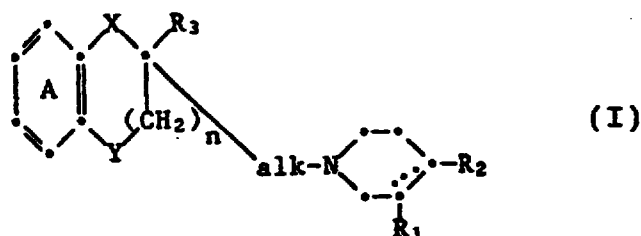


The invention relates to novel hydrogenated 1-benzooxa-cycloalkylpyridinecarboxylic acid compounds of the formula



in which either R₁ represents carboxy, lower alkoxy-carbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl or optionally acylated hydroxymethyl and R₂ represents hydrogen, an optionally etherified or acylated hydroxy group or an optionally acylated amino group, or R₁ represents hydrogen and R₂ represents carboxy, lower alkoxy-carbonyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl or optionally acylated hydroxymethyl, R₃ represents hydrogen or lower alkyl, alk represents lower alkylene or lower alkylidene, the ring A is unsubstituted or is mono- or poly-substituted by hydroxy, lower alkoxy, lower alkanoyloxy, halogen, lower alkyl and/or by trifluoromethyl, the dotted line is intended to indicate the presence of a single or a double bond between the carbon atoms carrying the radicals R₁ and R₂, and either each of X and Y represents an oxygen atom and n represents 1, or X represents a methylene group, Y represents an oxygen atom and n represents 1, or X represents an oxygen atom, Y represents a methylene group and n represents 1, or X represents a direct bond, Y represents an oxygen atom and n represents 2, and to their tautomers and/or salts, to the use of these compounds, to processes for their manufacture and to pharmaceutical compositions comprising a compound of the formula I or a tautomer and/or a pharmaceutically

acceptable salt thereof.

Etherified hydroxy R_2 is, for example, lower alkoxy or optionally substituted phenyl-lower alkoxy.

Acyl in acylated hydroxymethyl R_1 and R_2 and also in acylated hydroxy R_2 and acylated amino R_2 is, for example, acyl derived from an organic carboxylic or sulphonic acid.

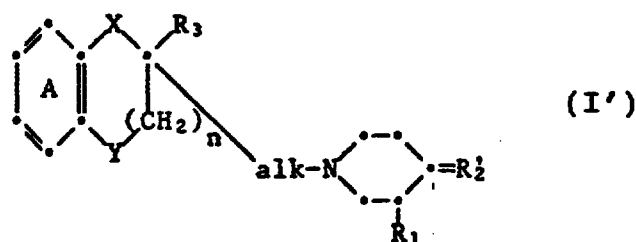
Acyl derived from an organic carboxylic acid is, for example, the radical of an aliphatic or monocyclic-aromatic carboxylic acid, such as lower alkanoyl or optionally substituted benzoyl, and also pyridoyl.

Acyl derived from an organic sulphonic acid is, for example, lower alkanesulphonyl.

The invention relates, for example, to compounds of the formula I in which R_1 represents carboxy, lower alkoxy-carbonyl, carbamoyl, N-lower alkylcarbamoyl or N,N-di-lower alkylcarbamoyl, R_2 represents hydrogen, an optionally etherified or acylated hydroxy group or an optionally acylated amino group, R_3 represents hydrogen or lower alkyl, alk represents lower alkylene or lower alkylidene, the ring A is unsubstituted or is mono- or poly-substituted by hydroxy, lower alkoxy, lower alkanoyloxy, halogen, lower alkyl and/or by trifluoromethyl, the dotted line is intended to indicate the presence of a single or a double bond between the carbon atoms carrying the radicals R_1 and R_2 , X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n represents 1, and to their tautomers and/or salts, to the use of these compounds, to processes for

their manufacture and to pharmaceutical compositions comprising such a compound of the formula I or a tautomer and/or a pharmaceutically acceptable salt thereof.

Tautomeric forms of compounds of the formula I exist, for example, when R_2 represents hydroxy or amino and the dotted line is intended to indicate the presence of a double bond between the carbon atoms carrying the radicals R_1 and R_2 . That is to say, the enols and enamines, respectively, of the formula I are in equilibrium with the corresponding keto and ketimine tautomers, respectively, of the formula



in which R_2 represents oxo or imino. Representatives of both tautomeric forms can be isolated.

The compounds according to the invention can also be in the form of stereoisomers. Since the compounds of the formula I have at least one chiral carbon atom (C-atom) (the C-atom having the radical R_3), they may be, for example, in the form of pure enantiomers or enantiomeric mixtures, such as racemates, and if, also, there is at least one further chiral centre present (for example the C_4 -atom of a 4-substituted piperidine radical and/or the C_3 -atom of a 3-substituted piperidine radical), they may also be in the form of diastereoisomers, diastereoisomeric mixtures or mixtures of racemates. Thus, for example, geometrical isomers with respect to R_1 and R_2 , such as cis- and trans-isomers, may be formed if R_1 and

R_2 are other than hydrogen.

Salts of compounds of the formula I and their tautomers are especially corresponding acid addition salts, preferably pharmaceutically acceptable acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulphuric acid, a phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as lower alkanecarboxylic acids, for example acetic acid, optionally unsaturated dicarboxylic acids, for example malonic, maleic or fumaric acid, or hydroxycarboxylic acids, for example tartaric or citric acid, or with sulphonic acids, such as lower alkanesulphonic acids or optionally substituted benzenesulphonic acids, for example methane- or p-toluene-sulphonic acid. If, for example, R_1 or R_2 represents carboxy, corresponding compounds may form salts with bases. Suitable salts with bases are, for example, corresponding alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, pharmaceutically acceptable transition metal salts, such as zinc or copper salts, or salts with ammonia or organic amines, such as cyclic amines, mono-, di- or tri-lower alkylamines, hydroxy-lower alkylamines, for example mono-, di- or tri-hydroxy-lower alkylamines, hydroxy-lower alkyl-lower alkylamines or polyhydroxy-lower alkylamines. Cyclic amines are, for example, morpholine, thiomorpholine, piperidine or pyrrolidine. As mono-lower alkylamines there come into consideration, for example, ethylamine or tert.-butylamine; as di-lower alkylamines, for example, diethylamine or diisopropylamine, and as tri-lower alkylamines, for example, trimethylamine or triethylamine. Corresponding hydroxy-lower alkylamines are, for example, mono-, di- or tri-

ethanolamine; hydroxy-lower alkyl-lower alkylamines are, for example, N,N-dimethylamino- or N,N-diethylamino-ethanol; as polyhydroxy-lower alkylamine there comes into consideration, for example, glucosamine.

