also dimethyl sulphoxide, dimethyl-formamide, diphenyl ether and high-boiling hydrocarbons, such as xylene. Basic condensation agents are, for example, alkali alcoholates, such as alkali-lower alkoxides, for example sodium methoxide, sodium ethoxide or sodium tert-butoxide, or alkali metal hydrides, such as sodium hydride.

The starting materials of the formula (VI), insofar as they are novel, can be manufactured according to methods known per se, for example by reacting a compound of the

formula R_1-X-C(=O)-Ph(NHR_5)-C(=O)-Z_1 (VII), or a derivative thereof, with a compound of the formula Z_2-COOH (VIII), or with a reactive functional derivative thereof, such as an ester, for example a lower alkyl ester, or an anhydride, for example the chloride, or the symmetric or internal anhydride, thereof, and, if desired, in the resulting compound of the formula (VI), converting groups Z_1 and/or Z_2 in customary manner into other such groups. Thus, for example, a corresponding anthranilic acid ester can be reacted with a malonic acid ester chloride or a malonic acid diester, or a corresponding 2-aminobenzoylacetic acid ester can be reacted with phosgene or a haloformic acid lower alkyl ester or a haloformic acid phenyl ester.

Compounds of the formula (I) in which R_3 represents hydroxy, can also be manufactured by subjecting a compound of the formula (IX)



(IX),

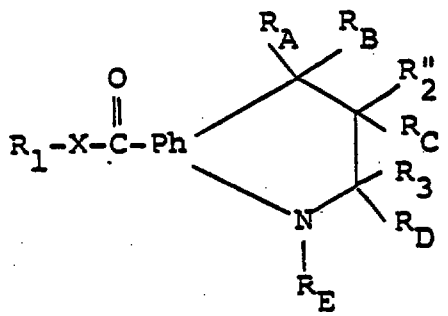
in which Z_3 represents hydroxy or a reactive modified hydroxy group, or a tautomer and/or salt thereof, to intramolecular condensation and, if desired, converting a resulting compound into a different compound of the formula (I) and/or converting a resulting free compound into a salt or a resulting salt into the free compound or into a different salt.

Reactive modified hydroxy groups are, for example, etherified or especially esterified hydroxy groups. Etherified hydroxy groups are, for example, lower alkoxy or optionally substituted phenoxy, and esterified hydroxy groups are hydroxy groups esterified especially by mineral acids, such as hydrohalic acids, or by halosulphonic acids or organic sulphonic acids, such as halogen, for example

chlorine, bromine or iodine, or methane-, benzene-, p-toluene, p-bromobenzene- or fluoro-sulphonyloxy. The intramolecular cyclisation of compounds of the formula (IX) can be carried out in customary manner, for example in a solvent that is inert under the reaction conditions, such as a hydrocarbon, for example benzene, toluene or mineral oil, an ether, for example diethyl ether or tetrahydrofuran, dimethylformamide, dimethyl sulphoxide, and the like, if necessary while heating, for example to approximately from 50 to 150°C, advantageously in the presence of a basic condensation agent, such as an alkali metal hydroxide, for example sodium or potassium hydroxide, or an organic nitrogen base, such as pyridine or triethylamine, if necessary under an inert gas, such as nitrogen, and/or in a closed vessel.

The starting materials of the formula (IX), insofar as they are novel, can be manufactured according to methods known per se, for example by reacting in customary manner a compound of the formula R_1-X-C(=O)-Ph-(NHR_5)-COOH (X) or a functional carboxy derivative, such as an ester or an anhydride, for example the symmetric anhydride, a corresponding acid chloride or the corresponding isatoic acid anhydride, with malonic acid or a suitable functional derivative, such as a diester, of the same, and, if desired, in the resulting compound, converting the group Z_3 into a different such group.

The compounds of the formula (I) can also be manufactured by, in a compound of the formula (XI)



(XI),

in which the radical R_2'' represents a radical that can be converted into the optionally esterified or amidated carboxy group R_2, or in a tautomer and/or salt thereof, converting the group R_2'' into the optionally esterified or amidated carboxy group R_2 and, if desired, converting a resulting compound into a different compound of the formula (I) or converting a resulting salt-forming compound into a salt or a resulting salt into the free compound or into a different salt.

Groups R_2'' which can be converted into optionally esterified or amidated carboxy are, for example, functionally modified carboxy groups that can be converted by solvolysis into optionally esterified or amidated carboxy and that are other than esterified or amidated carboxy R_2. Such groups are, for example, cyano, anhydridised carboxy groups, iminoether groups, iminoester groups and etherified and/or esterified trihydroxymethyl groups. Anhydridised carboxy groups are, for example, carboxy groups anhydridised by a mineral acid, such as a hydrohalic acid, by a halosulphonic acid, such as fluorosulphonic acid, or an organic sulphonic or carboxylic acid, such as an aliphatic or aromatic sulphonic or carboxylic acid. Iminoether groups are, for example, iminoether groups derived from esterified carboxy groups R_2, such as O-lower alkylcarbamoyl, or cyclic iminoether groups, such as 4,4- or 5,5-di-lower alkyl-, for example 4,4- or 5,5-dimethyl-4,5-dihydrooxazol-2-yl, or 4,4,6-tri-lower alkyl-, for example 4,4,6-trimethyl-, 5,6-dihydrooxazin-2-yl. Iminoester groups are, for example, iminoester groups that are derived from amidated carboxy groups R_2 and that are esterified by hydrohalic acids or organic carboxylic acids, such as lower alkanoic acids, such as, for example, chlorocarbimino or O-lower alkanoyl-carbamoyl. Etherified and/or esterified trihydroxymethyl groups are, for example, trihydroxymethyl groups that are esterified by mineral acids, such as hydrohalic acids,

and/or etherified and that correspond to esterified carboxy groups R_2, for example tri-lower alkoxymethyl, lower alkoxy dihalomethyl or trihalomethyl, especially those in which halogen is chlorine or bromine. Further groups that can be converted by solvolysis into amidated carboxy groups R_2 are, for example, dihalogenated carbamoyl groups corresponding to those groups, i.e. corresponding amino-dihalo-, especially -dichloro-methyl groups.

The mentioned groups can be converted by customary hydrolysis into carboxy groups; iminoether groups and etherified hydroxydihalomethyl groups, such as lower alkoxydihalomethyl groups, can similarly be converted into esterified carboxy groups, aminodihalomethyl groups into amidated carboxy groups and cyano into unsubstituted carbamoyl groups. The hydrolysis is carried out in customary manner, for example in the presence of an acidic or alkaline hydrolysis agent, generally in the presence of a solvent and/or diluent or a mixture thereof, and, if necessary, while cooling or heating, for example in a temperature range of from approximately 0°C to approximately 120°C, if necessary under an inert gas, such as nitrogen, and/or in a closed vessel. Acidic hydrolysis agents are, for example, mineral acids, such as hydrohalic acids, for example hydrochloric acid, or oxygen acids of sulphur or phosphorus, such as sulphuric or phosphoric acid, also organic sulphonic acids, for example p-toluenesulphonic acid or mesitylenesulphonic acid, or organic carboxylic acids, such as lower alkanecarboxylic acids, for example formic or acetic acid. Basic hydrolysis agents are, for example, alkali metal hydroxides, for example sodium or potassium hydroxide, also alkali metal carbonates, for example sodium or potassium carbonate. Suitable solvents or diluents are preferably water-miscible solvents, such as lower alkanols, for example ethanol or methanol, lower ketones, for example acetone, or tertiary alkanoic acid amides, for example dimethylformamide or N-methylpyrrolidone.

(44)

Anhydridised carboxy groups and cyclic iminoether groups can also be converted by alcoholysis, i.e. reaction with a corresponding alcohol, into esterified carboxy groups R_2. This operation is carried out in customary manner, starting from anhydridised carboxy groups, for example in the presence of a basic condensation agent, such as an alkali metal hydroxide or carbonate, for example sodium or potassium hydroxide or corresponding carbonates, or in the presence of organic nitrogen bases, such as pyridine or triethylamine, and, starting from cyclic iminoether groups, preferably under anhydrous conditions, for example in the presence of hydrogen chloride, phosphoric acid, sulphuric acid or p-toluenesulphonic acid, if necessary while heating, for example in a temperature range of from approximately 0°C to approximately 150°C, under an inert gas, such as nitrogen, and/or in a closed vessel.

Anhydridised carboxy groups can also be converted in customary manner into amidated carboxy groups R_2 by ammonolysis or aminolysis, i.e. reaction with, respectively, ammonia or a corresponding amine having at least one hydrogen atom.

Further radicals R_2'' that can be converted into optionally esterified carboxy groups R_2 are groups that can be converted by oxidation into those groups, such as the optionally hydrated formyl group that can be converted by oxidation into carboxy, or etherified hydroxymethyl groups that can be converted by oxidation into esterified carboxy groups. Further groups that can be converted by oxidation into carboxy are optionally substituted 2-furyl containing, for example, di-lower alkoxymethyl, such as diethoxymethyl, in the 5-position, or optionally 2-substituted vinyl, for example 2,2-diphenylvinyl.

The oxidation can be carried out in a manner known per se, for example by reaction with an oxidising heavy metal compound, preferably a compound containing chromium(VI) or manganese(VII), for example with chromium trioxide or especially potassium permanganate, also with compounds containing bismuth(III), manganese(IV) or silver(I), for

example with bismuth oxide, manganese dioxide or silver oxide, or by air oxidation. The operation is advantageously carried out in the presence of a solvent that is inert towards the reactants, for example acetone or pyridine, or a, preferably aqueous, mixture thereof, if necessary while cooling or heating, for example in a temperature range of approximately from 0°C to 80°C. Optionally etherified hydroxymethyl can advantageously be oxidised by potassium permanganate in aqueous acetone or pyridine to optionally esterified carboxy.

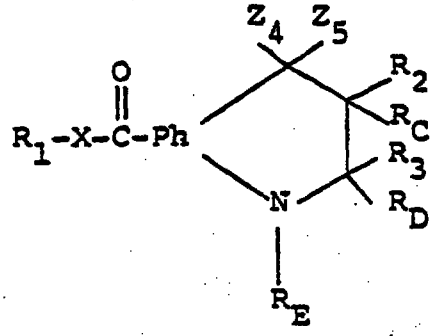
The starting materials of the formula (XI), insofar as they are novel, can be manufactured according to methods known per se.

Compounds of the formula (XI) in which R''_2 represents cyano, etherified hydroxymethyl, formyl or optionally substituted 2-furyl, can be manufactured, for example, by intramolecular condensation of corresponding compounds of the formula R_1-X-C(=O)-Ph(H)-N(R_5)-C(R_3)=C(R''_2)-C(=O)-Z (XII) in which Z represents a reactively esterified or etherified hydroxy group, for example halogen or lower alkoxy, such as methoxy. A formyl group R''_2 may also be in intermediately protected, such as acetalised or acylalised, form, for example it may be in the form of di-lower alkoxy-, lower alkylenedioxy- or dihalo-methyl. The nitriles of the formula (XI), obtainable, for example, in this manner, can be converted, by customary reaction, for example acid-catalysed reaction, with the corresponding alcohols or amino alcohols, into iminoethers of the formula (XI), for example with a lower alkanol into open-chain iminoethers or with the appropriate aminoalkanol or alkanediol, for example with 4-amino-2-methylpentan-2-ol or 2-methylpentan-2,4-diol, into cyclic iminoethers. Compounds of the formula (XI) having a trihalomethyl group R''_2 can be obtained, for example, by customary halogenation of a corresponding methyl compound, for example with N-chloro- or N-bromo-succinimide, or by analogous haloform degradation of corresponding alkanoyl, such as acetyl, compounds. Compounds of

(46)

the formula (XI) having an optionally hydrated formyl group R_2'' can also be formed in situ in the course of the oxidation reaction, for example from the methyl or amino-methyl group, or from the hydroxymethyl group optionally esterified by an inorganic acid, such as a hydrohalic acid or by an organic carboxylic acid, such as a lower alkane-carboxylic acid, or it can be freed from one of its derivatives, such as an acetal, acylal or imine, for example a lower alkylene- or di-lower alkyl-acetal of a dihalomethyl compound, such as a dichloromethyl compound, or an optionally substituted benzylimine. Amino- or lower alkoxy dihalo-methyl groups are likewise advantageously manufactured in situ by customary partial ammonolysis or aminolysis or alcoholysis of the corresponding trihalomethyl compound.

The compounds of the formula (I) can also be manufactured by, in a compound of the formula (XIII)



(XIII),

in which Z_4 represents a radical that can be converted into optionally etherified hydroxy, and Z_5 together with R_C and R_D together with R_E represent an additional bond in each case, or in which Z_4 and Z_5 each represents a monovalent, or together represent a divalent, radical that can be converted into oxo and R_C together with R_D represents an additional bond, or in a salt thereof, converting into optionally etherified hydroxy a radical Z_4 that can be converted into optionally etherified hydroxy, or converting together into oxo radicals Z_4 and Z_5 that can be converted into oxo, and, if desired, converting the resulting compound

into a different compound of the formula (I) and/or converting a resulting salt-forming compound into a salt or a resulting salt into the free compound or into a different salt.

Radicals that can be converted into optionally etherified hydroxy are, for example, esterified hydroxy groups, optionally etherified mercapto groups, sulphinyl groups, sulphonyl groups or optionally substituted amino groups. Monovalent radicals that can be converted jointly into the oxo group are, for example, esterified hydroxy groups or hydroxy groups etherified by a monohydric open-chain alcohol or mercapto groups etherified by an open-chain mercaptan. Divalent radicals that can be converted into oxo and that are represented by Z_4 and Z_5 together are, for example, the thio group or hydroxy groups etherified by a dihydric alcohol, mercapto alcohol or bimercaptan, or optionally substituted imino groups. Esterified hydroxy groups are, for example, hydroxy groups esterified by a mineral acid, an organic sulphonic acid or a carboxylic acid, such as halogen, for example chlorine, bromine or iodine, aliphatic or aromatic sulphonyloxy, for example methane-, ethane-, benzene- or p-toluene-sulphonyloxy, or acyloxy derived from an organic carboxylic acid or a monofunctional carbonic acid derivative, such as a carbonic acid semiester, a haloformic acid or from optionally substituted carbamic acid, for example lower alkanoyloxy, optionally substituted benzoyloxy, lower alkoxycarbonyloxy, optionally substituted phenoxy-carbonyloxy, chloro- or bromo-carbonyloxy or optionally substituted, such as lower alkylated, carbamoyloxy. Etherified mercapto is, for example, an aliphatic- or aryl-thio group, for example lower alkylthio or optionally substituted phenylthio. Substituted amino is, for example, amino mono-substituted by hydroxy or amino or mono- or di-substituted by aliphatic radicals or optionally substituted phenyl, it being possible for aliphatic radicals to be mono- or di-valent, monovalent aliphatic radicals being, for example,

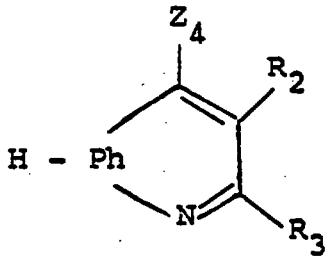
lower alkyl and divalent aliphatic radicals being, for example, lower alkylene or aza-, oxa- or thia-lower alkylene, for example hydroxyamino, hydrazino, mono- or di-lower alkylamino, optionally substituted anilino, pyrrolidin-1-yl, piperidino, morpholino, thiamorpholino or N'-lower alkylpiperazin-1-yl, such as N'-methylpiperazin-1-yl. Hydroxy etherified by a monohydric alcohol is, for example, lower alkoxy or optionally substituted phenyloxy. Hydroxy groups Z_4 + Z_5 etherified by a dihydric alcohol are, for example, lower alkylenedioxy or optionally substituted 1,2-phenylenedioxy groups, for example ethylenedioxy, 1,3-propylenedioxy or 1,2-phenylenedioxy. Hydroxy groups etherified by a dihydric mercapto alcohol or mercaptan are, for example, lower alkylenedithio or lower alkyleneoxythio groups or optionally substituted 1,2-phenyldithio groups or phenoxythio groups, for example ethylenedithio, 1,3-propylenedithio or 1,2-phenylenedithio. Optionally substituted imino groups are, for example, imino groups substituted by hydroxy, amino, lower alkyl or optionally substituted phenyl, for example oximino, hydrazono, lower alkylimino or anilo.

The conversion of the mentioned groups into optionally etherified hydroxy or into oxo is carried out in customary manner, preferably by solvolysis, especially hydrolysis or alcoholysis, i.e. reaction with water or the alcohol corresponding to the etherified hydroxy group to be formed. Thus, for example, the mentioned groups that can be converted into oxo or into hydroxy can be converted into oxo or hydroxy in customary manner, for example in the presence of an acidic or basic hydrolysis agent, advantageously in a solvent or diluent and, if necessary, at elevated or reduced temperature, for example in the temperature range of from 0 to 150°C, under an inert gas, such as nitrogen, and/or in a closed vessel. Acidic hydrolysis agents are, for example, protonic acids, such as mineral acids or their acidic salts, for example hydrochloric, hydrobromic or hydriodic acid, sulphuric acid or alkali metal bisulphates,

sulphonic acids, for example p-toluenesulphonic acid or sulphamic acid or organic carboxylic acids, such as lower alkanoic acids, also acidic ion exchangers. Basic condensation agents are, for example, alkali metal hydroxides or carbonates, for example sodium or potassium hydroxide or carbonate, also tertiary organic nitrogen bases, for example triethylamine or pyridine. Suitable solvents or diluents are especially water-miscible solvents, such as alcohols, for example lower alkanols, cyclic aliphatic ethers, for example dioxan or tetrahydrofuran, lower aliphatic ketones, for example acetone, tertiary aliphatic amides or lactams, for example dimethylformamide or N-methylpyrrolidone, or aliphatic sulphoxides, for example dimethyl sulphoxide. As already mentioned, reactively esterified hydroxy groups Z_4, i.e. hydroxy groups Z_4 esterified by a mineral acid or an organic sulphonic acid, can be converted according to customary methods of alcoholysis into etherified hydroxy, for example in the presence of a basic condensation agent, such as an alkali metal hydroxide or carbonate, or by using the appropriate alcohol in the form of an alcoholate, such as the appropriate alkali metal alcoholate, preferably in a solvent or diluent, if necessary while heating, for example in the temperature range of approximately from 0 to 150°C, and under an inert gas, such as nitrogen, and/or in a closed vessel.

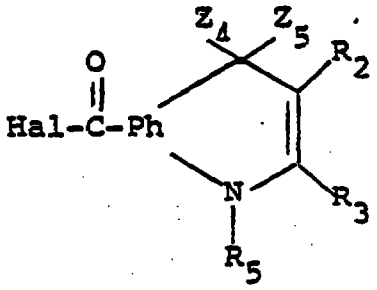
The starting materials of the formula XIII, insofar as they are novel, can be manufactured according to methods known per se.

Thus, compounds of the formula XIII in which Z_4 represents halogen can be obtained, for example, by condensing a compound of the formula XIV



(XIV)

in the presence of a Lewis acid, for example aluminium trichloride, with a halide of the acid of the formula R_1-COOH (XV). There can be obtained from the resulting halogen compounds by reaction with an isothiuronium salt and subsequent hydrolysis, or by reaction with sodium thiolacetate and subsequent reduction, compounds of the formula (XIII) in which Z_4 is mercapto, or, by reaction with an alkali metal mercaptide, compounds of the formula (XIII) in which Z_4 is etherified mercapto. Compounds of the formula (XIII) in which Z_4 represents an optionally substituted amino group and R_2 represents an optionally esterified or amidated carboxy group can be manufactured, for example, by condensing a compound of the formula R_1-X-C(=O)-Ph(NHR_5)-C(Z_4)=CHR_2 (XVI) with a compound of the formula R_3-COOH (XVII) or preferably with an anhydride, such as the chloride, thereof. Compounds of the formula (XIII) in which Z_4 and Z_5 represent etherified hydroxy or mercapto can be manufactured, for example, by reacting a compound of the formula (XVIII)

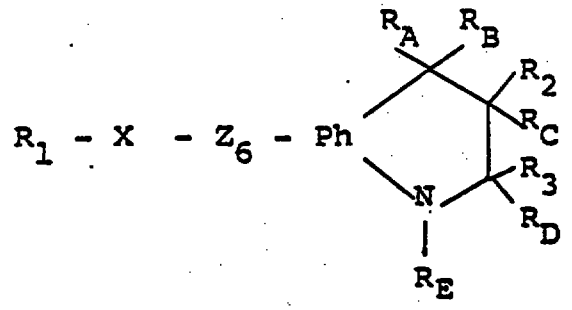


(XVIII),

in which Hal represents halogen, with a metal compound derived from the hydrocarbon of the formula R_1H, for example a corresponding halomagnesium or lithium compound. Compounds of the formula (XIII) in which $Z_4 + Z_5$ represents imino can be obtained, for example, by condensing a compound of the formula R_1-X-C(=O)-Ph(NHR_5)-H (V) with an R_3 methylenecyanoacetic acid or an R_3 methylenemalodinitrile or R_3 methylenemalonic acid ester nitrile, the condensation being carried out preferably in the manner indicated for the manufacture and intramolecular condensation of compounds of the formula IV

and VI.

The compounds of the formula I can also be obtained by, in a compound of the formula (XIX)



(XIX),

in which Z_6 represents a radical that can be converted into the carbonyl group, or in a salt thereof, converting Z_6 into the carbonyl group and, if desired, converting the resulting compound into a different compound of the formula I and/or converting a resulting salt-forming compound into a salt or a resulting salt into the free compound or into a different salt.

The radical Z_6 which can be converted into the carbonyl group is, for example, a radical that can be converted by solvolysis, especially hydrolysis, into that group, such as a functionally modified carbonyl group, for example thioxomethylene, optionally substituted iminomethylene or etherified or esterified dihydroxymethylene. Substituted iminomethylene groups are, for example, methyleneimino groups substituted by hydroxy, amino, lower alkyl or optionally substituted phenyl. Etherified dihydroxymethylene groups are, for example, dihydroxymethylene groups etherified by aliphatic alcohols, such as lower alkanols or lower alkanediols. Esterified dihydroxymethylene groups are, for example, dihydroxymethylene groups esterified by a hydrohalic acid, such as dichloro- or dibromo-methylene.

The conversion of the mentioned groups Z_6 into carbonyl is carried out according to customary methods of solvolysis, especially hydrolysis, for example in the presence of an acidic or basic hydrolysis agent, advantageously in a suitable solvent or diluent, if necessary while cooling or heating, for example in the

temperature range of from approximately 0 to approximately 150°C, under an inert gas, such as nitrogen, and/or in a closed vessel. Acidic hydrolysis agents are, for example, protonic acids, such as mineral acids, for example hydrochloric, hydrobromic or hydriodic acid, sulphuric acid or phosphoric acid, or the acidic salts thereof, for example potassium bisulphate, sulphonic acids, such as aliphatic or aromatic sulphonic acids, for example methane-, ethane- or p-toluene-sulphonic acid, sulphamic acid, or organic carboxylic acids, such as lower alkanecarboxylic acids. Suitable solvents or diluents are, for example, water-miscible solvents, such as aliphatic alcohols, for example lower alkanols or lower alkanediols, cyclic aliphatic ethers, for example dioxan or tetrahydrofuran, di-lower alkyl ketones, for example acetone, or tertiary lower alkanecarboxylic acid amides or lactams, for example dimethylformamide or N-methylpyrrolidone.

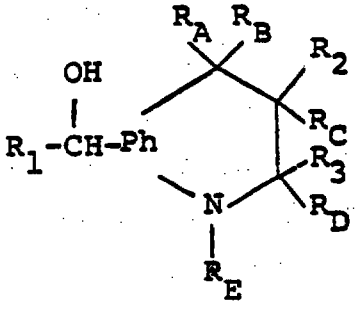
Further radicals that can be converted into carbonyl groups are groups that can be oxidised to form those groups, for example the hydroxymethylene group, which can also be formed in situ under the reaction conditions, for example by oxidation of the methylene group, or it can be freed from one of its functional derivatives, for example an ester, such as a mineral acid or carboxylic acid ester, for example from a halomethylene group, a lower alkanoyloxymethylene group or an optionally substituted benzoyloxymethylene group.

The oxidation can be carried out in a manner known per se, for example by treatment with oxidising heavy metal compounds, such as compounds containing chromium(VI), manganese(VII) or (IV), silver or bismuth, for example with chromic acid, potassium dichromate, potassium permanganate, manganese dioxide, silver oxide or silver acetate or bismuth oxide, with oxidising inorganic oxy-acids or their salts, for example with sodium hypochlorite, sodium hypoiodite, sodium chlorate, sodium iodate or sodium metaperiodate, or with organic oxidising agents, such as quinones, for example benzoquinone or 2,6-dicyano-benzoquinone, dimethyl sulphoxide/N-chlorosuccinimide or dimethyl sulphide trifluoromethyl trifluoromethanesulphonate advantageously in a solvent

or diluent that is inert towards the reactants, if necessary while cooling or heating, for example in the temperature range of approximately from -20 to 100°C, under an inert gas, such as nitrogen, and/or in a closed vessel. Especially advantageous is the use of potassium permanganate or manganese dioxide in aqueous acetone or aqueous pyridine, as the case may be, or of chromium trioxide in hexamethylphosphoric acid triamide.

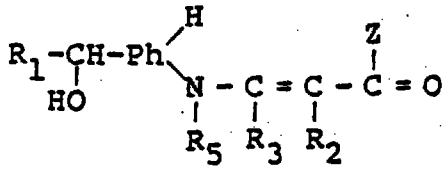
The starting materials of the formula XIX, in so far as they are novel, can be manufactured, for example, by condensing a compound of the formula R_1-X-Z_6-Ph(NHR_5)-H (Va) in customary manner, for example as described for the manufacture and intramolecular cyclisation of compounds of the formula IV, with a compound of the formula HO-C(R_3)(R_D)-C(R_2)(R_C)-COOH (XX) or a functional derivative, such as an ester and/or an ether, thereof in customary manner, for example as indicated for the manufacture and intramolecular condensation of compounds of the formula IV. Compounds of the formula XIX in which Z_6 represents hydroxymethylene, iminomethylene or etherified dihydroxymethylene, can also be obtained by reacting a corresponding aldehyde, nitrile or orthocarboxylic acid ester with a metal compound of the appropriate hydrocarbon of the formula R_1H, for example with a corresponding halomagnesium or lithium compound. Compounds of the formula XIX in which Z_6 represents dihalomethylene can also be manufactured by introducing the R_1 dihalomethyl radical into a corresponding compound that is unsubstituted in the benzene ring, for example by reaction with the corresponding R_1 trihalomethane in the presence of aluminium chloride.

Compounds of the formula XIX, wherein X denotes a direct bond and Z_6 represents hydroxymethylene, i.e. compounds of the formula



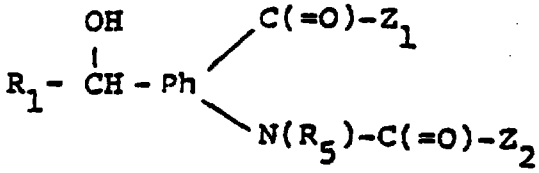
(XIXa),

are also obtained when a compound of the formula



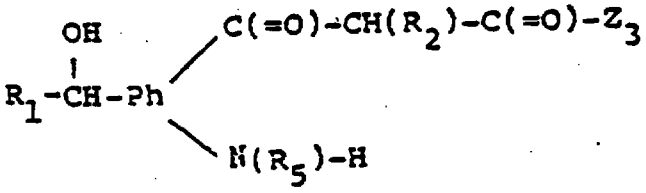
(IVa),

in which Z is a removable radical, or a tautomer and/or salt thereof, is subjected to intramolecular cyclisation, or a compound of the formula



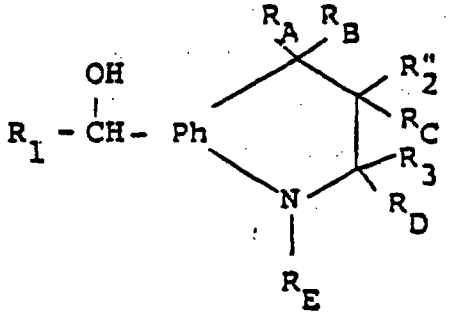
(VIa),

in which one of the radicals Z_1 and Z_2 represents a group of the formula CH_2-R_2 and the other represents an optionally reactively etherified or esterified hydroxy group, or a tautomer and/or salt thereof, is subjected to intramolecular cyclisation, or a compound of the formula



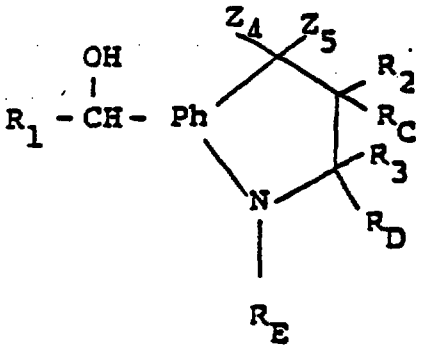
(IXa),

in which Z_3 represents hydroxy or a reactive modified hydroxy group, or a tautomer and/or a salt thereof, is subjected to intramolecular condensation, or, in a compound of the formula



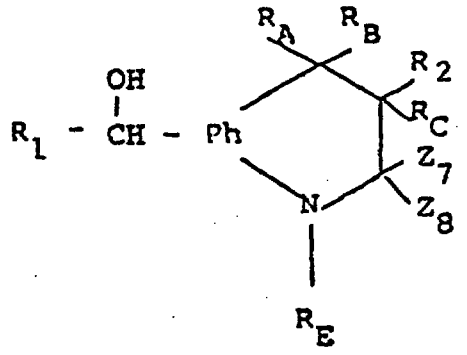
(XIa),

in which the radical R_2'' represents a radical that can be converted into the optionally esterified or amidated carboxy group R_2, or in a tautomer and/or a salt thereof, the group R_2'' is converted into the optionally esterified or amidated carboxy group R_2, or in a compound of the formula



(XIIIa) ,

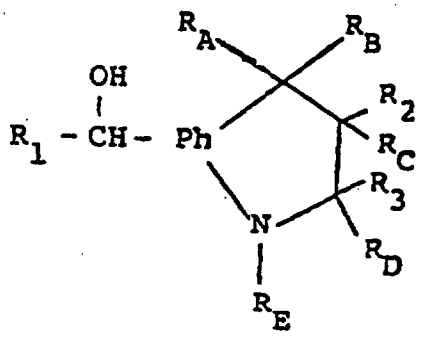
in which Z_4 represents a radical that can be converted into optionally etherified hydroxy, and Z_5 together with R_C and R_D together with R_E represent an additional bond in each case, or in which Z_4 and Z_5 each represents a monovalent, or together represent a divalent, radical that can be converted into oxo and R_C together with R_D represents an additional bond, or in a salt thereof, a radical Z_4 that can be converted into optionally etherified hydroxy is converted into optionally etherified hydroxy, or radicals Z_4 and Z_5 that can be converted into oxo are together converted into oxo, or for the manufacture of compounds of the formula XIXa in which R_A + R_B represents oxo, R_C + R_D represents an additional bond, R_2 represents optionally esterified or amidated carboxy, R_3 represents hydroxy and R_E represents a radical R_5, or of their tautomers in which R_A denotes hydroxy, R_B and R_C together represent an additional bond, R_3 and R_D together represent oxo and R_E denotes a radical R_5, in a compound of the formula



(XXIa) ,

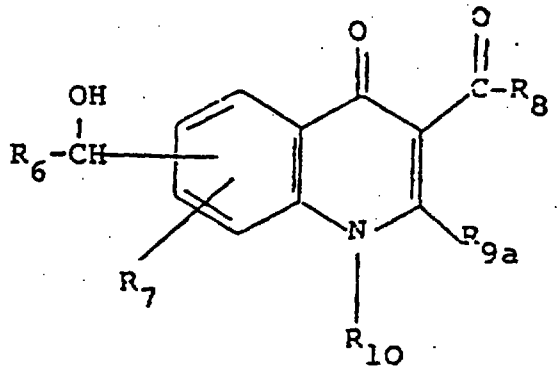
in which Z_7 represents a radical that can be converted into hydroxy and Z_8 represents a radical R_D, or Z_7 and Z_8 each represents a monovalent, or together represent a divalent, radical that can be converted into oxo, Z_7 is converted into hydroxy or $Z_7 + Z_8$ are converted into oxo.

The invention relates also to compounds of the formula XIX, wherein X denotes a direct bond and Z_6 represents hydroxymethylene, i.e. to compounds of the formula



(XIXa) ,

wherein R_1, R_A, R_B, R_2, R_C, R_3, R_D and R_E have the meanings given under formula I, especially to those of the formula (XIXb)

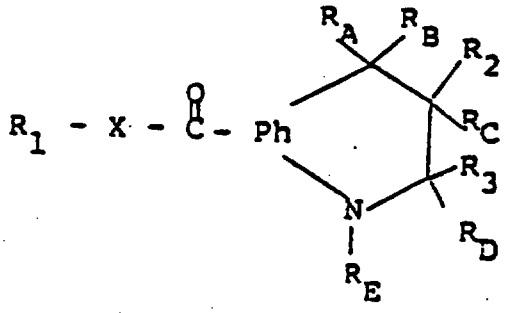


(XIXb),

in which the group

R_6 represents lower alkyl having up to 7 carbon atoms, R_7 represents hydrogen or lower alkyl having up to and including 4 carbon atoms, the group R_6-Z_6 being attached to the 6- and a lower alkyl group R_7 being attached to the 7-position, R_8 represents hydroxy or lower alkoxy having up to 4 carbon atoms, R_{9a} represents hydroxy, and R_{10} represents lower alkyl or lower alkenyl having up to 4 carbon atoms, or to the tautomeric 2-oxo-4-hydroxy-1,2-dihydro- or 2,4-dioxo-1,2,3,4-tetrahydroquinoline forms and/or salts thereof.

The invention relates also to a process for the manufacture of compounds of the formula XIXa utilising those process variants described hereinbefore in connection with the preparation of compounds of the formula XIX, as far as these process variants are suitable for the manufacture of compounds of the formula XIXa, as well as those process variants characterised in that in a compound of the formula

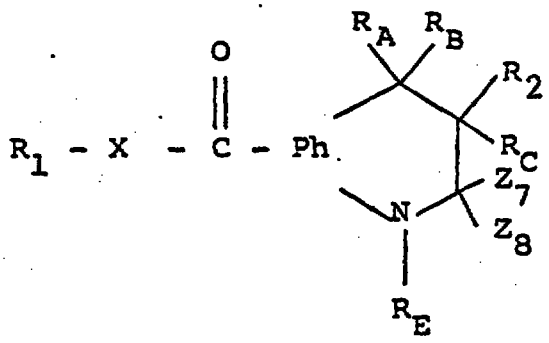


(I)

in which X denotes a direct bond and R_1 represents an aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic or heterocyclic-aliphatic radical, the group R_1-C(=O)- is, by reaction with a suitable reducing agent reduced to a group R_1-CH(OH)-, or in which a compound of the formula (I) in which R_1 denotes hydrogen and X denotes a direct bond, is reacted with a metal derivative of a hydrocarbon of the formula R_1-H, wherein R_1 is different from hydrogen, and,

if desired, in a resulting compound of the formula (XIXa) esterified or amidated carboxy is solvolysed to carboxy, carboxy is esterified or hydrogen R_E is replaced by an aliphatic residue and/or a resulting salt is converted into the free compound or a resulting free compound is converted into a salt.

Compounds of the formula I in which $R_A + R_B$ represents oxo, $R_C + R_D$ represents an additional bond, R_2 represents optionally esterified or amidated carboxy, R_3 represents hydroxy and R_E represents a radical R_5, or their tautomers in which R_A denotes hydroxy, R_B and R_C together represent an additional bond, R_3 and R_D together represent oxo and R_E denotes a radical R_5, can also be manufactured by, in a compound of the formula XXI



(XXI),

in which Z_7 represents a radical that can be converted into hydroxy and Z_8 represents a radical R_D, or Z_7 and Z_8 each represents a monovalent, or together represent a divalent, radical that can be converted into oxo, converting Z_7 into hydroxy or $Z_7 + Z_8$ into oxo, and, if desired, converting the resulting compound into a different compound of the formula I and/or converting a resulting salt-forming compound into a salt or a resulting salt into the free compound or into a different salt.