Also included are salts that are unsuitable for pharmaceutical uses, since they can be used, for example, for the isolation and purification of free compounds according to the invention and their pharmaceutically acceptable salts.

Hereinbefore and hereinafter, unless defined otherwise, radicals or compounds designated "lower" are to be understood as meaning those radicals or compounds which contain up to and including 7, especially up to and including 4, carbon atoms.

Lower alkoxy is C₁-C₄-alkoxy, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy or tert.-butoxy.

Lower alkyl is, for example, C₁-C₄-alkyl, that is to say methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl or tert.-butyl, and also includes C₅-C₇-alkyl radicals, that is to say pentyl, hexyl and heptyl radicals.

Lower alkylene alk is C₁-C₄-alkylene that bridges the two ring systems especially by up to and including 3 carbon atoms and may be, for example, methylene, ethylene or 1,3-propylene, but may also be 1,2-propylene, 1,2- or 1,3-(2-methyl)-propylene or 1,2- or 1,3-butylene, but may also bridge the two ring systems by 4 carbon atoms, that is to say it may be 1,4-butylene.

Lower alkylidene alk is C₁-C₄-alkylidene and may be, for example, methylene, ethylidene, 1,1- or 2,2-propylidene or 1,1- or 2,2-butylidene.

Lower alkanoyl is C₂-C₅-alkanoyl, such as acetyl, propionyl, butyryl, isobutyryl or pivaloyl.

Lower alkanoyloxy is C₂-C₅-alkanoyloxy, such as acetoxy, propionyloxy, butyryloxy, isobutyryloxy or pivaloyloxy.

Lower alkoxycarbonyl is C₁-C₄-alkoxycarbonyl, such as methoxy-, ethoxy-, n-propoxy-, isopropoxy-, n-butoxy-, isobutoxy- or tert.-butoxy-carbonyl.

N-lower alkylcarbamoyl is N-C₁-C₄-alkylcarbamoyl, such as N-methyl-, N-ethyl-, N-(n-propyl)-, N-isopropyl-, N-(n-butyl)-, N-isobutyl- or N-tert.-butyl-carbamoyl.

N,N-di-lower alkylcarbamoyl is N,N-di-C₁-C₄-alkyl-carbamoyl, in which the two N-alkyl groups may be the same or different, such as N,N-dimethyl-, N,N-diethyl-, N,N-diisopropyl- or N-butyl-N-methyl-carbamoyl.

Optionally substituted phenyl-lower alkoxy is phenyl-C₁-C₄-alkoxy optionally substituted in the phenyl moiety, such as benzyloxy, p-chlorobenzyloxy, 1-phenylethoxy or 1-(p-bromophenyl)-n-butoxy.

Optionally substituted benzoyl is, for example, benzoyl, p-chlorobenzoyl or p-nitrobenzoyl.

Lower alkanesulphonyl is C₁-C₄-alkanesulphonyl, such as methane- or ethane-sulphonyl.

Halogen is especially halogen having an atomic number of up to and including 35, that is to say fluorine, chlorine or bromine, and also includes iodine.

The compounds of the formula I and their tautomers and/or their pharmaceutically acceptable salts have, for example, valuable pharmacological, especially nootropic, properties. Thus, for example, in mice, in the Two-Compartment Passive Avoidance Test model according to Mondadori and Classen, Acta Neurol. Scand. 69, Suppl. 99, 125 (1984), at dosages of approximately 0.1 mg/kg and above i.p. and p.o. they bring about a reduction in the amnesic effect of a cerebral electric shock.

The compounds according to the invention also exhibit a considerable memory-improving action which can be detected in mice in the Step-down Passive Avoidance Test according to Mondadori and Waser, Psychopharmacol. 63, 297 (1979) at a dose of approximately 0.1 mg/kg and above i.p. and p.o..

Accordingly, the compounds of the formula I and their tautomers and/or their pharmaceutically acceptable salts can be used as pharmaceuticals, for example nootropics, for example for the therapeutic and/or prophylactic treatment of the symptoms of cerebral insufficiency, especially memory disorders. The invention therefore relates also to the use of the compounds of the formula I and their tautomers and/or their pharmaceutically acceptable salts for the manufacture of medicaments, especially nootropics, for the treatment of the symptoms of cerebral insufficiency, especially memory disorders. The commercial formulation of the active ingredients may

also be included.

The invention relates especially to compounds of the formula I in which either R_1 represents carboxy, lower alkoxy-carbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, hydroxymethyl, C_2 - C_5 alkanoyloxy-methyl, lower alkanesulphonyloxymethyl, benzoyloxymethyl or pyridoyloxymethyl and R_2 represents hydrogen, hydroxy, lower alkoxy, benzyloxy, C_2 - C_5 alkanoyloxy, lower alkane-sulphonyloxy, benzoyloxy, pyridoyloxy, amino, C_2 - C_5 -alkanoylamino, lower alkanesulphonylamino, benzoylamino or pyridoylamino, or R_1 represents hydrogen and R_2 represents carboxy, lower alkoxy-carbonyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, hydroxy-methyl, C_2 - C_5 alkanoyloxymethyl, lower alkanesulphonyloxy-methyl, benzoyloxymethyl or pyridoyloxymethyl, R_3 represents hydrogen or C_1 - C_7 alkyl, alk represents lower alkyl that bridges the two ring systems by up to and including 3 carbon atoms, or alk represents lower alkylidene, the ring A is unsubstituted or is mono-, di- or poly-substituted by hydroxy, lower alkoxy, C_2 - C_5 -alkanoyloxy, halogen having an atomic number of up to and including 53, C_1 - C_7 alkyl and/or by trifluoromethyl, the dotted line is intended to indicate the presence of a single or a double bond between the carbon atoms carrying the radicals R_1 and R_2 , and either each of X and Y represents an oxygen atom and n represents 1, or X represents a methylene group, Y represents an oxygen atom and n represents 1, or X represents an oxygen atom, Y represents a methylene group and n represents 1, or X represents a direct bond, Y represents an oxygen atom and n represents 2, radicals designated "lower" having from 1 up to and including 4 carbon atoms, for example compounds of the formula I in which R_1 represents carboxy, lower

alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl or N,N-di-lower alkylcarbamoyl, R_2 represents hydrogen, hydroxy, lower alkoxy, benzyloxy, C_2 - C_5 alkanoyloxy, lower alkane-sulphonyloxy, benzoyloxy, pyridoyloxy, amino, C_2 - C_5 -alkanoylamino, benzoylamino or pyridoylamino, R_3 represents hydrogen or C_1 - C_7 alkyl, alk represents lower alkylene that bridges the two ring systems by up to and including 3 carbon atoms, or alk represents lower alkylidene, the ring A is unsubstituted or is mono-, di- or poly-substituted by hydroxy, lower alkoxy, C_2 - C_5 -alkanoyloxy, halogen having an atomic number of up to and including 53, C_1 - C_7 alkyl and/or by trifluoromethyl, the dotted line is intended to indicate the presence of a single or a double bond between the carbon atoms carrying the radicals R_1 and R_2 , X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n represents 1, radicals designated "lower" containing from 1 up to and including 4 carbon atoms, and to their tautomers and/or salts.

The invention relates more especially to compounds of the formula I in which either R_1 represents C_1 - C_4 alkoxy-carbonyl, such as methoxy- or ethoxy-carbonyl, carbamoyl, hydroxymethyl or C_2 - C_5 alkanoyloxymethyl, such as acetoxymethyl, and R_2 represents hydrogen or hydroxy, or R_1 represents hydrogen and R_2 represents C_1 - C_4 alkoxy-carbonyl, such as ethoxycarbonyl, R_3 represents hydrogen or C_1 - C_4 alkyl, such as methyl, alk represents C_1 - C_4 -alkylene that bridges the two ring systems by up to and including 3 carbon atoms, such as methylene or ethylene, the ring A is unsubstituted or is substituted, especially in the 7-position, by C_1 - C_4 alkoxy, such as methoxy, the dotted line is intended to indicate the presence of a single or a double bond between the carbon atoms carrying

the radicals R_1 and R_2 , and either each of X and Y represents an oxygen atom and n represents 1, or X represents a methylene group, Y represents an oxygen atom and n represents 1, or X represents an oxygen atom, Y represents a methylene group and n represents 1, or X represents a direct bond, Y represents an oxygen atom and n represents 2, for example compounds of the formula I in which R_1 represents C_1 - C_4 alkoxycarbonyl, such as methoxycarbonyl, R_2 represents hydrogen or hydroxy, R_3 represents hydrogen or C_1 - C_4 alkyl, such as methyl, alk represents C_1 - C_4 alkylene that bridges the two ring systems by up to and including 3 carbon atoms, such as methylene or ethylene, the ring A is unsubstituted, the dotted line is intended to indicate the presence of a single or a double bond between the carbon atoms carrying the radicals R_1 and R_2 , X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n represents 1, and their tautomers and/or salts.

The invention relates especially to compounds of the formula I in which R_1 represents C_1 - C_4 alkoxycarbonyl, such as methoxy- or ethoxy-carbonyl, R_2 represents hydrogen or hydroxy, R_3 represents hydrogen, alk represents methylene or ethylene, the ring A is unsubstituted, the dotted line is intended to indicate the presence of a single or a double bond between the carbon atoms carrying the radicals R_1 and R_2 , X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n represents 1, and their tautomers and/or salts.

The invention relates most especially to compounds of the formula I in which R_1 represents C_1 - C_4 alkoxycarbonyl, such as methoxycarbonyl, R_2 represents hydrogen, R_3 represents hydrogen, alk represents methylene or

ethylene, the ring A is unsubstituted, the dotted line is intended to indicate the presence of a single or a double bond between the carbon atoms carrying the radicals R_1 and R_2 , X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n represents 1, or in which R_1 represents C_1 - C_4 alkoxy-carbonyl, such as methoxycarbonyl, R_2 represents hydroxy, R_3 represents hydrogen, alk represents methylene, the ring A is unsubstituted, the dotted line is intended to indicate the presence of a double bond between the carbon atoms carrying the radicals R_1 and R_2 , X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n represents 1, and in each case their tautomers and/or salts.

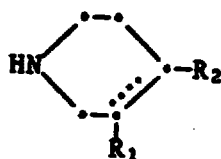
The invention relates specifically to the novel compounds of the formula I mentioned in the Examples and their tautomers and/or salts and to processes for their manufacture.

The present invention relates also to a process for the manufacture of compounds of the formula I or their tautomers and/or their salts, for example characterised in that

a) a compound of the formula

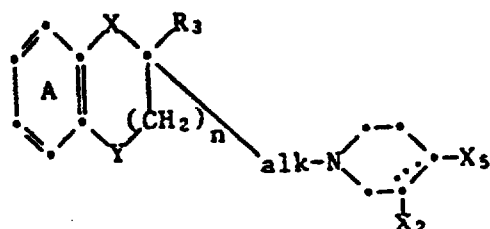


or a salt thereof, in which X_1 represents hydroxy or reactive esterified hydroxy, is reacted with a compound of the formula



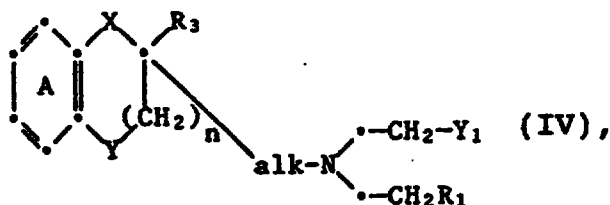
(IIb)

or a tautomer and/or salt thereof, or
b) in a compound of the formula



(III)

or a tautomer and/or salt thereof, in which X_2 represents a radical that can be converted into R_1 that is other than hydrogen, and X_5 represents a radical R_a , and R_a represents hydrogen, hydroxy, lower alkoxy, benzyloxy, C_2 - C_5 alkanoyloxy, lower alkanesulphonyloxy, benzoyloxy, pyridoyloxy, amino, C_2 - C_5 alkanoylamino, lower alkane-sulphonylamino, benzoylamino or pyridoylamino, X_2 is converted into R_1 that is other than hydrogen, or in a compound of the formula III in which X_2 represents hydrogen and X_5 represents a radical that can be converted into R_b , and R_b represents a radical R_2 other than a radical R_a , X_5 is converted into R_b , or
c) for the manufacture of a compound of the formula I or a tautomer and/or salt thereof, in which R_2 represents hydroxy or amino and R_1 is other than hydrogen and represents especially lower alkoxycarbonyl, a compound of the formula