Radicals that can be converted into optionally etherified hydroxy are, for example, esterified hydroxy groups, optionally etherified mercapto groups or optionally substituted amino groups. Monovalent radicals that can be converted jointly into the oxo group are, for example, esterified hydroxy groups or hydroxy groups etherified by a monohydric open-chain alcohol, or mercapto groups etherified by an open-chain mercaptan. Divalent radicals that can be converted into oxo and that are represented by Z_7 and Z_8 together are, for example, thioxo, hydroxy groups etherified by a dihydric alcohol, mercapto alcohol or bimercaptan, or optionally substituted imino groups. Esterified hydroxy groups are, for example, hydroxy groups esterified by a mineral acid, an organic sulphonic acid or a carboxylic acid, such as halogen, for example chlorine, bromine or iodine, aliphatic or aromatic sulphonyloxy, for example methane-, ethane-, benzene- or p-toluene-sulphonyloxy, or acyloxy derived from an organic carboxylic acid or a monofunctional carbonic acid derivative, such as a carbonic acid semiester, from a haloformic acid or optionally substituted carbamic acid, for example lower alkanoyloxy, optionally substituted benzoyloxy, lower alkoxycarbonyloxy, optionally substituted phenoxycarbonyloxy, chloro- or bromo-carbonyloxy or optionally substituted, such as lower alkylated, carbamoyloxy. Etherified mercapto is, for example, an aliphatic- or aryl-thio group, for example lower alkylthio or optionally substituted phenylthio. Substituted amino is, for example, amino that is mono-substituted by hydroxy or amino mono- or di-substituted by aliphatic radicals or optionally substituted phenyl, it being possible for aliphatic radicals to be mono- or di-valent, monovalent aliphatic radicals being, for example, lower alkyl and divalent aliphatic radicals being, for example, lower alkylene or aza-, oxa- or thia-lower alkylene, for example hydroxyamino, hydrazino, mono- or di-lower alkylamino, optionally substituted anilino, pyrrolidin-1-yl, piperidino, morpholino, thiamorpholino or N'-lower alkylpiperazin-1-yl, such as N'-methylpiperazin-1-yl. Hydroxy etherified by a monohydric alcohol is, for example, lower alkoxy or optionally substituted phenyloxy. Hydroxy groups etherified by a dihydric alcohol are, for example, lower alkylenedioxy or

optionally substituted 1,2-phenylenedioxy groups, for example ethylenedioxy, 1,3-propylenedioxy or 1,2-phenylenedioxy. Hydroxy groups etherified by a dihydric mercapto alcohol or mercaptan are, for example, lower alkylenedithio or lower alkyleneoxythio groups or optionally substituted 1,2-phenyldithio or phenoxythio groups, for example ethylenedithio, 1,3-propylenedithio or 1,2-phenylenedithio. Optionally substituted imino groups are, for example, imino groups substituted by hydroxy, amino, lower alkyl or optionally substituted phenyl, for example oximino, hydrazono, lower alkylimino or anilo.

The conversion of the mentioned groups into hydroxy or into oxo is carried out in customary manner, for example by solvolysis, especially hydrolysis. The operation is carried out in customary manner, for example in the presence of an acidic or basic hydrolysis agent and/or a suitable solvent or diluent, if necessary while cooling or heating, for example in a temperature range of approximately from 0 to 100°C, under an inert gas, such as nitrogen, and/or in a closed vessel. Acidic hydrolysis agents are, for example, protonic acids, such as mineral acids, for example hydrochloric, hydrobromic or hydriodic acid, sulphuric acid or phosphoric acid, sulphonic acids, for example methane-, ethane-, benzene- or p-toluene-sulphonic acid, or sulphamic acid, or organic carboxylic acids, such as lower alkanoic acids or optionally substituted benzene acids. Basic hydrolysis agents are, for example, alkali metal hydroxides or carbonates, for example sodium hydroxide or carbonate, potassium hydroxide or carbonate or calcium hydroxide, also nitrogen bases, such as ammonia or organic amines. Suitable solvents or diluents are especially water-miscible solvents.

Reactively esterified hydroxy groups, i.e. hydroxy groups esterified by a hydrohalic acid or an organic sulphonic acid, can also be converted into etherified hydroxy by customary alcoholysis, i.e. reaction with the alcohol corresponding to the desired etherified hydroxy group, for example in the presence of a basic agent, if necessary in a solvent or diluent, while cooling or heating, for example in the temperature range of approximately from 0 to 100°C, under an inert gas, such as nitrogen, and/or

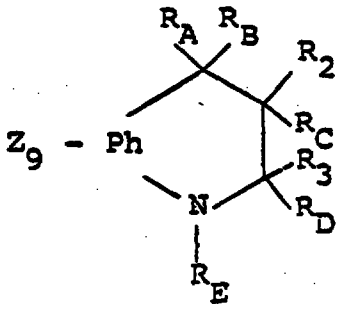
in a closed vessel. Suitable basic agents are, for example, alkali metal hydroxides or carbonates, for example sodium hydroxide or carbonate or potassium hydroxide or carbonate, organic, especially tertiary organic, nitrogen bases, such as tri-lower alkylamines, for example triethylamine, or pyridine. Instead of using a basic agent, it is also possible to use the appropriate alcohol advantageously in the form of an alcoholate, such as an alkali metal alcoholate, for example sodium or potassium alcoholate.

The starting materials of the formula XXI, in so far as they are novel, can be obtained according to methods known per se, for example by cyclising a compound of the formula

R_1-X-C(=O)-Ph(H)-N(R_5)-C(Z_7)(Z_8)-C(R_2)-(R_C)-COOH (XXII)

or a suitable functional derivative, such as an ester, thereof. The manufacture of compounds of the formula XXII and their cyclisation is carried out especially in the manner indicated for the manufacture and cyclisation of compounds of the formula IV.

Compounds of the formula I in which X represents oxy, and their tautomers, can also be manufactured by, in a compound of the formula XXIII



(XXIII),

in which Z_9 represents a functionally modified carboxy group other than the group R_1-X-C(=O)-, solvolysing Z_9 to a corresponding group R_1-O-C(=O)- and, if desired, converting the resulting compound into a different compound of the formula I and/or converting a resulting salt-forming compound into a salt or a resulting salt into the free compound or into a different salt.

Such groups are, for example, cyano, anhydridised carboxy groups, iminoether groups, iminoester groups and etherified and/or esterified trihydroxymethyl groups. Anhydridised carboxy groups are, for example, carboxy groups anhydridised by a mineral acid, such as a hydrohalic acid, by a halosulphonic acid, such as fluorosulphonic acid, or an organic sulphonic or carboxylic acid, such as an aliphatic or aromatic sulphonic or carboxylic acid. Iminoether groups are, for example, iminoether groups derived from esterified carboxy groups R_1-O-C(=O)-, such as O-lower alkylcarbamoyl, or cyclic iminoether groups, such as 4,4- or 5,5-di-lower alkyl-, for example 4,4- or 5,5-dimethyl-4,5-dihydrooxazol-2-yl or 4,4,6-tri-lower alkyl-, for example 4,4,6-trimethyl-5,6-dihydrooxazin-2-yl. Iminoester groups are, for example, iminoester groups derived from amidated carboxy groups R_4 and esterified by hydrohalic acids or organic carboxylic acids, such as lower alkanoic acids, such as, for example, chlorocarbimino or O-lower alkanoylcarbamoyl. Etherified and/or esterified trihydroxymethyl groups are, for example, tri-lower alkoxymethyl or trihalomethyl groups.

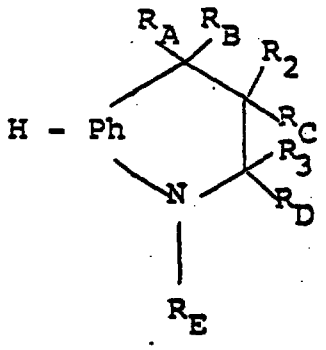
The mentioned groups can be converted by customary hydrolysis into carboxy groups; iminoether groups and etherified hydroxydihalomethyl groups, such as lower alkoxydihalomethyl groups, can similarly be converted into esterified carboxy groups R_1-O-C(=O)-. The hydrolysis is carried out in customary manner, for example in the presence of an acidic or alkaline hydrolysis agent, generally in the presence of a solvent and/or diluent or a mixture thereof, and, if necessary, while cooling or heating, for example in a temperature range of from approximately 0°C to approximately 120°C, if necessary under an inert gas, such as nitrogen, and/or in a closed vessel. Acidic hydrolysis agents are, for example, mineral acids, such as hydrohalic acids, for example hydrochloric acid, or oxygen acids of sulphur or phosphorus, such as sulphuric or phosphoric acid, also organic sulphonic acids, for example p-toluenesulphonic acid or mesitylenesulphonic acid, or organic carboxylic acids, such as lower alkanecarboxylic acids,

for example formic or acetic acid. Basic hydrolysis agents are, for example, alkali metal hydroxides, for example sodium or potassium hydroxide, also alkali metal carbonates, for example sodium or potassium carbonate. Suitable solvents or diluents are preferably water-miscible solvents, such as lower alkanols, for example ethanol or methanol, lower ketones, for example acetone, or tertiary alkanoic acid amides, for example dimethylformamide or N-methylpyrrolidone.

Anhydridised carboxy groups and cyclic iminoether groups can also be converted by alcoholysis, i.e. reaction with a corresponding alcohol, into esterified carboxy groups R_1-O-C(=O)-. This operation is carried out in customary manner, starting from anhydridised carboxy groups, for example in the presence of a basic condensation agent, such as an alkali metal hydroxide or carbonate, for example sodium or potassium hydroxide or corresponding carbonates, or in the presence of organic nitrogen bases, such as pyridine or triethylamine, and, starting from cyclic iminoether groups, preferably under anhydrous conditions, for example in the presence of hydrogen chloride, phosphoric acid, sulphuric acid or p-toluenesulphonic acid, if necessary while heating, for example in the temperature range of from approximately 0°C to approximately 150°C, under an inert gas, such as nitrogen, and/or in a closed vessel.

The starting materials of the formula XXIII, in so far as they are novel, can be manufactured according to methods known per se, for example by reaction of a compound of the formula Z_9-Ph(NH_2)-COOH (XXIV) with phosgene to form the isatoic acid anhydride, N-substitution of the same and condensation with malonic acid or an ester or anhydride thereof, especially in a manner analogous to that described for the intramolecular condensation of compounds of the formula VI.

The compounds of the formula I, wherein X denotes a direct bond, can also be manufactured by reacting a compound of the formula XXV



(XXV)

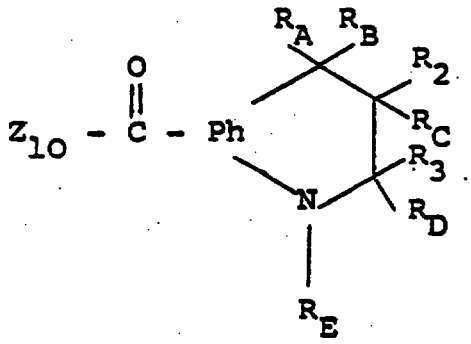
in the presence of a Lewis acid with a compound of the formula R_1-COOH (XXVI) or a suitable functional derivative thereof, and, if desired, converting the resulting compound into a different compound of the formula I and/or converting a resulting salt-forming compound into a salt or a resulting salt into the free compound or into a different salt.

Functional derivatives of acids of the formula XXVI suitable for the above reaction are especially esters or anhydrides of the same, such as lower alkyl esters or optionally substituted phenyl esters, their symmetric anhydrides or their mixed anhydrides with other carboxylic acids, such as formic acid, or especially with mineral acids, such as hydrohalic acids, for example with hydrochloric acid. Lewis acids are, for example, coordinatively unsaturated halides of zinc, boron, aluminium, gallium, tin antimony or iron, such as zinc chloride, boron trichloride or boron trifluoride, aluminium chloride or aluminium bromide, gallium bromide, tin chloride, antimony trichloride or antimony pentachloride or iron trichloride.

The reaction is carried out in the manner known for analogous reactions, for example in a substantially anhydrous solvent that is inert towards the reactants, if necessary while cooling or heating, for example in the temperature range of from -30 to 100°C, under an inert gas, such as nitrogen, and/or in a closed system.

The starting materials of the formula XXV, in so far as they are novel, can be manufactured according to methods known per se, for example by customary cyclisation, for example cyclisation corresponding to the manufacture and intramolecular cyclisation of compounds of the formula VI, of compounds of the formula $H\text{-}Ph(H)\text{-}N(R_E)\text{-}C(R_3)(R_D)\text{-}C(R_2)(R_C)\text{-}C(R_A)(R_B)\text{-}Z$ (XXVI), in which Z represents an etherified or reactively esterified hydroxy group, for example lower alkoxy or halogen.

The compounds of the formula I in which X is a direct bond, can also be manufactured by reacting a compound of the formula XXVII



(XXVII)

in which Z_{10} represents a free, etherified or reactively esterified hydroxy group or a suitable heteroaryl group bonded via a ring nitrogen atom, or a salt thereof, with a compound of the formula $R_1\text{-}M$ (XXVIII) in which M represents a metal radical, to form a compound of the formula (I), wherein R_1 differs from hydrogen, or reacting a compound of the formula (XXVII), wherein Z_{10} denotes reactively esterified hydroxy, with bis-(triphenylphosphino)-copper boranate to form a compound of the formula (I), wherein R_1 denotes hydrogen, and, if desired, converting the resulting compound into a different compound of the formula I and/or a resulting salt-forming compound into a salt or a resulting salt into the free compound or into a different salt.

Etherified hydroxy groups are, for example, hydroxy groups etherified by an aliphatic alcohol, for example a lower alkanol, or an optionally substituted phenol. Reactively esterified hydroxy groups are especially hydroxy groups esterified by a hydrohalic acid, especially by hydrochloric acid. A heteroaryl radical bonded via

a ring nitrogen atom is, for example, 1-imidazolyl. Metal radicals M are, for example, alkali metal atoms, for example lithium, or magnesium or cadmium radicals, especially of the formula -Mg/2, -Cd/2, -MgHal or -CdHal, in which Hal represents halogen, especially chlorine, bromine or iodine, or copper radicals. Salts of compounds of the formula (XXVII) are, for example, alkali metal salts, such as sodium, potassium or lithium salts, or ammonium salts of the same.

The reaction is carried out in customary manner, especially in the manner known for analogous reactions, preferably in a substantially anhydrous solvent that is inert towards the reactants, if necessary while cooling or while heating gently, for example in the temperature range of from -100 to +80°C, under an inert gas, such as nitrogen, and/or in a closed vessel. Thus, for example, a compound of the formula XXVII in which Z_{10} represents halogen, can be reacted at temperatures of up to approximately 40°C with an organo-cadmium compound of the formula XXVIII, or at temperatures below -25°C, preferably below -50°C, with a halomagnesium compound, a lithium compound or especially a copper compound of the formula XXVIII.

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

Thus, a compound of the formula I in which R_1 is lower alkyl or optionally substituted phenyl and X denotes oxy, can be converted in the manner indicated above into a compound of the formula I in which X represents a direct bond. Furthermore, carboxylic acids of the formula I (R_1-X = hydroxy) optionally present in salt form can advantageously be reacted in the temperature range of from approximately 20 to approximately 50°C, for example in boiling diethyl ether, with a lower alkenyllithium compound. Conversely, a compound of the formula I in which R_1 represents a non-aromatic radical can be oxidised in customary manner to a compound of the formula I in which R_1-X is hydroxy, for example with an alkali metal hypohalite. In addition, in a compound of the formula I or XIXa, carboxy R_2 or R_1-X-C(=O)- can be converted according to known esterification

processes into an esterified carboxy group. Thus, for example, the reaction can be carried out by treatment with an alcohol in the presence of a suitable condensation agent, such as a dehydrating agent, for example dicyclohexyl carbodiimide, or a mineral acid, for example sulphuric acid or hydrochloric acid, or, to form a hydroxy-lower alkyl group, with a corresponding epoxy-lower alkane.

The esterification can also be carried out by treatment with a suitable N,N-di-lower alkylformamide acetal, for example N,N-dimethylformamide diethyl acetal, or N,N,O-trimethylformamidinium methosulphate, a carbonate or pyrocarbonate, for example with diethyl(pyro)carbonate, or with an organic sulphite or phosphite, such as a di-lower alkyl sulphite or tri-lower alkyl phosphite, in the last-mentioned case in the presence of a suitable acidic agent, for example p-toluenesulphonic acid. Furthermore, an acid of the formula I to be esterified in which the free carboxy group is in salt form, for example in an alkali metal salt form, such as the sodium salt form, can be reacted with a reactive ester of an alcohol, such as a corresponding halide, for example chloride, bromide or iodide, or with a sulphuric acid ester. It is, however, also possible to carry out the esterification by reaction with a lower alkene corresponding to the lower alkoxy group to be introduced, preferably in the presence of an acidic condensation agent, such as a strong protonic acid, for example sulphuric acid, or a Lewis acid, for example boron trifluoride etherate. Substituents optionally present in one of the esterification reagents mentioned can be in functionally modified form and in that case, in a compound of the formula I in which R_2 represents, for example, substituted lower alkoxycarbonyl in which substituents are in functionally modified form, they can be freed. Thus, there may be used as esterification reagent, for example, the 2,3-epoxypropyl chloride and, in the resulting ester, the 2,3-epoxypropoxy grouping can be subsequently hydrolysed to the desired 2,3-dihydroxypropoxy grouping.

Also, in compounds of the formula I or XIXa esterified carboxy R_2 and/or R_1-X-C(=O)- can be converted into a different esterified carboxy group by transesterification, for example by treatment with an alcohol, if necessary in the presence of a suitable transesterification catalyst, such as an appropriate alkali metal alcoholate, for example the appropriate sodium or potassium alcoholate, or a mineral acid, for example sulphuric acid or hydrochloric acid.

Moreover, in compounds of the formula I or XIXa, free or esterified carboxy R_2 can be converted in a manner known per se into optionally substituted carbamoyl. Thus, an ester of the formula I can be treated with ammonia, hydroxylamine or a corresponding primary or secondary amine to obtain amides of the formula I. In addition, the ammonium salt or an amine salt of an acid of the formula I can be converted into an amide of the formula I by dehydration, for example while heating or by the action of a suitable dehydrating agent, such as sulphuric acid.