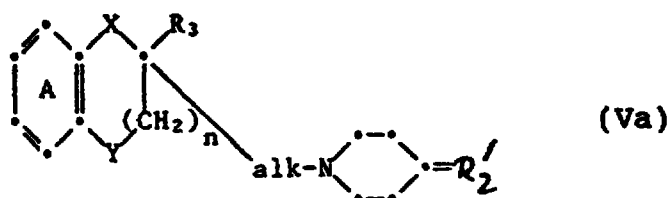


(IV),

in which Y_1 represents a group of the formula $-CH=R_2^1$, $-C(Y_2)=R_2^1$, $-CH(Y_2)-R_2$ or cyano, wherein R_2^1 represents oxo

or imino and Y_2 represents a removable radical, or a salt thereof, is cyclised, or

d) for the manufacture of a compound of the formula I' or a tautomer and/or salt thereof, in which R_2 represents oxo or imino and R_1 is other than hydrogen and represents especially lower alkoxycarbonyl, a compound of the formula

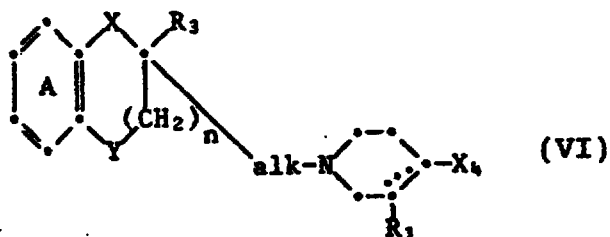


or a tautomer or a salt thereof, is reacted with a compound of the formula



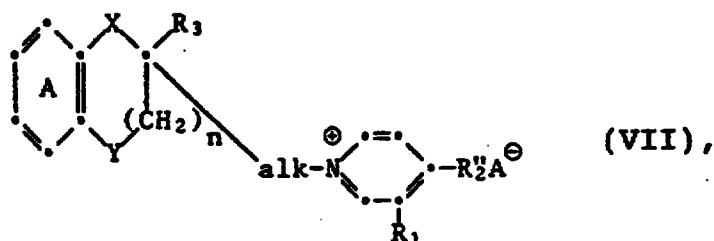
or a salt thereof, in which R_1 is other than hydrogen and X_3 represents halogen or lower alkoxy, or

e) for the manufacture of a compound of the formula I or a tautomer and/or salt thereof, in which R_2 represents hydroxy, lower alkoxy, benzyloxy, C_2 - C_5 alkanoyloxy, lower alkanesulphonyloxy, benzoyloxy, pyridoyloxy, amino, C_2 - C_5 alkanoylamino, lower alkanesulphonylamino, benzoylamino or pyridoylamino, in a compound of the formula



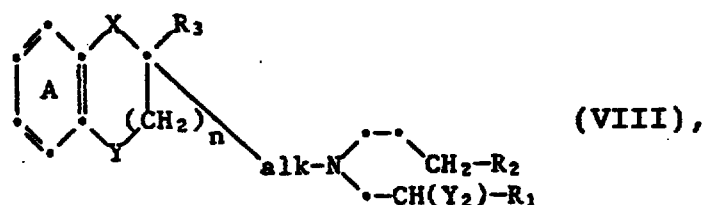
or in a salt thereof, in which X_4 represents a radical that can be converted into R_2 , X_4 is converted into R_2 , or

f) especially for the manufacture of a compound of the formula I or a tautomer and/or salt thereof, in which R_2 is hydrogen, hydroxy, amino, carboxy, lower alkoxy-carbonyl, N-lower alkylcarbamoyl, N,N-di-lower alkyl-carbamoyl or hydroxymethyl, in a compound of the formula



in which $A^{\ominus}$ represents the anion of an acid and R_2^H represents hydrogen, lower alkoxy, benzyloxy, C_2 - C_5 -alkanoyloxy, lower alkanesulphonyloxy, benzoyloxy, pyridoyloxy, protected hydroxy, C_2 - C_5 alkanoylamino, lower alkanesulphonylamino, benzoylamino, pyridoylamino, protected amino, carboxy, lower alkoxy-carbonyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, C_2 - C_5 -alkanoyloxymethyl, lower alkanesulphonyloxymethyl, benzoyloxymethyl, pyridoyloxymethyl or etherified or protected hydroxymethyl, the excess double bonds are reduced to single bonds, or

g) for the manufacture of a compound of the formula I or a tautomer and/or salt thereof, in which R_2 represents carboxy, N-lower alkylcarbamoyl, N,N-di-lower alkyl-carbamoyl or especially lower alkoxy-carbonyl, a compound of the formula



in which Y_2 represents a removable radical, or a salt thereof, is cyclised, and in the case of each of

processes a) to g), a protecting group which may be present is removed, and, if desired, a compound of the formula I obtainable in accordance with the process or by other means is converted into a different compound of the formula I, an isomeric mixture obtainable in accordance with the process is separated into the components, an enantiomeric or diastereoisomeric mixture obtainable in accordance with the process is separated into the enantiomers or diastereoisomers, respectively, and/or a free compound of the formula I obtainable in accordance with the process is converted into a salt or a salt obtainable in accordance with the process is converted into the free compound of the formula I or into a different salt, radicals designated "lower" having from 1 up to and including 4 carbon atoms.

The reactions described in the variants hereinbefore and hereinafter are carried out in a manner known per se, for example in the absence, or customarily in the presence, of a suitable solvent or diluent or a mixture thereof, the reactions being carried out, as necessary, while cooling, at room temperature or while heating, for example in a temperature range of from approximately -10° to the boiling temperature of the reaction medium, preferably at from approximately 20° to approximately 150° , and, if necessary, in a closed vessel, under pressure, in an inert gas atmosphere and/or under anhydrous conditions.

The starting materials of the formulae IIa and IIb, III, IV, Va and Vb, VI, VII and VIII, which are mentioned hereinbefore and hereinafter and which were developed for the manufacture of the compounds of the formula I or their tautomers and/or salts, are in some cases known or

they can be manufactured likewise by methods known per se, for example analogously to the process variants described hereinbefore.

Starting materials having basic centres may, for example, be in the form of acid addition salts, for example with the acids listed hereinbefore, whilst starting compounds having acidic groups may form salts with bases, for example of the kind mentioned hereinbefore. Starting compounds may also be in the form of tautomers, especially compounds of the formula IIb wherein R_2 represents hydroxy and the dotted line is intended to indicate the presence of a double bond between the carbon atoms carrying the radicals R_1 and R_2 .