The conversion of carboxy into esterified or amidated carboxy can, however, alternatively be carried out by converting the carboxy compound first into a reactive carboxy derivative, for example, by reaction with N,N'-bis-(imidazol-1-yl)-urea, into the 1-imidazolide, by reaction with a reactive alcohol, for example with 4-nitrophenol or cyanomethanol, into a reactive ester or by reaction with a halogenating agent, such as thionyl chloride, into the acid chloride, and then reducing with the corresponding alcohol or with ammonia or an amine having at least one hydrogen atom.

In compounds of the formula I or XIXa, an esterified or amidated carboxy group R_2 or R_1-X-C(=O)- can be converted in customary manner into the free carboxy group, for example by hydrolysis, generally in the presence of an acidic or basic hydrolysis agent, such as a mineral or carboxylic acid, for example hydrochloric acid, sulphuric acid or acetic acid, or an alkali metal hydroxide or carbonate, for example sodium hydroxide or carbonate or potassium hydroxide or carbonate.

Furthermore, compounds of the formula I or XIXa in which R_A and R_B together represent oxo, R_C and R_D together represent an additional bond and R_E represents hydrogen, and their tautomers, can be substituted in customary manner at the nitrogen atom in the 1-position by a radical other than hydrogen and/or they can be etherified at the oxygen atom in the 4-position and/or at a hydroxy group R_3. The substitution of the ring nitrogen atom by R_5 or the etherification of ring-bonded hydroxy groups is carried out in customary manner, for example by reaction with a reactive ester of a corresponding alcohol, if necessary in the presence of a basic condensation agent, such as an alkali metal hydride, amide, alcoholate or hydroxide, for example sodium hydride, sodium amide, lithium diisopropylamide, sodium methoxide, potassium tert-butoxide or potassium hydroxide, while cooling or heating, for example in the temperature range of approximately from 0 to 120°C, under an inert gas, such as nitrogen and/or in a closed vessel. Reactive esters of corresponding alcohols are especially mineral acid esters, such as hydrohalic or sulphuric acid esters, or organic sulphonic acid esters, for example methane-, ethane-, benzene- p-toluene- or fluoro-sulphonic acid esters. In the case of treatment of an ester of the formula I with an alkyl halide in the presence of sodium hydride in dimethylformamide, when starting from compounds in which R_2 is the esterified carboxy group, there are obtained practically exclusively N-alkyl derivatives.

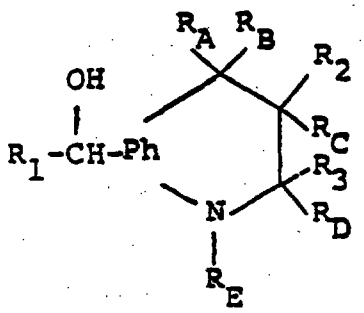
Moreover, in compound of the formula I or XIXa, additional substituents can be introduced into the radical Ph, preferably lower alkyl groups and/or halogen. Thus, for example, lower alkyl can be introduced, especially into the 8-position, by reaction with a lower alkyl halide, a lower alkanol or a lower alkene in the presence of a Lewis acid, for example aluminium trichloride, It is also possible to introduce halogen, again preferably into the 8-position, in customary manner, for example by reaction with the appropriate

halogen in the presence of a Lewis acid, such as the corresponding iron halide, which can also be formed in situ from finely divided iron and the appropriate halogen, or by treatment with N-chloro-succinimide.

Salt-forming compounds of the formula I or XIXa can be converted in a manner known per se into salts, for example by treatment with a base or an acid, generally in the presence of a solvent or diluent. Resulting salts can be converted in a manner known per se into the free compounds, for example by treatment with an acidic reagent, such as a mineral acid, or a basic reagent, such as an alkali metal hydroxide. The compounds of the formula I, including their salts, can also be obtained in the form of their hydrates or include the solvent used for crystallisation. Owing to the close relationship between the compounds of the formula I in free form and in the form of their salts, hereinbefore and hereinafter there shall optionally be understood by free compounds and their salts, where appropriate with regard to meaning and purpose, also the corresponding salts and free compounds, respectively.

The invention also relates to those embodiments of the process in which a compound obtainable as an intermediate at any stage of the process is used as the starting material and the remaining process steps are carried out, or a starting material is formed under the reaction conditions or used in the form of a derivative or, optionally, a salt. In the process of the present invention, preferably those starting materials are used that result in the compounds pointed out at the beginning as being especially valuable. The present invention also relates to novel starting materials, analogous processes for their manufacture and their use.

The compounds of the formula I and those compounds of the formula XIX, wherein X denotes a direct bond and Z_6 represents hydroxy-methylene, i.e. compounds of the formula



(XIXa),

and their salts have valuable pharmacological properties. They have, especially, antiallergic effects which can be demonstrated, for example, in rats in doses of from approximately 1 mg/kg in the case of intravenous administration and in doses of from approximately 1 mg/kg in the case of oral administration in the passive cutaneous anaphylaxis test (PCA reaction), which is carried out analogously to the method described by Goose and Blair, Immunology, vol. 16, p. 794 (1969). The passive cutaneous anaphylaxis is produced according to the process described by Ovary Progr. Allergy, vol. 5, p. 459 (1958). The antiallergic, especially degranulation-inhibiting, effect of the compounds of the formula I and their salts can also be established in vitro on the basis of histamine release from peritoneal cells of the rat in the dosage range of from approximately 1 to approximately 100 mg/l in the case of immunologically induced release, rats infected with Nippostrongilus brasiliensis being used, and from approximately 1.0 to approximately 100 mg/l in the case of chemically induced release, this release being brought about, for example, by a polymer of N-4-methoxyphenylethyl-N-methylamine. The compounds of the present invention can accordingly be used as inhibitors of allergic reactions, for example in the treatment and propylaxis of allergic diseases, such as bronchial asthma both of the extrinsic and intrinsic form, or other allergic diseases, such as allergic rhinitis, for example hay fever, conjunctivitis or allergic dermatides, for example urticaria or eczemas.

As already mentioned, the present invention also relates to pharmaceutical preparations that contain compounds of the formula I or XIXa or pharmaceutically acceptable salts of the same. The pharmaceutical preparations according to the invention are those that are intended for enteral, such as oral, nasal or rectal, and also parenteral or buccal, administration to warm-blooded animals and that contain the pharmacological active ingredient alone or together with a pharmaceutically acceptable carrier. The dosage of the active ingredient depends on the species of the warm-blooded animal, age and the individual condition and on the method of administration.

The pharmaceutical preparations according to the invention contain, for example, up to approximately 95%, preferably from approximately 5% to approximately 90%, of the active ingredient. Pharmaceutical preparations according to the invention are, for example, those in dosage unit forms, such as dragées, tablets, capsules, suppositories or ampoules, also inhalation preparations, or topically or locally administrable pharmaceutical preparations, for example for insufflation.

The pharmaceutical preparations of the present invention are manufactured in a manner known per se, for example by means of conventional mixing, granulating, dissolving or lyophilising processes. Thus, pharmaceutical preparations for oral administration can be obtained by combining the active ingredient with solid carriers, optionally granulating the 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 sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, also binders, such as starch pastes, for example maize, wheat, rice or potato starch paste, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrating agents, 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 and lubricating agents, for example silica, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable coatings which are optionally resistant to gastric juices, for which purpose there are used, for example, 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 manufacture of coatings resistant to gastric juices, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colouring substances or pigments may be added to the tablets or dragée coatings, for example for identification or for distinguishing different doses of the active ingredient. Further orally administrable pharmaceutical preparations are dry-filled capsules made of gelatin, and also soft, sealed capsules made of gelatin 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 with 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 likewise being possible for stabilisers to be added.

There come into consideration as rectally administrable pharmaceutical preparations, for example, suppositories that consist of a combination of the active ingredient and a suppository base substance. Suitable as a suppository base substance are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. It is also possible to use gelatin rectal capsules that

contain a combination of the active ingredient and a base substance; suitable base substances are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

There are suitable for parenteral administration especially aqueous solutions of the active ingredient in water-soluble form, for example in the form of 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 that increase viscosity, for example sodium carboxymethylcellulose, sorbitol and/or dextran and optionally stabilisers.

Inhalation preparations for the treatment of the respiratory system by nasal or buccal administration are, for example, aerosols or sprays that can disperse the pharmacological active ingredient in the form of a powder or in the form of drops of a solution or suspension. Preparations having powder-dispersing properties generally contain, apart from the active ingredient, a liquid propellant gas having a boiling point of below room temperature and, if desired, carriers, such as liquid or solid, non-ionic or anionic surface-active agents and/or solid diluents. Preparations in which the pharmacological active ingredient is in solution, contain, in addition, a suitable propellant, and also, if necessary, an additional solvent and/or a stabiliser. Instead of the propellant gas, it is also possible to use compressed air, and this can be produced as required by means of a suitable compression and release device.

Pharmaceutical preparations for topical and local use are, for example, for skin treatment, lotions and cream that contain a liquid or semi-solid oil-in-water or water-in-oil emulsion, and ointments, optionally containing a preservative; for the eyes, eye drops that contain the active compound in aqueous or oily solution, and eye ointments that are preferably manufactured in sterile form; for the treatment of the nose, powders, aerosols and sprays (similar to those described above for the treatment of the respiratory system), and also coarse powders that are administered by rapid inhalation through the nose, and nose drops that contain the active compound in aqueous or oily solution; or for local treatment of the mouth, lozenges that contain the active compound in a composition that is formed generally from sugar and gum arabic or tragacanth and to which flavouring substances may have been added, and also pastilles that contain the active ingredient in an inert composition, for example of gelatin and glycerin or sugar and gum arabic.

The invention relates finally to the use of compounds of the formula I or their salts as pharmacologically active compounds, especially as antiallergic agents, preferably in the form of pharmaceutical preparations. The daily dose administered to a warm-blooded animal weighing approximately 70 kg is, in the case of an oral form of administration, from approximately 100 mg to approximately 1000 mg, preferably from approximately 250 mg to approximately 750 mg.

The following Examples illustrate the invention described above; they are not, however, intended to limit its scope in any way. Temperatures are given in degrees Centigrade.

(46)

Examples

Example 1

17.7 g of 4-amino-2-methyl-butyrophenone and 20.2 ml of ethoxymethylenemalonic acid diethyl ester are mixed in a round flask provided with a distillation attachment and heated for 1 hour at 130°. The ethanol released during distillation is distilled off first of all at normal pressure and, after 10 minutes, at reduced pressure. On cooling, the reaction mixture solidifies to a crystalline mass. 100 ml of diphenyl ether are added thereto and the mixture is heated to the boil. Approximately 20 ml of distillate are distilled off and this is cooled, dissolved in approximately 500 ml of hot dimethylformamide, diluted with water, left to crystallise out and filtered with suction. 6-Butyryl-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester is obtained.

Example 2

A mixture of 300 ml of ethanol and 100 ml of 2N sodium hydroxide solution is added to 50 g of 6-butyryl-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester and the mixture is heated to 70° and maintained at that temperature for 1 hour. The ethanol is removed, the remaining mixture is diluted with water and extracted by shaking with ether, and the aqueous phase is separated off and acidified with concentrated hydrochloric acid. The precipitated crude product is filtered off and recrystallised from ethanol. 6-Butyryl-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid having a melting point of 249-252.5° is obtained.

Example 3

30 g of 6-butyryl-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester are dissolved in 1000 ml of dimethylformamide and, in the course of one hour, 4.8 g of a 50 % strength sodium hydride dispersion in mineral oil are added in portions. Stirring is carried out for 1 hour at room temperature and then 31.2 g of ethyl iodide are added, and the mixture is then stirred at room temperature for 1 hour, concentrated under reduced pressure, cooled with ice-water and filtered with suction. The product obtained by filtering with suction is dissolved in ethyl acetate, washed with water, dried over sodium sulphate, concentrated and cooled in an ice bath. The precipitated crystallisate is filtered with suction and recrystallised from ethyl acetate. 1-Ethyl-6-butyryl-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester having a melting point of 145-146° is obtained.

Example 4

10 g of 1-ethyl-6-butyryl-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester are dissolved in 250 ml of ethanol, 30.4 ml of N sodium hydroxide solution are added and the mixture is stirrred for 1 hour at room temperature. The ethanol is removed under reduced pressure, and the aqueous phase is extracted with chloroform and acidified with hydrochloric acid. The precipitated crystallisate is filtered with suction. 1-Ethyl-6-butyryl-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid having a melting point of 208-209° is obtained.

Example 5

1.681 g of malonic acid diethyl ester in 25 ml of dimethyl acetamide are cooled to 5° and sodium hydride (0.47 g of a 50 % strength suspension in mineral oil, de-oiled with hexane) is added in portions. The internal temperature should not exceed 20° in the course of this addition. Once the exothermic reaction has subsided, stirring is carried out for 15 minutes at room temperature, then the mixture is heated to approximately 100° and, in the course of 60 minutes, 2.628 g of N-ethyl-5-butyryl-4-methyl-isatoic acid anhydride dissolved in 25 ml of dimethylacetamide are added dropwise. The mixture is then heated at 115° for 5 hours, concentrated to dryness by evaporation under reduced pressure, poured into a mixture of 50 ml of ice-water and 10 ml of 2N hydrochloric acid, and stirred until crystallisation occurs. The crystals are filtered with suction, washed with a little diethyl ether, and recrystallised from methanol yielding 1-ethyl-6-butyryl-4-hydroxy-7-methyl - carbostyril-3-carboxylic acid ethyl ester having a melting point of 124-126°C.

The starting material can be produced, for example, in the following manner:

14.6 g of 4-amino-2-methyl-butyrophenone are dissolved in 85 ml of acetic acid, 15.07 g of mesoxalic acid diethyl ester are added and the mixture is heated under reflux for 60 minutes. The reaction mixture is concentrated to dryness by evaporation under reduced pressure, and the residue obtained by concentration by evaporation is stirred with 25 ml of diethyl ether, filtered with suction, then washed twice with ice-cold diethyl ether and dried under reduced pressure. 5-Butyryl-3-hydroxy-6-methyl-oxindole-3-carboxylic acid ethyl ester is obtained. M.p. 180-181°.

13.0 g of 5-butyryl-3-hydroxy-6-methyl-oxindole-3-carboxylic acid ethyl ester are suspended in 200 ml of methanol and 85 ml of 2N sodium hydroxide solution are added. The mixture is stirred at room temperature for 90 minutes, the methanol is removed under reduced pressure, the mixture is acidified to pH 3-4 with 2N hydrochloric acid, filtered with suction, then the residue is washed with water, dissolved in ethyl acetate, dried over magnesium sulphate, concentrated to dryness by evaporation under reduced pressure, digested with a little methylene chloride and filtered with suction. 5-Butyryl-4-methyl-anthranilic acid having a melting point of 184-186° is obtained.

8.0 g of 5-butyryl-4-methyl-anthranilic acid are dissolved in 100 ml of dioxan with the addition of 20 ml of 2N hydrochloric acid. Then, while cooling gently at 40-50°, a weak current of phosgene is introduced for a period of 30 minutes. Subsequently, the solution is concentrated to 30 ml under reduced pressure, filtered with suction, washed twice with a little diethyl ether and dried under reduced pressure. 5-Butyryl-4-methyl-isatoic acid anhydride having a melting point of 224-226° is obtained.

3.5 g of 5-butyryl-4-methyl-isatoic acid anhydride are dissolved, while heating gently, in 30 ml of hexamethylphosphoric acid triamide, the solution is cooled to 20° and sodium hydride (0.68 g of a 50 % strength suspension in mineral oil, de-oiled with hexane) is added. The mixture is stirred until a clear solution is formed and this is cooled to 10°, 2.21 g of ethyl iodide are added, and the mixture is then stirred for 30 minutes at room temperature, poured into a mixture of 300 ml of ice-water and 20 ml of 2N hydrochloric acid, filtered with suction, subsequently washed twice with ice-water, taken up in methylene chloride, dried over magnesium sulphate and concentrated to dryness by evaporation.

N-ethyl-5-butyryl-4-methyl-isatoic acid anhydride having a melting point of 141-143° is obtained.

Example 6

Analogously to Examples 1-5, or according to one of the methods described in the description, it is also possible to produce the following:

6-butyryl-1,7-dimethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester, m.p. 184-186°,
6-butyryl-1,7-dimethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid,
6-butyryl-7-methyl-4-oxo-1-propyl-1,4-dihydro-3-quinoline-3-carboxylic acid ethyl ester, m.p. 109-111°,
1-allyl-6-butyryl-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester, m.p. 137-139°,
6-butyryl-4-hydroxy-1,7-dimethyl-carbostyril-3-carboxylic acid ethyl ester, m.p. 130-131°,
6-butyryl-4-hydroxy-7-methyl-1-propyl-carbostyril-3-carboxylic acid ethyl ester, m.p. 116-117°,
1-allyl-6-butyryl-4-hydroxy-7-methyl-carbostyril-3-carboxylic acid ethyl ester, m.p. 112-114°. and
6-butyryl-4-hydroxy-7-methyl-1-propargyl-carbostyril-3-carboxylic acid ethyl ester.

Example 7

2.65 g of malonic acid diethyl ester are dissolved in 40 ml of dimethylacetamide, and the solution is cooled to 10° and converted into the sodium salt with sodium hydride (0.768 g of a 50 % strength suspension in mineral oil, de-oiled with hexane) under nitrogen. The sodium salt is heated to 105°, in the course of 1 hour 3.80 g of N-ethyl-5-butyryl-isatoic acid anhydride in 20 ml of dimethyl acetamide are added dropwise, and the mixture

is stirred for 10 hours at 120° and overnight at room temperature. It is then filtered over diatomaceous earth, the dimethyl acetamide is distilled off under reduced pressure, and 250 ml of ice-water and 20 ml of 2N hydrochloric acid are added to the mixture which is then stirred for some time, filtered with suction and dried in the atmosphere. The crude product is recrystallised from methanol/water (90 ml + 45 ml), filtered with suction, washed with 50 % strength methanol and dried under reduced pressure. 1-Ethyl-6-butyryl-4-hydroxy-carbostyril-3-carboxylic acid ethyl ester having a melting point of 163-165° is obtained.