Variant a):

Reactive esterified hydroxy is especially hydroxy esterified by a strong inorganic acid or organic sulphonic acid, for example halogen, such as chlorine, bromine or iodine, sulphonyloxy, such as hydroxy-sulphonyloxy, halosulphonyloxy, for example fluoro-sulphonyloxy, lower alkanesulphonyloxy optionally substituted, for example, by halogen, for example methane- or trifluoromethane-sulphonyloxy, cycloalkane-sulphonyloxy, for example cyclohexanesulphonyloxy, or benzenesulphonyloxy optionally substituted, for example, by lower alkyl or by halogen, for example *p*-bromophenyl- or *p*-toluene-sulphonyloxy.

The N-alkylation is carried out especially in the presence of a condensation agent, such as a suitable base. Suitable bases are, for example, alkali metal hydroxides, hydrides, amides, alkoxides, carbonates, triphenylmethyllides, di-lower alkylamides, amino-lower

alkylamides or lower alkylsilylamides, or naphthalene-amines, lower alkylamines, basic heterocycles, ammonium hydroxides and carbocyclic amines. There may be mentioned by way of example: sodium hydroxide, hydride, amide or ethoxide, potassium tert.-butoxide or carbonate, lithium triphenylmethyllide, lithium diisopropylamide, potassium 3-(aminopropyl)-amide or bis-(trimethylsilyl)-amide, or dimethylaminonaphthalene, di- or tri-ethylamine, pyridine, benzyltrimethylammonium hydroxide, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU).

The starting materials of the formulae IIa and IIb are in some cases known or they can be manufactured analogously to the known starting materials.

Variant b):

A radical X_2 that can be converted into R_1 that is other than hydrogen, or a radical X_5 that can be converted into a radical R_b is, for example, functionally modified carboxy other than R_1 or R_b , respectively, such as cyano, anhydridised carboxy, optionally substituted amidino, optionally esterified or anhydridised carboximidoyl, esterified or amidated carboxy other than esterified or amidated carboxy R_1 , tri-lower alkoxy- or trihalo-methyl.

Anhydridised carboxy is, for example, carboxy anhydridised with a mineral acid, such as a hydrohalic acid, or with a carboxylic acid, such as an optionally substituted lower alkanoic or benzoic acid or with a carbonic acid halide lower alkyl semiester. As examples there may be mentioned: halocarbonyl, such as chlorocarbonyl, lower alkanoyloxycarbonyl, such as acetoxycarbonyl, or lower alkoxycarbonyloxycarbonyl, such as ethoxycarbonyloxy-

carbonyl.

Substituted amidino is, for example, amidino substituted by an aliphatic radical, for example lower alkyl, such as lower alkylamidino, for example ethylamidino.

Esterified or anhydridised carboximidoyl is to be understood as being, for example, alkoxy- or halo-carboximidoyl, for example lower alkoxy-, such as ethoxy-, or chloro-carboximidoyl, respectively.

Tri-lower alkoxy- or trihalo-methyl is, for example, trimethoxymethyl or trichloromethyl, respectively.

Radicals R_D are, for example, carboxy, lower alkoxy-carbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl or optionally acylated hydroxymethyl radicals R_2 .

X_2 can be converted into R_1 that is other than hydrogen, for example, by solvolysis, just as X_5 can be converted into a radical R_D , for example, by solvolysis.

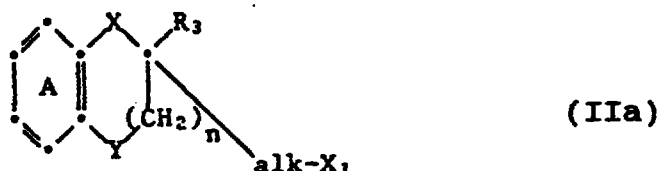
Solvolysis agents are, for example, water, lower alkanols corresponding to the desired esterified carboxy R_1 and R_2 , ammonia, or amines corresponding to the desired amidated carboxy group R_1 and R_2 . The treatment with a corresponding solvolysis agent is optionally carried out in the presence of an acid or base. Suitable acids are, for example, inorganic or organic protonic acids, such as mineral acids, for example sulphuric acid or a hydrohalic acid, for example hydrochloric acid, sulphonic acids, for example lower alkanesulphonic or optionally substituted benzenesulphonic acids, for example methane- or p-toluene-sulphonic acid, or carboxylic acids, for example

lower alkanecarboxylic acids, for example acetic acid, whilst as bases there may be used, for example, those mentioned under Variant a), especially sodium or potassium hydroxide.

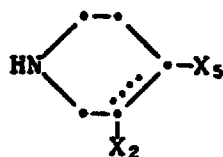
In the solvolysis with water (hydrolysis), the cyano group, anhydridised carboxy, optionally substituted amidino, optionally esterified or anhydridised carboximidoyl, esterified or amidated carboxy other than esterified or amidated carboxy R_1 or R_2 , tri-lower alkoxymethyl or trihalomethyl is hydrolysed to carboxy. Lower alkanoyloxy radicals which may be present at ring A may be hydrolysed to hydroxy in the course of the hydrolysis.

Cyano, anhydridised carboxy, and esterified or amidated carboxy other than esterified or amidated carboxy R_1 or R_2 are alcoholysed, for example with a suitable lower alkanol, to esterified carboxy R_1 and R_2 , respectively, and cyano and anhydridised carboxy are ammonolysed or aminolysed, respectively, for example, with ammonia or with an amine corresponding to the amidated carboxy R_1 or R_2 , respectively.

The starting material of the formula III can be manufactured, for example, in a manner analogous to that described under Variant a) by reacting a compound of the formula



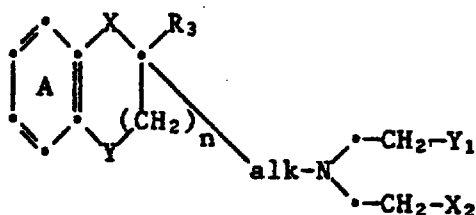
with a compound of the formula



(IIIa),

a tautomer and/or salt thereof, in the presence of one of the mentioned bases.

Compounds of the formula III in which X₂ represents a radical that can be converted into R₁ that is other than hydrogen and X₅ represents hydroxy or amino, can advantageously be manufactured also by cyclisation of a compound of the formula



(IVg),

in which Y₁ represents a group of the formula -CH=R₂['], -C(Y₂)=R₂['], -CH(Y₂)-R₂ or cyano, wherein R₂['] represents oxo or imino, R₂ represents hydroxy or amino, and Y₂ represents a removable radical, or a salt thereof, the operation being carried out, for example, in a manner analogous to that given in Process Variant c).