The starting material can be produced, for example, in the following manner :

81.3 g of acetanilide are suspended in 600 ml of carbon disulphide and 76.7 g of butyryl chloride and, in portions, 198 g of aluminium trichloride are added while stirring. The mixture is stirred for some time at 30-35° and heated at the boil for 18 hours. It is then allowed to cool, stirred into 200 ml of ice-water and extracted twice with 500 ml of ethyl acetate each time. The organic phases are combined, washed with 500 ml of additional acid and twice with 500 ml of 15 % strength sodium carbonate solution each time, dried over magnesium sulphate and concentrated to 150 ml under reduced pressure. The residue obtained by concentration is allowed to cool, filtered with suction, washed twice with diethyl ether and dried under reduced pressure. p-Acetaminobutyrophenone having a melting point of 141-143° is obtained.

20 g of p-acetaminobutyrophenone are suspended in 40 ml of semi-concentrated hydrochloric acid and the suspension is heated under reflux for 25 minutes and poured into a mixture of 100 ml of ice and 30 ml of concentrated sodium hydroxide solution. The mixture is filtered with suction, then the residue is washed twice

with ice-cold water, dried in the atmosphere and re-crystallised from methanol/water (20 ml + 100 ml). p-Aminobutyrophenone having a melting point of 93-94° is obtained.

8.15 g of p-aminobutyrophenone are dissolved in 300 ml of methylene chloride and the solution is cooled to -30° under nitrogen. 5.96 g of tert-butyl hypochlorite are then added dropwise and, in the course of this, the mixture is slowly cooled to -65°. Stirring is then carried out for 10 minutes at -65°, 7.37 g of methylthio-acetic acid ethyl ester are added dropwise, the mixture is left for one hour at -65°, 5.55 g of triethylamine are added, and the mixture is slowly allowed to warm to room temperature. 100 ml of water are then added, the organic layer is separated off and subsequently washed with 100 ml of water, the aqueous phases are extracted twice with methylene chloride, and the organic phases are combined, dried over magnesium sulphate, filtered and concentrated to dryness by evaporation under reduced pressure. The residue obtained by concentration by evaporation is dissolved in 200 ml of diethyl ether, 25 ml of 2N hydrochloric acid are added and the mixture is stirred overnight at room temperature. The mixture is then diluted with 50 ml of water, the organic phase is separated off, the aqueous phase is washed with 100 ml of diethyl ether, the organic phases are combined, washed with a mixture of 50 ml of water and 10 ml of 2N hydrochloric acid, dried over magnesium sulphate and concentrated to dryness by evaporation, and the residue is suspended in diethyl ether, filtered with suction and dried under reduced pressure. 5-Butyryl-3-methylthio-oxindole having a melting point of 133-136° is obtained.

1.10 g of potassium hydroxide are added to 1.50 g of 5-butyryl-3-methylthio-oxindole in 50 ml of tetra-hydrofuran and the mixture is stirred intensively for 3 hours in a stream of air. The mixture is acidified to

pH 1 with 2N hydrochloric acid, the tetrahydrofuran is distilled off under reduced pressure, 10 ml of 2N sodium hydroxide solution are added, 0.5 ml of 30 % strength hydrogen peroxide is added while stirring, and the mixture is stirred at room temperature for 15 minutes, acidified to pH 1 with 2N hydrochloric acid, filtered with suction and left to dry in the atmosphere.. The crude product is dissolved in aqueous potassium carbonate solution, clarified with activated carbon, filtered, acidified again with 2N hydrochloric acid to pH 1, filtered with suction and dried under reduced pressure. 5-Butyrylanthranilic acid (2-amino-5-butyryl-benzoic acid) having a melting point of 195-197° is obtained.

Into a solution of 4.4 g of the 5-butyrylanthranilic acid in 60 ml of dioxan and 20 ml of 2N hydrochloric acid, phosgene is cautiously introduced with external cooling (strong exothermic reaction!) until the exothermic reaction has subsided (approximately 90 minutes). The mixture is filtered with suction, washed twice in each case with water and diethyl ether and dried under reduced pressure. 5-Butyrylisatoic acid anhydride having a melting point of 218-220° is obtained.

4.00 g of the anhydride are dissolved in 35 ml of hexamethylphosphoric acid triamide, the solution is cooled to 5° and sodium hydride (0.864 g of a 50 % strength suspension in mineral oil, de-oiled with hexane) is added under nitrogen. The mixture is allowed to warm to room temperature, 2.8 g of ethyl iodide are added and stirring is then carried out for 1 hour first at room temperature, then at 40°, and the reaction mixture is poured into a mixture of 300 ml of ice-water and 20 ml of 2N hydrochloric acid, filtered with suction, washed with water and allowed to dry in the atmosphere.

N-Ethyl-5-butyryl-isatoic acid anhydride having a melting point of 130-132° is obtained.

Example 8

3.8 g of malonic acid di-tert-butyl ester are dissolved in 40 ml of dimethyl acetamide and converted into the sodium salt by treating with sodium hydride (0.843 g of a 50 % strength suspension in mineral oil, de-oiled with hexane). The sodium salt is heated to 105° and, in the course of 1 hour, a solution of N-ethyl-5-butyryl-4-methyl-isatoic acid anhydride in 30 ml of dimethyl acetamide is added. The mixture is stirred at 120° for 5 hours, the dimethyl acetamide is substantially distilled off under reduced pressure, 100 ml of ice-water are added and the reaction mixture is poured into a mixture of 10 ml of 2N hydrochloric acid and 200 ml of ice-water. The crystalline precipitate is filtered with suction, washed twice with cold water and taken up in methylene chloride. The organic phase is separated off, dried over magnesium sulphate, filtered and concentrated by evaporation. The crude product is dissolved in 20 ml of a mixture of 3 parts toluene and 1 part ethyl acetate and chromatographed over 60 g of silica gel using the above solvent mixture as eluant. 30 ml fractions are collected. Fractions 3-9, which according to the thin layer chromatogram contain the desired product, are combined, concentrated by evaporation and recrystallised from 15 ml of methanol. 1-Ethyl-6-butyryl-4-hydroxy-7-methyl-carbostyril-3-carboxylic acid tert-butyl ester having a melting point of 124-126° is obtained.

Example 9

7.13 g of 1-ethyl-6-butyryl-4-hydroxy-7-methyl-carbostyril-3-carboxylic acid tert-butyl ester are suspended

in 100 ml of diethyl ether and, while stirring, 2.0 ml of 70 % strength perchloric acid are carefully added. The reaction mixture is stirred for 10 minutes at 30°, cooled by means of an ice bath and suction-filtered and the residue is washed twice with a little diethyl ether and subsequently with hexane, then allowed to dry at room temperature. In this manner 1-ethyl-6-butyryl-4-hydroxy-7-methyl-carbostyril-3-carboxylic acid having a melting point of 157-158° is obtained.

Examole 10

3.64 g of malonic acid diethyl ester are dissolved in 50 ml of dimethyl acetamide and converted into the sodium salt in the cold, under nitrogen, with sodium hydride (1.09 g of a 50 % strength suspension in mineral oil, de-oiled with hexane). The sodium salt is then heated to 105°, in the course of 1 hour 5.95 g of N-allyl-5-butyryl-4-methyl-isatoic acid anhydride in 30 ml of dimethyl acetamide are added dropwise, and the mixture is stirred for 9 hours at 120° and overnight at room temperature. The dimethyl acetamide is then substantially distilled off under reduced pressure. Approximately 100 g of ice and 20 ml of 2N hydrochloric acid are added to the reaction mixture while stirring and the precipitated crystals are filtered with suction, then washed with cold diethyl ether, dried under reduced pressure and recrystallised from approximately 30 ml of methanol. 1-Allyl-6-butyryl-4-hydroxy-7-methyl-carbostyril-3-carboxylic acid ethyl ester having a melting point of 112-114° is obtained.

The starting material can be produced by reacting 5-butyryl-4-methyl-isatoic acid anhydride with allyl bromide in a manner analogous to that described in Example 5.

Example 11

3.95 g of malonic acid diethyl ester are dissolved in 50 ml of dimethyl acetamide and converted into the sodium salt with sodium hydride (1.07 g of a 50 % strength suspension in mineral oil, de-oiled with hexane). The sodium salt is heated to 105°, in the course of 90 minutes 6.20 g of N-butyl-5-butyryl-4-methyl-isatoic acid anhydride in 30 ml of dimethyl acetamide are added dropwise and the mixture is stirred for 10 hours at 120° and overnight at room temperature. The dimethyl acetamide is then distilled off, 200 ml of ice-water and 20 ml of 2N hydrochloric acid are added to the reaction mixture and this is stirred intensively for some time and filtered with suction, and the residue is then washed twice with ice-water and dried in the atmosphere. The crude product is purified by chromatography over 60 g of silica gel with toluene/ethyl acetate (9:1) as eluant. The product is concentrated by evaporation, digested with 30 ml of diethyl ether and then with 50 ml of hexane, filtered with suction, subsequently washed with hexane and dried under reduced pressure. 1-Butyl-6-butyryl-4-hydroxy-7-methyl-carbostyril-3-carboxylic acid ethyl ester having a melting point of 104-105° is obtained.

The starting material can be produced by reacting 5-butyryl-4-methyl-isatoic acid anhydride with butyl iodide in the manner described in Example 5.

Example 12

2.98 g of malonic acid diethyl ester are dissolved in 50 ml of dimethyl acetamide and converted into the sodium salt with sodium hydride (0.895 g of a 50 % strength suspension in mineral oil, de-oiled with hexane). The sodium salt is heated to 105°, in the course of 1 hour

4.9 g of 5-butyryl-4-methyl-N-propyl-isatoic acid anhydride in 30 ml of dimethyl acetamide are added dropwise thereto, and the mixture is heated for 10 hours at 120° and stirred overnight at room temperature. The dimethyl acetamide is distilled off under reduced pressure, 200 g of ice and 20 ml of 2N hydrochloric acid are added and the reaction mixture is stirred intensively for a short time. The crystalline precipitate is filtered with suction, washed twice with ice-water, dried, suspended in diethyl ether, filtered with suction again and washed with diethyl ether. The crude product is purified by chromatography over 60 g of silica gel with toluene as eluant. The eluate is concentrated by evaporation under reduced pressure, suspended in diethyl ether, filtered with suction, washed with cold diethyl ether and dried. 6-Butyryl-4-hydroxy-7-methyl-1-propyl-carbostyril-3-carboxylic acid ethyl ester having a melting point of 116-117° is obtained.

The starting material is obtained by reacting 5-butyryl-4-methyl-isatoic acid anhydride as described in Example 5.

Example 13

2.6 g of a sodium hydride-mineral oil dispersion (60 % strength) are added in portions at room temperature, while stirring and with the introduction of nitrogen gas, to a solution of 6.1 g of malonic acid diethyl ester in 210 ml of anhydrous dimethylformamide. The mixture is stirred for 30 minutes at room temperature and 30 minutes at 120° and cooled to room temperature, and a solution of 14.0 g of N-allyl-5-methoxycarbonyl-isatoic acid anhydride in 140 ml of anhydrous dimethylformamide is added. The reaction mixture is then stirred for 4

hours at 120°, cooled and concentrated to dryness by evaporation at 0.13 mbar and 60°. 350 ml of water are added to the residue and extraction is carried out twice with 120 ml of methylene chloride each time. The aqueous phase is acidified at 0° with 2N hydrochloric acid. The separated oil is extracted three times with 170 ml of methylene chloride each time. The combined organic phases are washed with 50 ml of water, dried over magnesium sulphate and concentrated to dryness by evaporation under reduced pressure. The residue is then crystallised from methylene chloride/petroleum ether. 1-Allyl-6-methoxycarbonyl-4-hydroxy-carbostyril-3-carboxylic acid ethyl ester having a melting point of 123-125° is obtained.

In an analogous manner it is possible starting from N-ethyl- and N-propargyl-5-methoxycarbonyl-isatoic acid anhydride, respectively, and malonic acid diethyl ester, also to produce 1-ethyl-6-methoxycarbonyl-4-hydroxy-carbostyril-3-carboxylic acid ethyl ester, m.p. 178-180° (from methylene chloride/petroleum ether) and 4-hydroxy-6-methoxycarbonyl-1-propargyl-carbostyril 3-carboxylic acid ethyl ester, respectively.

The starting material can be produced, for example, in the following manner:

100 ml of 2N hydrochloric acid are added, while stirring, to a solution of 34.5 g of 5-methoxycarbonyl-anthranilic acid in 200 ml of dioxan. Phosgene gas is introduced into the suspension at 40°, while stirring, and first of all a solution forms and then crystals precipitate out. After introducing phosgene for 2 hours, the mixture is cooled to 5° and filtered. The crystals are washed with 50 ml of water, dried under reduced pressure, suspended in 200 ml of ether, filtered and dried for 15 minutes at 50°

and 0.13 mbar. 5-Methoxycarbonylisatoic acid anhydride having a melting point of 256-257° is obtained.

A solution of 20.0 g of 5-methoxycarbonylisatoic acid anhydride in 630 ml of anhydrous dimethylformamide is added dropwise, while stirring and with the introduction of nitrogen, to a suspension of 4.33 g of sodium hydride-mineral oil dispersion (60 % strength) in 180 ml of anhydrous dimethylformamide. The mixture is stirred at room temperature for 15 minutes and a solution of 23.2 g of allyl bromide in 130 ml of anhydrous dimethylformamide is added. The reaction mixture is stirred at room temperature for 20 hours, concentrated to 300 ml at 0.13 mbar and 50°, and the residue is poured into 2000 ml of ice-water. The precipitated crystals are extracted three times with 500 ml of diethyl ether each time. The combined ether extracts are washed with 200 ml of water, dried over magnesium sulphate and concentrated to dryness by evaporation under reduced pressure. The residue is crystallised first from diethyl ether/petroleum ether and then from tetrahydrofuran/n-hexane. The N-allyl-5-methoxycarbonyl-isatoic acid anhydride melts at 116-118°.

The following are produced analogously: N-ethyl-5-methoxycarbonyl-isatoic acid anhydride, m.p. 145-147° (from tetrahydrofuran/n-hexane) and 5-methoxycarbonyl-N-propargyl-isatoic acid anhydride (by reaction with ethyl bromide and propargyl bromide respectively).

Example 14

A solution of 3.3 g of 1-allyl-6-methoxycarbonyl-4-hydroxy-carbostyril-3-carboxylic acid ethyl ester in 20.0 ml of N sodium hydroxide solution is stirred at room temperature for 15 hours, extracted with 10.0 ml of diethyl ether and acidified with hydrochloric acid. The precipitated crystals are filtered off and recrystallised from methanol. The resulting 1-allyl-6-carboxy-4-hydroxy-carbostyril-3-carboxylic acid ethyl ester melts above 280°.

In an analogous manner, 1-ethyl-6-carboxy-4-hydroxy-carbostyril-3-carboxylic acid ethyl ester, m.p. > 280° (from methanol) can be produced starting from 1-ethyl-6-methoxycarbonyl-4-hydroxy-carbostyril-3-carboxylic acid ethyl ester.

Example 15

A solution of 4.45 g of N-allyl-5-methoxycarbonyl-isatoic acid anhydride in 400 ml of anhydrous dimethylformamide is added, while stirring, to a solution of 7.0 g of the sodium salt of formylacetic acid ethyl ester in 600 ml of anhydrous dimethylformamide. While introducing nitrogen, the mixture is stirred for 4 hours at 110° and then concentrated to dryness by evaporation under reduced pressure at 70°. 40 ml of water are added to the residue and extraction is carried out three times with 70 ml of diethyl ether each time. The combined ether phases are dried over magnesium sulphate and concentrated to dryness by evaporation under reduced pressure. The residue is crystallised from methylene chloride/n-hexane. 1-Allyl-6-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-3-

carboxylic acid ethyl ester having a melting point of 156-163° is obtained.

Example 16

3.66 g of formylacetic acid ethyl ester are converted into the sodium salt in 75 ml of dimethyl acetamide with sodium hydride (1.41 g of a 50 % strength suspension in mineral oil, de-oiled with hexane). 6.08 g of N-ethyl-5-butyryl-4-methyl-isatoic acid anhydride in 75 ml of dimethyl acetamide are added, the reaction mixture is heated at 110° for 4 hours, concentrated to 50 ml under reduced pressure, 200 ml of ice-water and 30 ml of 2N hydrochloric acid are added, the mixture is suction-filtered, and the residue is subsequently washed with a little cold diethyl ether and recrystallised twice from methanol. 1-Ethyl-6-butyryl-7-methyl-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid ethyl ester having a melting point of 145-146° is obtained.

Example 17

1.4 g of 1-ethyl-6-butyryl-4-hydroxy-7-methyl-carbostyril-3-carboxylic acid nitrile are heated under reflux overnight in 50 ml of 96 % strength ethanol and 10 g of anhydrous ammonium chloride. The mixture is filtered, and the residue is concentrated to dryness by evaporation under reduced pressure and recrystallised from 50 % strength methanol. 1-Ethyl-6-butyryl-4-hydroxy-7-methyl-carbostyril-3-carboxylic acid ethyl ester having a melting point of 125-126° is obtained.

The starting material can be obtained in a manner analogous to that described in Example 5 by reacting cyanoacetic acid ethyl ester/sodium hydride with N-ethyl-5-butyryl-4-methyl-isatoic acid anhydride.

Example 18

Analogously to Examples 1-17 it is possible furthermore to produce the following:
6-ethoxycarbonyl-1-ethyl-4-hydroxy-carbostyril-3-carboxylic acid ethyl ester,
1-ethyl-6-pivaloyloxymethoxycarbonyl-4-hydroxy-carbostyril-3-carboxylic acid ethyl ester,
1-ethyl-6-[2-(2-hydroxyethoxy)-ethoxycarbonyl]-4-hydroxy-carbostyril-3-carboxylic acid ethyl ester,
1-ethyl-6-{2-[2-(2-methoxyethoxy)-ethoxy]-ethoxycarbonyl}-4-hydroxy-carbostyril-3-carboxylic acid ethyl ester,
1-ethyl-6-{2-[2-(2-hydroxyethoxy)-ethoxy]-ethoxycarbonyl}-4-hydroxy-carbostyril-3-carboxylic acid ethyl ester,
1-ethyl-4-hydroxy-6-(1-hydroxybutyl)-7-methyl-carbostyril-3-carboxylic acid ethyl ester and
6-ethoxycarbonyl-1-ethyl-4-hydroxy-carbostyril-3-carboxylic acid tert-butyl ester.