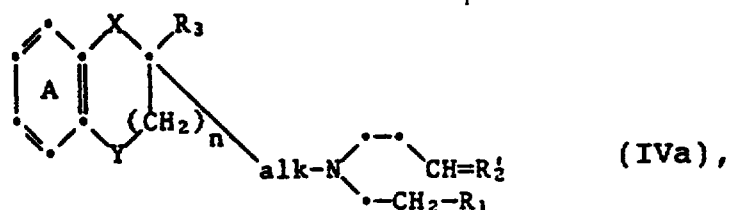
Variant c):

Removable radicals Y₂ in groups of the formula -C(Y₂)=R₂['] or -CH(Y₂)-R₂ are, for example, reactive esterified hydroxy groups, such as hydroxy esterified by a strong inorganic acid or organic sulphonic acid, for example halogen, such as chlorine, bromine or iodine, sulphonyloxy, such as hydroxysulphonyloxy, halosulphonyloxy, for example fluorosulphonyloxy, lower alkanesulphonyloxy

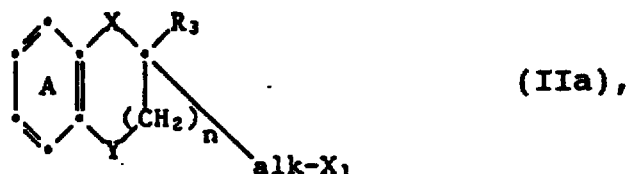
optionally substituted, for example, by halogen, for example methane- or trifluoromethane-sulphonyloxy, cycloalkanesulphonyloxy, for example cyclohexane-sulphonyloxy, or benzenesulphonyloxy optionally substituted, for example, by lower alkyl or by halogen, for example p-bromophenyl- or p-toluene-sulphonyloxy, or etherified hydroxy groups, for example lower alkoxy or optionally substituted phenyl-lower alkoxy.

The cyclisation can be carried out, for example, analogously to the Dieckmann reaction, especially in the presence of one of the bases mentioned in Variant a) and with subsequent working-up by means of hydrolysis.

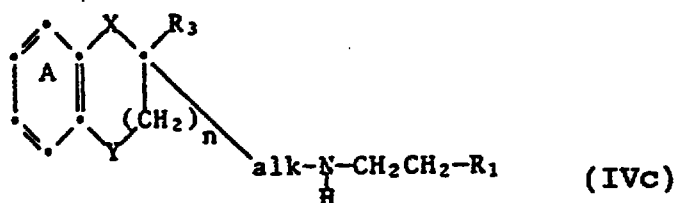
In a preferred embodiment, for example a compound of the formula



in which R_2 represents oxo or imino, can be subjected to treatment with one of the mentioned bases, especially with an alkali metal lower alkoxide, for example with sodium methoxide or sodium ethoxide. During this treatment, the compound IVa cyclises to form a compound of the formula I in which the dotted line indicates the presence of a single bond between the carbon atoms carrying the radicals R_1 and R_2 , and in which R_2 represents hydroxy or amino. Starting materials of the formula IVa are obtained, for example, by reacting a reactive alkyl ester of the formula



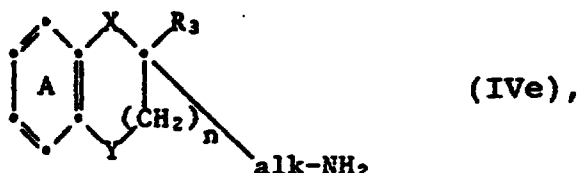
in which X_1 is reactive esterified hydroxy, with a compound of the formula $H_2N-CH_2-CH_2-R_1$ (IVb) and reacting the resulting intermediate of the formula



with acrolein or with an optionally functionally modified aldehyde of the formula $Y_1-CH_2-CH_2-CH=R_2^1$ (IVd; Y_1 = reactive esterified hydroxy; R_2^1 = oxo or imino).

In another preferred form of Variant c), a compound of the formula IV in which Y_1 and R_1 represent lower alkoxy carbonyl, that is to say in which Y_1 represents a group of the formula $-C(Y_2)=R_2^1$, in which R_2^1 represents oxo and the removable radical Y_2 represents etherified hydroxy in the form of a lower alkoxy group, is cyclised to form the corresponding compound of the formula I' in which R_2^1 represents oxo.

For the manufacture of the last-mentioned starting compounds of the formula IV, it is possible to use as starting materials, for example, compounds of the formula



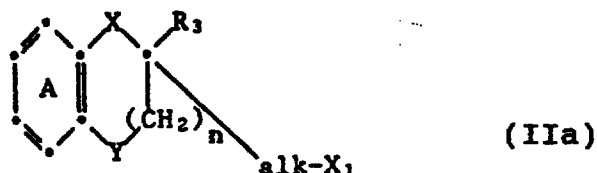
example, radicals that can be converted into a group R_2 by solvolysis, that is to say by reaction with a compound of the formula R_2H or a salt thereof, for example reactive esterified hydroxy groups, such as halogen atoms, for example chlorine, bromine or iodine. Radicals X_4 that can be converted into hydroxy R_2 are also diazonium groups, for example of the formula $-N_2^{\oplus}A^{\ominus}$ in which $A^{\ominus}$ represents the anion of a strong acid, such as a mineral acid, for example the chloride or sulphate ion.

The solvolysis is effected in customary manner, for example in the presence of a base, such as an alkali metal or alkaline earth metal hydroxide, for example sodium or potassium hydroxide, or a tertiary nitrogen base, for example a tri-lower alkylamine, such as triethylamine, or a heteroaromatic nitrogen base, such as pyridine, or a quaternary ammonium hydroxide, such as benzyltrimethylammonium hydroxide, or by using the compound R_2H in the form of a metal salt, for example of the formula $R_2^{\ominus}M^{\oplus}$ (VIb) in which $M^{\oplus}$ represents an alkali metal cation, such as the sodium ion. The operation is advantageously carried out in the presence of a solvent or diluent, for example in an excess of the reactant R_2H and/or in an inert solvent that is miscible with the latter, if necessary while cooling or heating, for example in a temperature range of approximately from 0° to $120^{\circ}C$, and/or under inert gas, such as nitrogen.

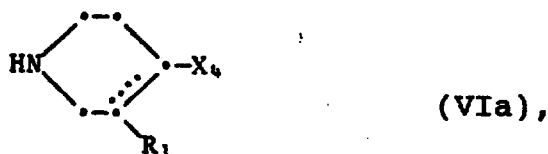
The solvolysis of radicals X_4 to groups R_2 can optionally be combined with the solvolytic conversion of solvolysable groups R_1 into other groups R_1 according to the invention; for example in the ammonolysis of radicals X_4 to amino R_2 , if desired also lower alkoxy carbonyl groups R_1 or other groups R_1 that can be solvolysed to

carbamoyl R_1 can be ammonolysed to form carbamoyl groups R_1 at the same time.