The higher esters of N-ethyl-5-carboxy-isatoic acid anhydride to be used as starting materials can be obtained starting from the methyl ester by transesterification or hydrolysis by means of sodium hydroxide solution to the acid as well as esterification of the same with the relevant alcohol in the presence of dicyclohexyl carbodiimide and 4-dimethylaminopyridine in tetrahydrofuran as solvent.

Example 19

19.6 g of N-ethyl-5-butyryl-4-methyl-N-(1'-oxo-2'-ethoxycarbonylethyl)-anthranilic acid ethyl ester in 60 ml of absolute ethanol are added dropwise, at room temperature, to a solution of 1.15 g of sodium in 30 ml of absolute ethanol. The yellow solution is refluxed for 3 hours. The resulting suspension is then freed of ethanol in vacuo. The residue is dissolved in ice-water and acidified with hydrochloric acid. The separated oil

is extracted with methylene chloride and the methylene chloride solution is washed with water, dried over sodium sulphate, filtered and concentrated to dryness by evaporation in vacuo. An oil is obtained, which is caused to crystallise from methanol. In this manner 1-ethyl-6-butyryl-4-hydroxy-7-methyl-carbostyril-3-carboxylic acid ethyl ester having a melting point of 124-126° is obtained.

The N-ethyl-5-butyryl-4-methyl-N-(1'-oxo-2'-ethoxycarbonylethyl)-anthranilic acid ethyl ester required as starting material can be obtained in the following manner:

2.3 g of sodium are dissolved in 250 ml of ethanol. There are added to this solution 27.5 g of N-ethyl-5-butyryl-4-methyl-isatoic acid anhydride suspended in 300 ml of ethanol. The mixture is refluxed for 1 hour. The solution is concentrated to dryness by evaporation and ice-water is added and acidification with 2N HCl is cautiously carried out. The mixture is then extracted with methylene chloride, dried over magnesium sulphate and concentrated by evaporation. The N-ethyl-5-butyryl-4-methyl-anthranilic acid ethyl ester obtained in this manner is further reacted in the following manner without being purified:

13.86 g of the above anthranilic acid ethyl ester are dissolved in 140 ml of absolute toluene and 6.45 g of ethyl diisopropylamine are added. A solution of 7.6 g of chlorocarbonylacetic acid ethyl ester in 75 ml of absolute toluene is added dropwise at room temperature to this solution over a period of 30 minutes. After stirring for 10 hours at room temperature, a further 7.6 g of chlorocarbonylacetic acid ethyl ester in toluene are added dropwise in the course of 15 minutes

and the mixture is stirred for a further 15 hours at room temperature. The reaction mixture is washed with water, sodium bicarbonate solution and water, dried over anhydrous sodium sulphate, filtered and concentrated to dryness by evaporation in vacuo. In this manner N-ethyl-5-butyryl-4-methyl-N-(1'-oxo-2'-ethoxycarbonyl-ethyl)-anthranilic acid ethyl ester is obtained in the form of a pale yellow oil, which is further processed without further purification.

Example 20

10.1 g of 1-ethyl-4-hydroxy-6-carboxy-carbostyril-3-carboxylic acid ethyl ester are dissolved in 100 ml of pyridine and stirred for 2 hours at room temperature with 2.4 ml of thionyl chloride. The dark solution is then concentrated to dryness by evaporation, two 30 ml portions of toluene are added and concentration by evaporation is carried out again. The resulting acid chloride is dissolved in 100 ml of absolute tetrahydrofuran, the solution is filtered and, at -20°, added dropwise to a solution of propyl lithium in diethyl ether. The mixture is stirred for 30 minutes at -20° and is then stirred for 2 hours at room temperature. With external cooling, a saturated aqueous ammonium chloride solution is then added dropwise and the organic layer is separated off and dried over sodium sulphate. The filtered-off solution is concentrated to dryness by evaporation. The crude material is chromatographed over 100 g of silica gel. 1-Ethyl- -butyryl-4-hydroxy-carbostyril-3-carboxylic acid ethyl ester having a melting point of 163-165° is eluted with toluene/ethyl acetate 1:1.

Example 21

Capsules suitable for insufflation containing 0.025 g of 1-ethyl-6-butyryl-4-hydroxy-7-methyl-carbostyril-3-carboxylic acid ethyl ester can be produced as follows:

Composition (for 1000 capsules)

1-ethyl-6-butyryl-4-hydroxy-7-methoxy-carbostyril-3-carboxylic acid ethyl ester (active ingredient)	25.00 g
lactose, ground	25.00 g

The active ingredient and the lactose (very finely ground) are mixed thoroughly with each other. The resulting powder is sieved and filled in portions of 0.05 g each into gelatin capsules.

(16)

Example 22

Tablets containing 100 mg of 1-ethyl-6-butyryl-4-hydroxy-7-methyl-carbostyril-3-carboxylic acid ethyl ester as active ingredient can be produced, for example, in the following composition.

Composition	per tablet
active ingredient	100 mg
lactose	50 mg
wheat starch	73 mg
colloidal silica	13 mg
talc	12 mg
magnesium stearate	2 mg
	250 mg

Manufacture

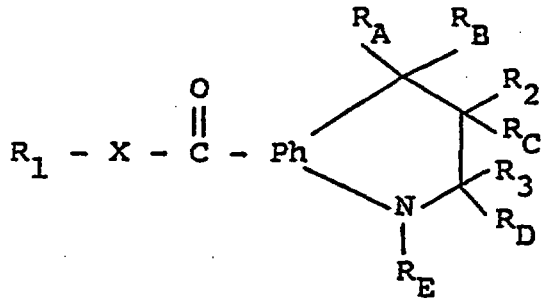
The active ingredient is mixed with the lactose, a portion of the wheat starch and with the colloidal silica, and the mixture is forced through a sieve. A further portion of the wheat starch is made into a paste with 5 times the amount of water on a water bath and the pulverulent mixture is kneaded with this paste until a weakly plastic mass is obtained. This mass is forced through a sieve having a mesh width of approximately 1 mm and dried, and the dry granules are forced through a sieve again. The remainder of the wheat starch, the talc and the magnesium stearate are then admixed. The resulting tabletting mixture is pressed into tablets each weighing 250 mg and having one or more breaking notches.

Example 23

Analogously to Examples 21 and 22 it is also possible to produce pharmaceutical preparations containing another compound according to any one of Examples 1-20.

Claims

1. A quinoline-3-carboxylic acid derivative of the formula (I)



(I)

in which X represents oxy or a direct bond, R_1 represents an aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic or heterocyclic-aliphatic radical, or hydrogen,

Ph represents an optionally additionally substituted 1,2-phenylene radical containing the group R_1-X-C(O)- and R_2 represents an optionally esterified or amidated carboxy group and in which <u>either</u> R_A and R_B together represent oxo, R_C and R_D together represent an additional bond and R_3 denotes hydroxy, hydrogen or an aliphatic radical, or R_C is hydrogen and R_3 and R_D together represent oxo, and R_E, in either case, represents a radical R_5 which represents hydrogen or an aliphatic, cycloaliphatic, araliphatic or heterocyclic-aliphatic radical, <u>or</u> R_A represents an optionally etherified hydroxy group, R_3 denotes hydroxy, hydrogen or an aliphatic radical and R_B together with R_C and also R_D together with R_E represent an additional bond in each case, or R_B and R_C together represent an additional bond and R_3 and R_D together represent oxo and

R_E represents a radical R_5, with the proviso that in compounds of formula I, wherein R_2 denotes carboxy or lower alkoxy-carbonyl, R_3 represents hydrogen or alkyl, R_A and R_B together represent oxo, R_C and R_D together represents an additional bond and R_E denotes hydrogen or R_A denotes hydroxy or lower alkoxy and R_B together with R_C and R_D together with R_E each represent an additional bond, respectively, the group R_1-X-C(=O)- is not carboxy,
and with the additional proviso that in the group of compounds of the formula I, wherein R_3 denotes hydrogen or alkyl, R_A and R_B together represent oxo, R_C and R_D together represent an additional bond and R_E denotes alkyl or alkenyl, the group R_1-X-C(=O)- is not acetyl, or a salt thereof.

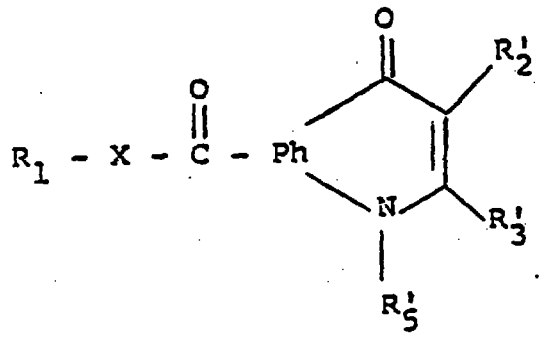
2. A compound according to claim 1, in which X represents a direct bond and R_1, R_2, R_3, R_5, R_A, R_B, R_C, R_D, and R_E have the meanings given in claim 1, R_1 being different from hydrogen or X represents
oxy, R_1 represents lower alkyl or phenyl that is optionally substituted, and R_2, R_3, R_5, R_A, R_B, R_C, R_D, and R_E have the meanings given in claim 1.

3. A compound according to claim 1 in which R_1 represents lower alkyl, lower alkenyl or cycloalkyl each of which is optionally substituted by hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, hydroxy-lower alkoxy-lower alkoxy, lower alkoxy-lower alkoxy-lower alkoxy, lower alkylthio, lower alkanesulphinyl or by lower alkanesulphonyl, phenyl or phenyl-lower alkyl each of which is optionally substituted in the phenyl moiety by lower alkyl, lower alkoxy and/or by halogen, furyl, thienyl or pyridyl, or furyl-lower alkyl, thienyl-lower alkyl or pyridyl-lower alkyl or hydrogen, Ph represents

1,2-phenylene that is optionally additionally substituted by lower alkyl, lower alkoxy, hydroxy and/or by halogen, and R_2 represents carboxy, lower alkoxycarbonyl, hydroxy-lower alkoxycarbonyl, lower alkoxy-lower alkoxycarbonyl, di-lower alkylamino-lower alkoxy- or 5 to 7-membered lower alkyleneamino- or aza-, oxa- or thia-lower alkylene-amino-lower alkoxy-carbonyl or amidated carboxy containing, as amino group, amino, hydroxyamino, lower alkylamino, di-lower alkylamino or 5- to 7-membered lower alkylene- or aza-, oxa-, or thia-lower alkylene-amino, and in which either R_A and R_B together represent oxo, R_C and R_D together represent an additional bond, and R_3 represents hydrogen, lower alkyl or hydroxy or R_C is hydrogen and R_3 and R_D together represent
oxo, and R_E represents hydrogen, lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, di-lower alkylamino-lower alkyl, 5- to 7-membered lower alkyleneamino- or aza-, oxa- or thia-lower alkyleneamino-lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl having from 3 to 8, especially from 5 to 7, ring members, phenyl-lower alkyl, furyl-lower alkyl, thienyl-lower alkyl or pyridyl-lower alkyl, each of which is optionally substituted by lower alkyl, lower alkoxy and/or by halogen, or R_A represents hydroxy or lower alkoxy, R_3 represents hydrogen, lower alkyl or hydroxy, R_B together with R_C and also R_D together with R_E represent an additional bond in each case, or R_B and R_C together represent an additional bond and R_3 and R_D together represent oxo, and R_E represents hydrogen, lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, di-lower alkylamino-lower alkyl, 5- to 7-membered lower alkyleneamino- or aza-, oxa- or thia-lower alkylene-amino-lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl having from 3 to 8, especially from 5 to 7, ring members, phenyl-lower alkyl, furyl-lower alkyl, thienyl-lower alkyl

or pyridyl-lower alkyl, each of which is optionally substituted by lower alkyl, lower alkoxy and/or by halogen, or a salt thereof.

4. A compound of the formula (Ia)



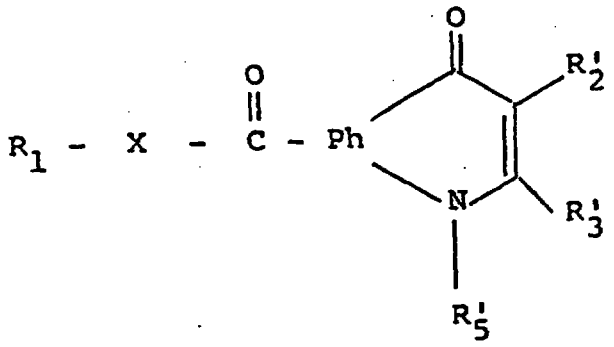
(Ia)

in which R_1 represents lower alkyl having up to 7 carbon atoms; lower alkoxy-, lower alkylthio-, lower alkanesulphinyl- or lower alkanesulphonyl-lower alkyl each having up to 4 carbon atoms in the alkyl moiety; phenylthio-, benzenesulphinyl- or benzenesulphonyl-lower alkyl having up to 4 carbon atoms in the alkyl moiety; lower alkenyl having up to 4 carbon atoms; 3- to 8-membered cycloalkyl; phenyl or phenyl-lower alkyl having up to 4 carbon atoms in the alkyl moiety, each of which is optionally substituted by lower alkyl having up to 4 carbon atoms, lower alkoxy having up to 4 carbon atoms, and/or by halogen having an atomic number of up to and including 35; furyl, thienyl or pyridyl, or furyl-, thienyl- or pyridyl-lower alkyl having up to 4 carbon atoms in the alkyl moiety, and X represents a direct bond, or R_1 represents hydrogen or lower alkyl having up to 7 carbon atoms and X represents oxy, and in which Ph represents 1,2-phenylene that contains the group R_1-X-C(=O)- and that is optionally additionally substituted by lower alkyl having up to 4 carbon atoms, lower alkoxy having

up to 4 carbon atoms, hydroxy or by halogen having an atomic number of up to and including 35, R_2' represents carboxy, lower alkoxycarbonyl having up to 5 carbon atoms, hydroxy-lower alkoxycarbonyl having up to 5 carbon atoms, lower alkoxy-lower alkoxycarbonyl having up to 4 carbon atoms in the alkoxy moieties, di-lower alkylamino-lower alkoxycarbonyl having up to 4 carbon atoms in the alkyl moiety and up to 4 carbon atoms in the alkoxy moiety, carbamoyl, N-hydroxycarbamoyl or N-lower alkyl- or N,N-di-lower alkyl-carbamoyl having up to 4 carbon atoms in the alkyl moiety, R_3' represents hydrogen, lower alkyl having up to 4 carbon atoms, or, hydroxy, and R_5' represents lower alkyl or lower alkenyl having up to 4 carbon atoms; phenyl-, furyl-, thienyl- or pyridyl-lower alkyl that have up to 4 carbon atoms in the alkyl moiety and each of which is optionally substituted by lower alkyl having up to 4 carbon atoms, lower alkoxy having up to 4 carbon atoms, and/or by halogen having an atomic number of up to and including 35; lower alkoxy-lower alkyl having up to 4 carbon atoms in the alkoxy moiety and up to 4 carbon atoms in the alkyl moiety; or di-lower alkylamino-lower alkyl in which lower alkyl has up to 4 carbon atoms or lower alkylene or aza-, oxa- or thia-lower alkylene having from 5 to 7 ring members, provided that in compounds of the formula Ia, wherein X denotes a direct bond, lower alkyl R_1 has at least 2 carbon atoms, when R_3' represents hydrogen or lower alkyl and R_5' denotes lower alkyl or lower alkenyl, or a tautomer and/or salt thereof.

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5. A compound of the formula (Ia)



(Ia)

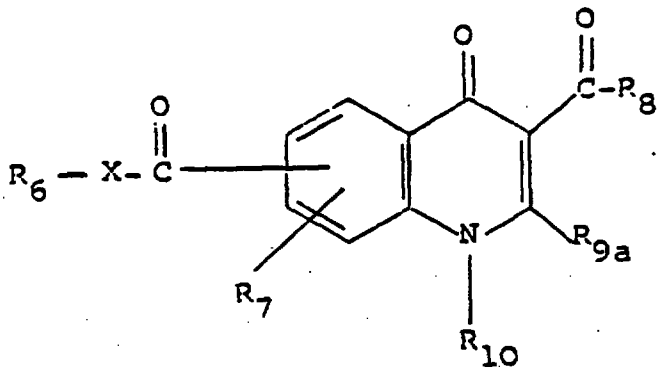
in which R_1 represents lower alkyl having up to 7 carbon atoms, lower alkoxy-, lower alkylthio-, lower alkanesulphinyl- or lower alkanesulphonyl-lower alkyl each having up to 4 carbon atoms in the alkyl moiety, lower alkenyl having up to 4 carbon atoms, or 3- to 8-membered cycloalkyl, and X represents a direct bond, or R_1 represents hydrogen, lower alkyl having up to 7 carbon atoms, lower alkoxy-, lower alkylthio-, lower alkanesulphinyl- or lower alkanesulphonyl-lower alkyl each having up to 4 carbon atoms in the alkyl moiety, lower alkenyl having up to 4 carbon atoms or 3- to 8-membered cycloalkyl, ω-hydroxy-lower alkyl having from 2 to 4 carbon atoms,

alkanoyloxymethyl having up to and including 7 carbon atoms in the alkyl moiety or ω-(ω-hydroxy-lower alkoxy)-lower alkyl, ω-(ω-lower alkoxy-lower alkoxy)-lower alkyl, ω-[ω-(ω-hydroxy-lower alkoxy)-lower alkoxy]-lower alkyl or ω-[ω-(ω-lower alkoxy-lower alkoxy)-lower alkoxy]-lower alkyl each having from 1 to 4 carbon atoms in the alkyl moiety and from 2 to 4 carbon atoms in the alkylene moiety, and X represents oxy, Ph represents 1,2-phenylene that contains the group R_1-X-C(=O)- and is optionally additionally substituted by lower alkyl having up to 4

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carbon atoms, lower alkoxy having up to 4 carbon atoms, hydroxy or by halogen having an atomic number of up to and including 35, R_2' represents carboxy, lower alkoxycarbonyl having up to 5 carbon atoms, lower alkoxy-lower alkoxycarbonyl having up to 4 carbon atoms in the alkoxy moieties, carbamoyl, N-hydroxycarbamoyl or N-lower alkyl- or N,N-di-lower alkyl-carbamoyl having up to 4 carbon atoms in the alkyl moiety, and R_3' represents hydroxy, and R_5' represents hydrogen, lower alkyl or lower alkenyl or lower alkynyl having up to 4 carbon atoms, and tautomers thereof in which a hydroxy group R_3' is in the tautomeric oxo form, and salts of salt-forming compounds of the formula (Ia) or their tautomers.

6. A compound of the formula (II)



(II)

in which X represents a direct bond and R_6 represents lower alkyl having up to 7 carbon atoms, or X represents oxy and R_6 represents hydrogen, lower alkyl having up to and including 7 carbon atoms, ω-hydroxy-lower alkyl having from 2 to 4 carbon atoms, lower alkanoyloxymethyl having up to and including 7 carbon atoms in the alkyl moiety, or ω-(ω-hydroxy-lower alkoxy)-lower alkyl, ω-(ω-lower alkoxy-lower alkoxy)-lower alkyl, ω-[ω-(ω-hydroxy-lower alkoxy)-lower alkoxy]-lower alkyl or ω-[ω-(ω-lower alkoxy-

lower alkoxy)-lower alkoxy]-lower alkyl each having from 1 to 4 carbon atoms in the alkyl moiety and from 2 to 4 carbon atoms in the alkylene moiety, and in which R_7 represents hydrogen or lower alkyl having up to and including 4 carbon atoms, lower alkoxy having up to and including 4 carbon atoms, halogen having an atomic number of up to and including 35, or hydroxy, R_8 represents hydroxy or lower alkoxy having up to 4 carbon atoms, R_{9a} represents hydrogen or hydroxy, and R_{10} represents lower alkyl, lower alkenyl or lower alkynyl having up to 4 carbon atoms, provided that lower alkyl R_6 has at least 2 carbon atoms, when X denotes a direct bond, R_{9a} denotes hydrogen and R_{10} represents lower alkyl or lower alkenyl, it also being possible for a 2-hydroxy-4-oxo-1,4-dihydroquinoline compound of the formula (II) to be in the tautomeric 2-oxo-4-hydroxy-1,2-dihydro- or 2,4-dioxo-1,2,3,4-tetrahydroquinoline form, or a salt thereof.

7. A compound of the formula II according to claim 6 in which X represents oxy, the group R_6-O-C(=O)- is bonded in the 6-position, R_6 is hydrogen, lower alkyl having up to 7 carbon atoms, lower alkanoyloxymethyl having up to and including 7 carbon atoms in the alkyl moiety, or ω-(ω-hydroxy-lower alkoxy)-lower alkyl, ω-(ω-lower alkoxy-lower alkoxy)-lower alkyl, ω-[ω-(ω-hydroxy-lower alkoxy)-lower alkoxy]-lower alkyl or ω-[ω-(ω-lower alkoxy-lower alkoxy)-lower alkoxy]-lower alkyl each having from 1 to 4 carbon atoms in the alkyl moiety and from 2 to 4 carbon atoms in the alkylene moiety, R_7 represents hydrogen, R_8 represents hydroxy or lower alkoxy having up to 4 carbon atoms, R_{9a} represents hydroxy, and R_{10} represents lower alkenyl having up to 4 carbon atoms, or X represents a direct bond, R_6 represents hydrogen or lower alkyl having up to 7 carbon atoms, R_7 represents lower alkyl having up to and including 4 carbon atoms,

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* C L M S *

the group R_6-C(=O)- taking up the 6-position and the lower alkyl group R_7 the 7-position, R_8 represents hydroxy or lower alkoxy having up to and including 4 carbon atoms, R_{9a} represents hydroxy and R_{10} represents lower alkyl having up to and including 4 carbon atoms, or the 2-oxo-4-hydroxy-1,2-dihydroquinoline or 2,4-dioxo-1,2,3,4-tetrahydroquinoline tautomer and/or a salt thereof.

8. A compound of the formula II according to claim 6 in which X represents a direct bond, R_6 represents lower alkyl having up to 7 carbon atoms, R_7 represents hydrogen or lower alkyl having up to and including 4 carbon atoms, the group R_6-X-C(=O)- taking up the 6-position and the lower alkyl group R_7 the 7-position, R_8 represents hydroxy or lower alkoxy having up to and including 4 carbon atoms, R_{9a} represents hydroxy and R_{10} represents lower alkyl or lower alkenyl having up to and including 4 carbon atoms, or the 2-oxo-4-hydroxy-1,2-dihydroquinoline or 2,4-dioxo-1,2,3,4-tetrahydroquinoline tautomer and/or a salt thereof.

9. A compound of the formula II according to claim 6 in which X represents oxy, R_6 represents hydrogen or lower alkyl having up to 7 carbon atoms, R_7 represents hydrogen or lower alkyl having up to and including 4 carbon atoms, the group R_6-X-C(=O)- taking up the 6-position and the lower alkyl group R_7 the 7-position, R_8 represents hydroxy or lower alkoxy having up to and including 4 carbon atoms, R_{9a} represents hydroxy and R_{10} represents lower alkyl or lower alkenyl having up to and including 4 carbon atoms, or the 2-oxo-4-hydroxy-1,2-dihydroquinoline or 2,4-dioxo-1,2,3,4-tetrahydroquinoline tautomer and/or a salt thereof.

10. 6-Butyryl-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester.

11. 6-Butyryl-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a salt thereof.

12. 1-Ethyl-6-butyryl-4-hydroxy-7-methyl-carbostyril-3-carboxylic acid or a salt thereof.

13. 1-Ethyl-6-butyryl-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a salt thereof.

14. 1-Ethyl-6-butyryl-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester.

15. 6-Butyryl-4-hydroxy-1,7-dimethyl-carbostyril-3-carboxylic acid ethyl ester.

16. 6-Butyryl-4-hydroxy-7-methyl-1-propyl-carbostyril-3-carboxylic acid ethyl ester.

17. 1-Ethyl-6-butyryl-4-hydroxy-7-methyl-carbostyril-3-carboxylic acid ethyl ester.

18. 1-Allyl-6-butyryl-4-hydroxy-7-methyl-carbostyril-3-carbcxylic acid ethyl ester.

19. 1-Ethyl-6-buryryl-4-hydroxy-7-methyl-carbostyril-3-carboxylic acid tertiary butyl ester.

20. 6-Carboxy-1-ethyl-4-hydroxy-carbostyril-3-carboxylic acid ethyl ester.

21. 1-Ethyl-6-butyryl-4-hydroxy-carbostyril-3-carboxylic acid ethyl ester.

22. 6-Butyryl-1,7-dimethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester.

23. 6-Butyryl-1,7-dimethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a salt thereof.

24. 6-Butyryl-7-methyl-4-oxo-1-propyl-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester.

25. 1-Allyl-6-butyryl-7-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester.

26. 1-Butyl-6-butyryl-4-hydroxy-7-methyl-carbostyril-3-carboxylic acid ethyl ester.

27. 1-Allyl-6-methoxycarbonyl-4-hydroxy-carbostyril-3-carboxylic acid ethyl ester.

28. 1-Allyl-6-carboxy-4-hydroxy-carbostyril-3-carboxylic acid ethyl ester or a salt thereof.

29. 1-Allyl-6-methoxycarbonyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester.

30. 6-Ethoxycarbonyl-1-ethyl-4-hydroxy-carbostyril-3-carboxylic acid ethyl ester.

31. 1-Ethyl-6-pivaloyloxymethoxycarbonyl-4-hydroxy-carbostyril-3-carboxylic acid ethyl ester.

32. 6-Ethoxycarbonyl-1-ethyl-4-hydroxy-carbostyril-3-carboxylic acid tert-butyl ester.

33. 1-Ethyl-4-hydroxy-6-methoxycarbonyl-carbostyril-3-carboxylic acid ethyl ester.

34. 4-Hydroxy-6-methoxycarbonyl-1-propargyl-carbostyril-3-carboxylic acid ethyl ester.

35. 6-Butyryl-4-hydroxy-7-methyl-1-propargyl-carbostyril-3-carboxylic acid ethyl ester.

36. A compound claimed in claim 2 and described in any one of Examples 1 to 5.

37. A compound claimed in claim 1 and described in any one of Examples 6 to 20.

38. A compound according to any one of claims 1 to 35 for use in a method for the prophylactic and/or therapeutic treatment of the animal or human body.

39. A compound according to any one of claims 1 to 35 as antiallergic agents.

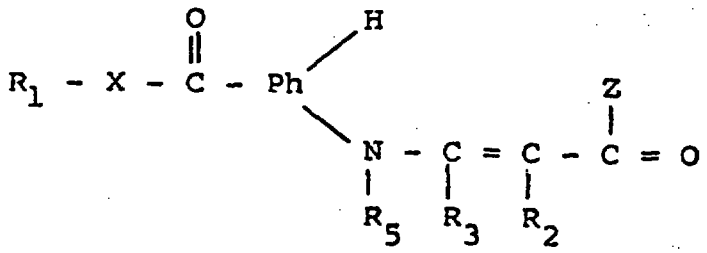
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40. Pharmaceutical preparations containing a compound according to any one of claims 1, 3, 5 to 7, 12, 19 to 21 and 26 to 35, optionally in the form of a pharmaceutically acceptable salt, in addition to customary pharmaceutical adjuncts and carriers.

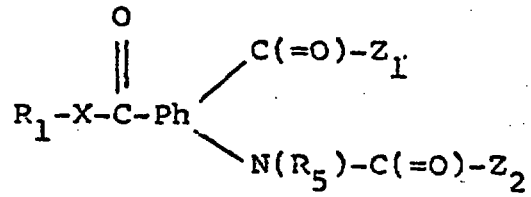
41. Pharmaceutical preparations containing a compound according to any one of claims 2, 4, 8, 9 to 11, 13 to 18 and 22 to 25, optionally in the form of a pharmaceutically acceptable salt, in addition to customary pharmaceutical adjuncts and carriers.

42. Process for the manufacture of novel derivatives of the formula (I) as claimed in claim 1, and of their salts, characterised in that a compound of the formula (IV)



(IV),

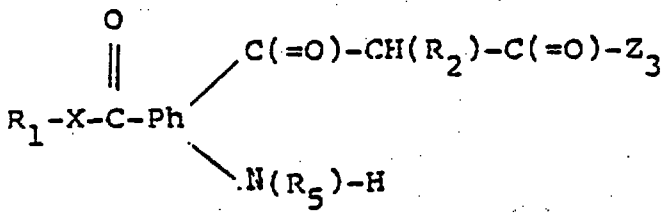
in which Z is a removable radical, or a tautomer and/or salt thereof, is subjected to intramolecular cyclisation, or, a compound of the formula (VI)



(VI),

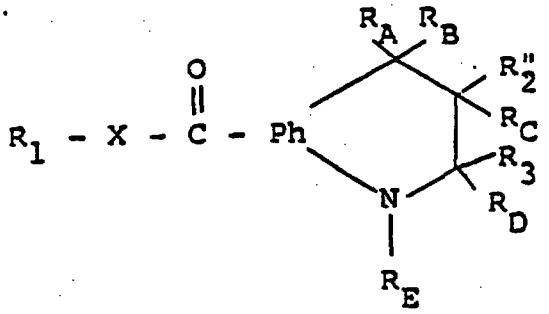
in which one of the radicals Z_1 and Z_2 represents a group of the formula CH_2-R_2 and the other represents an optionally reactively etherified or esterified hydroxy group, or a

tautomer and/or salt thereof, is subjected to intramolecular cyclisation, or a compound of the formula (IX)



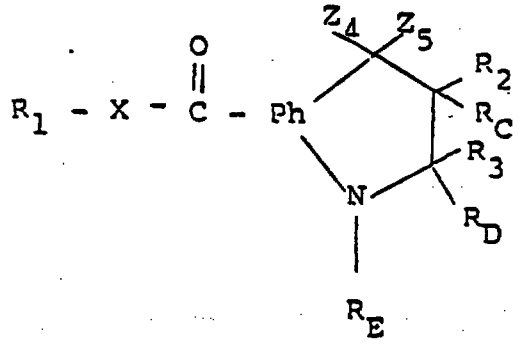
(IX),

in which Z_3 represents hydroxy or a reactive modified hydroxy group, or a tautomer and/or salt thereof, is subjected to intramolecular condensation, or in a compound of the formula (XI)



(XI),

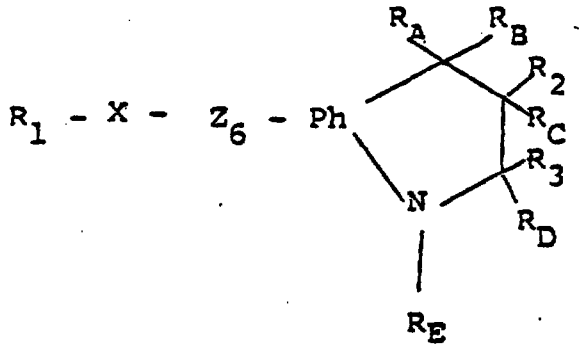
in which the radical R_2'' represents a radical that can be converted into the optionally esterified or amidated carboxy group R_2, or in a tautomer and/or salt thereof, the group R_2'' is converted into the optionally esterified or amidated carboxy group R_2, or in a compound of the formula (XIII)



(XIII)

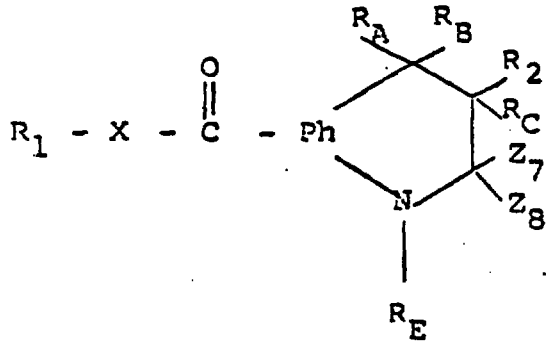
in which Z_4 represents a radical that can be converted into optionally etherified hydroxy, and Z_5 together with R_C and

R_D together with R_E represent an additional bond in each case, or in which Z_4 and Z_5 each represents a monovalent, or together represent a divalent, radical that can be converted into oxo and R_C together with R_D represents an additional bond, or in a salt thereof, a radical Z_4 that can be converted into optionally etherified hydroxy is converted into optionally etherified hydroxy, or radicals Z_4 and Z_5 that can be converted into oxo are together converted into oxo, or, in a compound of the formula (XIX)



(XIX)

in which Z_6 represents a radical that can be converted into the carbonyl group, or in a salt thereof, Z_6 is converted into the carbonyl group, or, for the manufacture of compounds of the formula I in which $R_A + R_B$ represents oxo, $R_C + R_D$ represents an additional bond, R_2 represents optionally esterified or amidated carboxy, R_3 represents hydroxy and R_E represents a radical R_5, or of their tautomers in which R_A denotes hydroxy, R_B and R_C together represent an additional bond, R_3 and R_D together represent oxo and R_E denotes a radical R_5, in a compound of the formula XXI

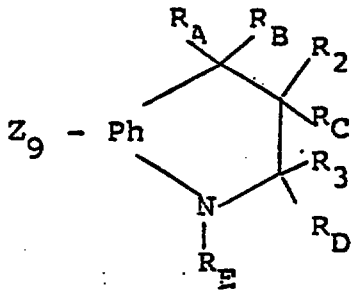


(XXI),

in which Z_7 represents a radical that can be converted into hydroxy and Z_8 represents

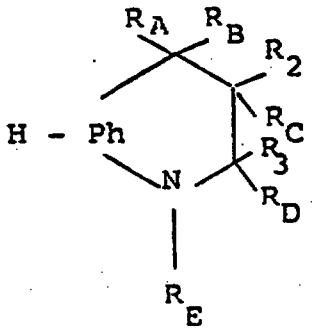
a radical R_D, or Z_7 and Z_8 each represents a monovalent, or together represent a divalent, radical that can be converted into oxo, Z_7 is converted into hydroxy or $Z_7 + Z_8$ are converted into oxo, or,

for the manufacture of compounds of the formula I, wherein X denotes oxy, in a compound of the formula XXIII



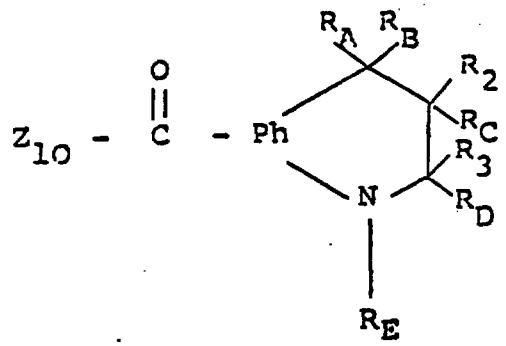
(XXIII),

in which Z_9 represents a functionally modified carboxy group other than the group R_1-X-C(=O)-, Z_9 is solvolysed to a corresponding group R_1-O-C(=O)-, or for the manufacture of compounds of the formula I, wherein X denotes a direct bond, a compound of the formula XXV



(XXV)

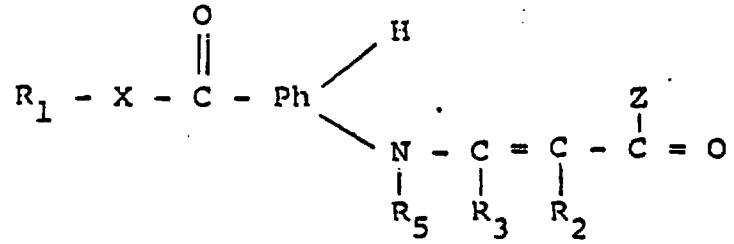
is reacted in the presence of a Lewis acid with a compound of the formula R_1-COOH (XXVI) or a suitable functional derivative thereof, or for the manufacture of compounds of the formula (I), wherein X denotes a direct bond, a compound of the formula XXVII



(XXVII)

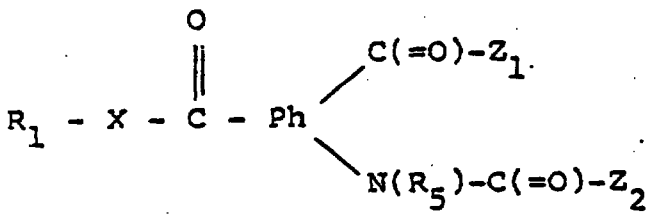
in which Z_{10} represents a free, etherified or reactively esterified hydroxy group or a suitable heteroaryl group bonded via a ring nitrogen atom, or a salt thereof, is reacted with a compound of the formula R_1-M (XXVIII) in which M represents a metal radical, to form a compound of the formula (I), wherein R_1 differs from hydrogen, or reacting a compound of the formula (XXVII), wherein Z_{10} denotes reactively esterified hydroxy, with bis-(triphenylphosphino)-copper boranate to form a compound of the formula (I), wherein R_1 denotes hydrogen, and, if desired, the resulting compound is converted into a different compound of the formula I and/or a resulting salt-forming compound is converted into a salt or a resulting salt is converted into the free compound or into a different salt.