For the manufacture of starting compounds of the formula VI and the salts thereof, for example compounds of the formula IIa



are used as starting materials and are reacted with a corresponding compound of the formula



or with a salt thereof, in the presence of one of the bases mentioned above, the operation being carried out, for example, in a manner analogous to that described in Process Variant a).

In a preferred form, compounds of the formula VI in which X_4 represents halogen and the dotted line indicates the presence of a single bond, and salts thereof, are obtained by reacting a compound of the formula I in which R_2 represents hydroxy and the dotted line indicates the presence of a single bond, or a salt thereof, with a halogenating agent, such as phosphorus trichloride or pentachloride or thionyl chloride, it being possible to obtain the corresponding compounds of the formula I and their salts, for example, in a manner analogous to that

described under Process Variant a) or c).

Variant f):

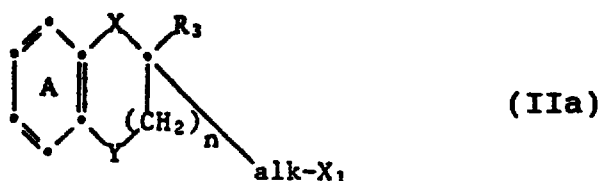
The anion $A^{\ominus}$ is, for example, the anion of a strong protonic acid, for example a halide ion, such as a chloride, bromide or iodide ion, or a sulphonate ion, such as an optionally substituted lower alkane- or benzene-sulphonate ion, for example the methane-sulphonate, ethanesulphonate or p-bromobenzenesulphonate or p-toluenesulphonate ion. R_2^1 is especially hydrogen, etherified hydroxy R_2 or protected hydroxy, but may also be carboxy, lower alkoxy-carbonyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl R_2 or etherified or protected hydroxymethyl. Protected hydroxy is, for example, silyloxy, such as tri-lower alkylsilyloxy, for example trimethylsilyloxy, but may also be triphenyl-lower alkoxy, for example trityloxy. Protected amino is, for example, silylamino, such as tri-lower alkylsilylamino, for example trimethylsilylamino, but may also be phenyl-, diphenyl- or triphenyl-lower alkylamino, such as benzyl-amino, diphenylamino or tritylamino. Etherified hydroxymethyl is, for example, lower alkoxymethyl, such as methoxy- or ethoxy-methyl, or optionally substituted phenyl-lower alkoxymethyl, for example phenyl- C_1 - C_4 -alkoxymethyl substituted in the phenyl moiety, such as benzyloxy-, p-chlorobenzyloxy-, 1-phenylethoxy- or 1-(p-bromophenyl)-n-butoxy-methyl. Protected hydroxymethyl is, for example, silyloxymethyl, such as tri-lower alkylsilyloxy-, for example trimethylsilyloxy-methyl, but may also be triphenyl-lower alkoxy-, for example trityloxy-methyl.

The reduction of the excess double bonds is effected by treatment with a suitable reducing agent, for example by

hydrogenation in the presence of a hydrogenation catalyst, by reduction with a hydride-transfer reagent or by reduction with a metallic reduction system consisting of metal and a proton-removing agent.

Hydrogenation catalysts that come into consideration are, for example, elements of sub-group VIII of the Periodic Table of Elements or derivatives thereof, such as palladium, platinum, platinum oxide, ruthenium, rhodium, tris(triphenylphosphane)rhodium(I) halide, for example chloride, or Raney nickel, which are optionally supported on a carrier, such as activated carbon, alkali metal carbonate or sulphate or a silica gel. Suitable as hydride-transfer reagents are, for example, suitable light metal hydrides, especially alkali metal aluminium hydrides or borohydrides, such as lithium aluminium hydride, lithium triethylborohydride, sodium borohydride, sodium cyanoborohydride, or tin hydrides, such as triethyl- or tributyl-tin hydride, or diborane. The metal component of the metallic reduction system is, for example, a base metal, such as an alkali metal or alkaline earth metal, for example lithium, sodium, potassium, magnesium or calcium, or a transition metal, for example zinc, tin, iron or titanium, whilst as proton-removing agents there are suitable, for example, protonic acids of the kind mentioned hereinbefore, such as hydrochloric or acetic acid, lower alkanols, such as ethanol, and/or amines or ammonia. Such systems are, for example, sodium/ammonia, zinc/hydrochloric acid, zinc/-acetic acid or zinc/ethanol.

The manufacture of starting compounds of the formula VII is effected, for example, by reacting compounds of the formula



in which X_1 represents reactive esterified hydroxy corresponding to the anion $A^{\ominus}$, with compounds of the formula



or with a salt thereof, the operation being carried out, for example, in a manner analogous to that described in Process Variant a).

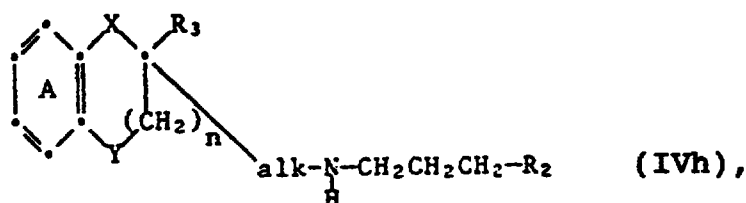
Variant g):

Removable radicals Y_2 in compounds VIII are, for example, reactive esterified hydroxy groups, such as hydroxy esterified by a strong inorganic acid or organic sulphonic acid, for example halogen, such as chlorine, bromine or iodine, sulphonyloxy, such as hydroxysulphonyloxy, halosulphonyloxy, for example fluorosulphonyloxy, lower alkanesulphonyloxy optionally substituted, for example, by halogen, for example methane- or trifluoromethane-sulphonyloxy, cycloalkanesulphonyloxy, for example cyclohexanesulphonyloxy, or benzenesulphonyloxy optionally substituted, for example, by lower alkyl or by halogen, for example p-bromophenyl- or p-toluene-sulphonyloxy, or etherified hydroxy groups, for example lower alkoxy or optionally substituted phenyl-lower alkoxy.

The cyclisation can be carried out, for example, in the

presence of one of the bases mentioned under Variant a), especially in the presence of an alkali metal lower alkoxide, for example with sodium methoxide or ethoxide.

The starting materials VIII are obtained, for example, by reacting a compound of the formula



or a salt thereof, with a compound of the formula $Y_2-CH_2-CH(Y_2)-R_1$ (IVi).