43. Process according to claim 42, for the manufacture of compounds of the formula (I) as claimed in claim 2 and of their salts, characterised in that a compound of the formula IV



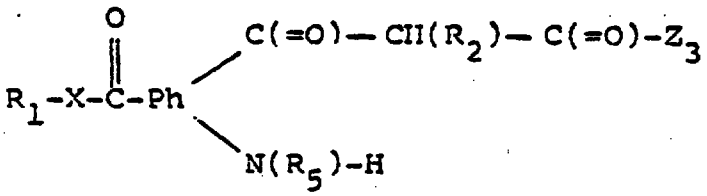
(IV),

in which Z is a removable radical, or a tautomer and/or salt thereof, is subjected to intramolecular cyclisation, or a compound of the formula (VI)



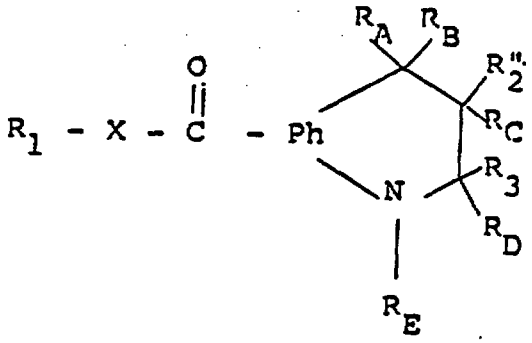
(VI)

in which one of the radicals Z_1 and Z_2 represents a group of the formula CH_2-R_2 and the other represents an optionally reactively etherified or esterified hydroxy group, or a tautomer and/or salt thereof, is subjected to intramolecular cyclisation, or a compound of the formula (IX)



(IX),

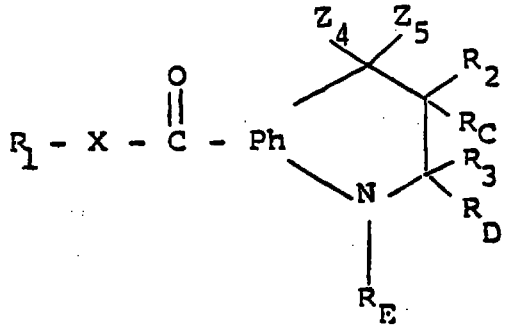
in which Z_3 represents hydroxy or a reactive modified hydroxy group, or a tautomer and/or salt thereof, is subjected to intramolecular condensation, or, in a compound of the formula (XI)



(XI),

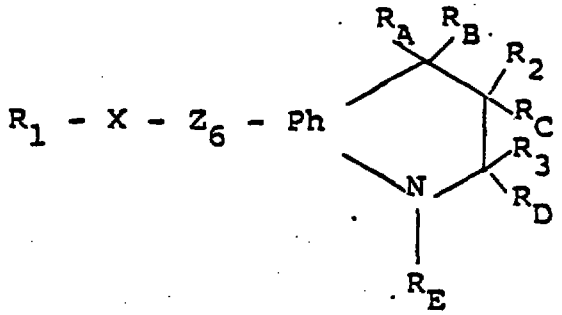
in which the radical R_2'' represents a radical that can be converted into the optionally esterified or amidated carboxy

group R_2, or in a tautomer and/or salt thereof, the group R_2'' is converted into the optionally esterified or amidated carboxy group R_2, or, in a compound of the formula (XIII)



(XIII)

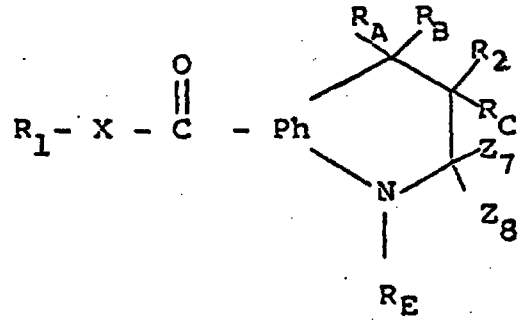
in which Z_4 represents a radical that can be converted into optionally etherified hydroxy, and Z_5 together with R_C and R_D together with R_E represent an additional bond in each case, or in which Z_4 and Z_5 each represents a monovalent, or together represent a divalent, radical that can be converted into oxo and R_C together with R_D represents an additional bond, or in a salt thereof, a radical Z_4 that can be converted into optionally etherified hydroxy is converted into optionally etherified hydroxy, or radicals Z_4 and Z_5 that can be converted into oxo are together converted into oxo, or, in a compound of the formula (XIX)



(XIX)

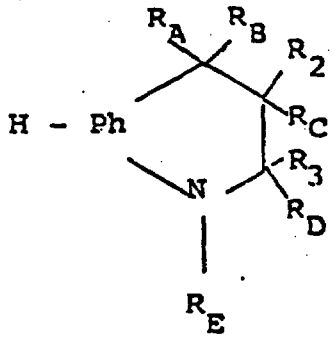
in which Z_6 represents a radical that can be converted into the carbonyl group, or in a salt thereof, Z_6 is converted into the carbonyl group, or, for the manufacture of compounds of the formula I, in which $R_A + R_B$ represents

oxo, $R_C + R_D$ represents an additional bond, R_2 represents optionally esterified or amidated carboxy, R_3 represents hydroxy and R_E represents a radical R_5, or their tautomers in which R_A denotes hydroxy, R_B and R_C together represent an additional bond, R_3 and R_D together represent oxo and R_E denotes a radical R_5, in a compound of the formula XXI



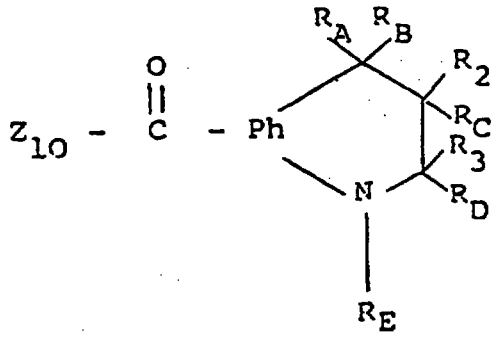
(XXI),

in which Z_7 represents a radical that can be converted into hydroxy and Z_8 represents a radical R_D, or Z_7 and Z_8 each represents a monovalent, or together represent a divalent, radical that can be converted into oxo, Z_7 is converted into hydroxy or $Z_7 + Z_8$ are converted into oxo, or for the manufacture of compounds of the formula I, wherein X denotes a direct bond, a compound of the formula XXV



(XXV)

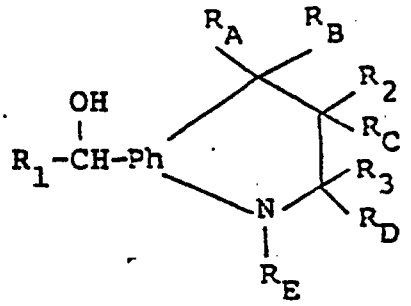
is reacted in the presence of a Lewis acid with a compound of the formula R_1-COOH (XXVI) or a suitable functional derivative thereof, or for the manufacture of a compound of the formula (I), wherein X denotes a direct bond, a compound of the formula XXVII



(XXVII)

in which Z_{10} denotes a free, etherified or reactively esterified hydroxy group or a suitable heteroaryl group bonded via a ring nitrogen atom, or a salt thereof, is reacted with a compound of the formula R_1-M (XXVIII) in which M represents a metal radical, R_1 being different from hydrogen, and, if desired, the resulting compound is converted into another compound of the formula (I) and/or a resulting salt-forming compound is converted into a salt or a resulting salt is converted into the free compound or into another salt.

44. A compound of the formula XIXa



(XIXa) ,

in which R_1 represents an aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic or heterocyclic-aliphatic radical or hydrogen, Ph represents an optionally additionally substituted 1,2-phenylene radical containing the group

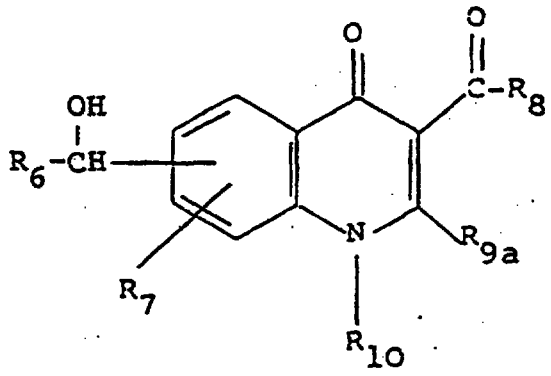
R_1-CH(OH)-, and R_2 represents an optionally esterified or amidated carboxy group, and in which either R_A and R_B together represent oxo and R_3 denotes hydroxy, hydrogen or an aliphatic radical and

R_C and R_D together represent an additional bond, or

R_C is hydrogen and R_3 and R_D together represent oxo, and

R_E, in either case represents hydrogen or an aliphatic, cycloaliphatic, araliphatic or heterocyclic-aliphatic radical, or R_A represents an optionally etherified hydroxy, R_3 denotes hydroxy, hydrogen or an aliphatic radical and R_B together with R_C and also R_D together with R_E represent an additional bond in each case, or R_B and R_C together represent an additional bond and R_3 and R_D together represent oxo and R_E represents hydrogen or an aliphatic, cycloaliphatic, araliphatic or heterocyclic-aliphatic radical, or a salt thereof.

45. A compound of the formula (XIXb)



(XIXb),

in which the group

R_6 represents lower alkyl having up to 7 carbon atoms, R_7 represents hydrogen or lower alkyl having up to and including 4 carbon atoms, the group R_6-Z_6 being attached to the 6- and a lower alkyl group R_7 being attached to the 7-position, R_8 represents hydroxy or lower alkoxy having up to 4 carbon

atoms, R_{9a} represents hydroxy, and R_{10} represents lower alkyl or lower alkenyl having up to 4 carbon atoms, or the tautomeric 2-oxo-4-hydroxy-1,2-dihydro- or 2,4-dioxo-1,2,3,4-tetrahydroquinoline form and/or a salt thereof.

46. 1-Ethyl-4-hydroxy-6-(1-hydroxybutyl)-7-methyl-carbostiryl-3-carboxylic acid ethyl ester.

47. A compound as claimed in any one of claims 44 to 46 for use in a method for the therapeutical treatment of the human or animal body.

48. A compound as claimed in any one of claims 44 to 46 as an antiallergic medicament.

49. A pharmaceutical preparation containing at least one compound as claimed in any one of claims 44 to 46, optionally in a pharmaceutically acceptable salt form, in admixture with conventional pharmaceutical adjuncts or carriers.

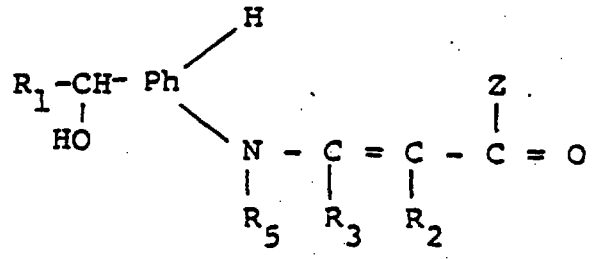
50. Process for the manufacture of novel quinoline-3-carboxylic acid derivatives as claimed in claim 44 of the formula (XIXa) and of their salts, characterised in that a compound of the formula

$$R_1\text{-}X\text{-}Z_6\text{-}Ph(NHR_5)\text{-}H \qquad (Va),$$

wherein X denotes a direct bond and Z_6 denotes hydroxy-methylene, is reacted with a compound of the formula

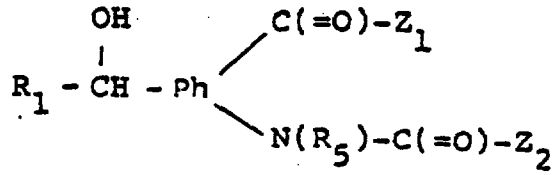
$$HO\text{-}C(R_3)(R_D)\text{-}C(R_2)(R_C)\text{-}COOH \qquad (XX)$$

or with a functional derivative thereof, or a compound of the formula



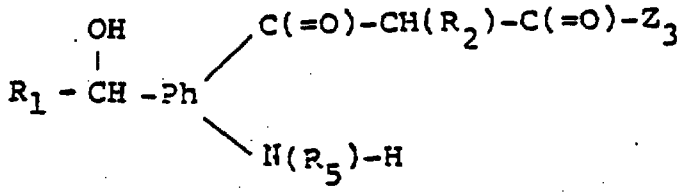
(IVa),

in which Z is a removable radical, or a tautomer and/or salt thereof, is subjected to intramolecular cyclisation, or a compound of the formula



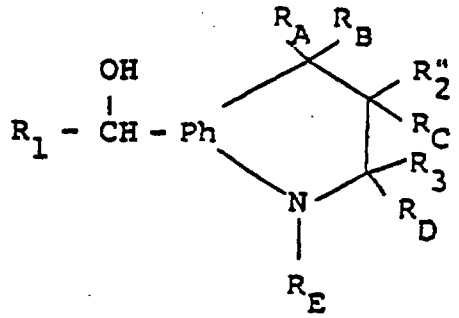
(VIa),

in which one of the radicals Z_1 and Z_2 represents a group of the formula CH_2-R_2 and the other represents an optionally reactively etherified or esterified hydroxy group, or a tautomer and/or salt thereof, is subjected to intramolecular cyclisation, or a compound of the formula



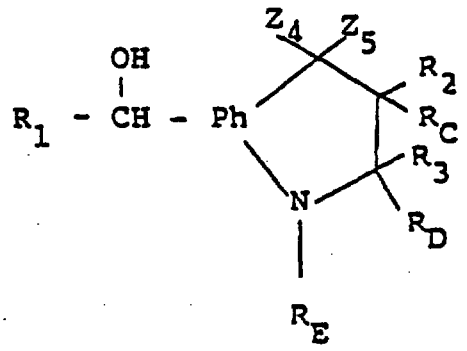
(IXa),

in which Z_3 represents hydroxy or a reactive modified hydroxy group, or a tautomer and/or salt thereof, is subjected to intramolecular condensation, or, in a compound of the formula



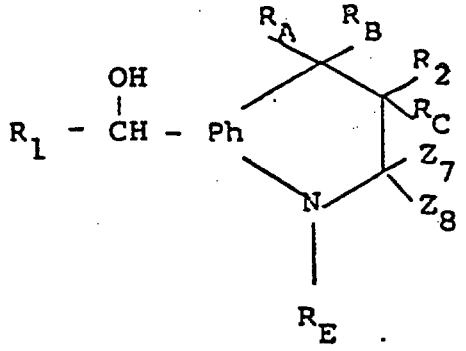
(XIa),

in which the radical R_2'' represents a radical that can be converted into the optionally esterified or amidated carboxy group R_2, or in a tautomer and/or salt thereof, the group R_2'' is converted into the optionally esterified or amidated carboxy group R_2, or, in a compound of the formula



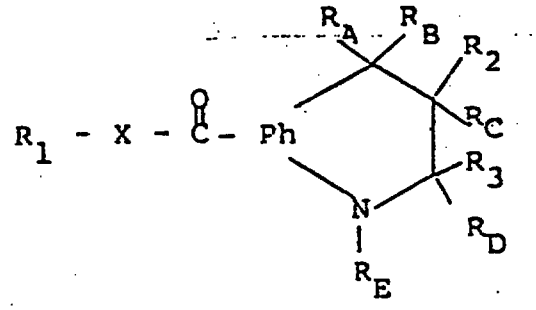
(XIIIa),

in which Z_4 represents a radical that can be converted into optionally etherified hydroxy, and Z_5 together with R_C and R_D together with R_E represent an additional bond in each case, or in which Z_4 and Z_5 each represents a monovalent, or together represent a divalent, radical that can be converted into oxo and R_C together with R_D represents an additional bond, or in a salt thereof, a radical Z_4 that can be converted into optionally etherified hydroxy is converted into optionally etherified hydroxy, or radicals Z_4 and Z_5 that can be converted into oxo are together converted into oxo, or for the manufacture of compounds of the formula XIXa, in which R_A+ R_B represents oxo, R_C + R_D represents an additional bond, R_2 represents optionally esterified or amidated carboxy , R_3 represents hydroxy and R_E represents a radical R_5 or of their tautomers in which R_A denotes hydroxy, R_B and R_C together represent an additional bond, R_3 and R_D together represent oxo and R_E denotes a radical R_5, in a compound of the formula



(XXIa),

in which Z_7 represents a radical that can be converted into hydroxy and Z_8 represents a radical R_D, or Z_7 and Z_8 each represents a monovalent, or together represent a divalent, radical that can be converted into oxo, Z_7 is converted into hydroxy or Z_7 + Z_8 are converted into oxo, or, in a compound of the formula



(I)

in which X denotes a direct bond and R_1 represents an aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic or heterocyclic-aliphatic radical, the group R_1-C(=O)- is, by reaction with a suitable reducing agent reduced to a group R_1-CH(OH)-, or in which a compound of the formula (I) in which R_1 denotes hydrogen and X denotes a direct bond, is reacted with a metal derivative of a hydrocarbon of the formula R_1-H, wherein R_1 is different from hydrogen, and, if desired, in a resulting compound of the formula (XIXa) esterified or amidated carboxy is

* C L M S *

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solvolysed to carboxy, carboxy is esterified or hydrogen R_E is replaced by an aliphatic residue and/or a resulting salt is converted into the free compound or a resulting free compound is converted into a salt.

51. The process as claimed in claim 43 and described in any one of Examples 1 to 5.

52. The process as claimed in claim 42 and described in any one of Examples 6 to 20.

53. The compounds of formula XIXa obtainable according to the process of claim 50.

54. The compounds of formula I obtainable according to the process of either one of claims 43 and 51.

55. The compounds of formula I obtainable according to the process of either one of claims 42 and 52.

56. Compounds according to any one of claims 1 to 33 and 44 to 46 as medicaments or for the manufacture of medicaments by non-chemical methods.