In the starting materials of the formulae IIb, III and IIIa, a hydroxy group R_2 may be in etherified form and a hydroxy or amino group R_2 may also be in intermediately protected form, just as a hydroxymethyl group R_2 in compounds IIb may be in etherified or intermediately protected form. Protected hydroxy is, for example, silyloxy, such as tri-lower alkylsilyloxy, for example trimethylsilyloxy, but may also be triphenyl-lower alkoxy, for example trityloxy. Protected amino is, for example, silylamino, such as tri-lower alkylsilylamino, for example trimethylsilylamino, but may also be phenyl-, diphenyl- or triphenyl-lower alkylamino, such as benzylamino, diphenylmethylamino or tritylamino. Etherified hydroxymethyl is, for example, lower alkoxymethyl, such as methoxy- or ethoxy-methyl, or optionally substituted phenyl-lower alkoxymethyl, for example phenyl-C₁-C₄-alkoxymethyl substituted in the phenyl moiety, such as benzyloxy-, p-chlorobenzyloxy-, 1-phenylethoxy- or 1-(p-

bromophenyl)-n-butoxy-methyl. Protected hydroxymethyl is, for example, silyloxymethyl, such as tri-lower alkylsilyloxy-, for example trimethylsilyloxy-methyl, but may also be triphenyl-lower alkoxy-, for example trityloxy-methyl.

The freeing of intermediately protected radicals R_2 , that is to say the removal of the intermediate protecting groups, is effected in customary manner, for example by solvolysis, such as mild hydrolysis, for example treatment with water under neutral or slightly acidic conditions, for example by the action of dilute aqueous mineral or carboxylic acids, for example dilute hydrochloric or acetic acid. The freeing of intermediately protected hydroxy, amino or hydroxymethyl groups R_2^H in starting materials of the formula VII and VIIa is effected in analogous manner.

Compounds of the formula I that are obtainable according to the process or by other means can be converted in customary manner into other compounds of the formula I.

For example, esterified or amidated carboxy groups R_1 and R_2 can be hydrolysed to carboxy R_1 and R_2 , respectively, in customary manner, for example in the presence of a basic or acidic hydrolysis agent, such as an alkali metal hydroxide or carbonate, for example sodium hydroxide or potassium carbonate, or a mineral acid, for example hydrochloric acid or sulphuric acid. Esterified carboxy groups R_1 and R_2 can also be converted into other esterified carboxy groups R_1 and R_2 , respectively, by transesterification, that is to say treatment with an alcohol in the presence of an acidic or basic solvolysis agent, such as a mineral acid, for example sulphuric

acid, or a corresponding alkali metal alcoholate or an alkali metal hydroxide, or converted into amidated carboxy R_1 and R_2 , respectively, by reaction with ammonia or with a corresponding amine having at least one hydrogen atom.

Free carboxy R_1 and R_2 can be converted into esterified carboxy R_1 and R_2 , respectively, in customary manner, for example by treatment with a corresponding alcohol in the presence of a mineral acid, for example sulphuric acid, or by conversion into a halide and subsequent reaction with a corresponding alcohol, for example in the presence of pyridine or triethylamine, or by conversion into an alkali metal salt and subsequent reaction with a reactive ester of the corresponding alcohol, such as a corresponding halide. Likewise, a carboxy compound can be esterified with a corresponding alcohol using a dehydrating agent, such as N,N'-dicyclohexylcarbodiimide. Free or esterified carboxy R_1 and R_2 can be converted into amidated carboxy R_1 and R_2 , respectively, also by reaction with ammonia or an amine having at least one hydrogen atom and dehydration of the intermediately formed ammonium salt, for example by heating or by means of a dehydrating agent, such as N,N'-dicyclohexylcarbodiimide, or by conversion into the halide and subsequent reaction with ammonia or with an amine having at least one hydrogen atom.

Furthermore, hydroxy groups which may be present can be esterified, for example converted by treatment with a lower alkanecarboxylic acid anhydride or halide into lower alkanoyloxy, or converted by reaction with a reactive ester, especially a hydrobromic or hydrochloric acid ester, of a lower alkanol into corresponding

etherified hydroxy. Conversely, in esterified or etherified hydroxy, such as lower alkanoyloxy or lower alkoxy, the hydroxy group(s) may be freed by solvolysis, preferably under acidic conditions. In an analogous manner, it is also possible to hydrolyse etherified or acylated hydroxy R_2 to hydroxy.

In corresponding manner, furthermore hydroxymethyl R_1 and R_2 can be esterified, for example converted by treatment with a lower alkanecarboxylic acid anhydride or halide into lower alkanoyloxymethyl R_1 and R_2 , respectively. Conversely, the hydroxy group may be freed from acylated hydroxymethyl R_1 and R_2 , for example lower alkanoyloxy-methyl, by solvolysis, preferably under acidic conditions.

Furthermore, hydroxymethyl R_1 and R_2 can be converted in customary manner into lower alkoxycarbonyl, N-lower alkylcarbamoyl or N,N-di-lower alkylcarbamoyl R_1 and R_2 , respectively, or into carbamoyl R_1 , the operation being carried out, for example, by first oxidising hydroxymethyl R_1 and R_2 to carboxy in customary manner, for example in the presence of an oxidising agent, such as potassium permanganate or potassium dichromate, and then: converting the carboxy group into lower alkoxycarbonyl R_1 and R_2 , respectively, in customary manner, for example by treatment with a corresponding alcohol in the presence of a mineral acid, for example sulphuric acid, or by conversion into a halide and subsequent reaction with a corresponding alcohol, for example in the presence of pyridine or triethylamine, or by conversion into an alkali metal salt and subsequent reaction with a reactive ester of the corresponding alcohol, such as a corresponding halide, or by using a dehydrating agent, such as

N,N'-dicyclohexylcarbodiimide, with a corresponding alcohol; or converting the carboxy group into amidated carboxy R_1 and R_2 , respectively, by reaction with ammonia or an amine having at least one hydrogen atom and dehydration of the intermediately formed ammonium salt, for example by heating or by means of a dehydrating agent, such as N,N'-dicyclohexylcarbodiimide, or by conversion into the halide and subsequent reaction with ammonia or with an amine having at least one hydrogen atom. It is also possible to convert acylated hydroxymethyl R_1 and R_2 into esterified or amidated carboxy R_1 and R_2 , respectively, by first freeing the acylated hydroxymethyl group by solvolysis, for example in the manner described above, and then converting the resulting free hydroxymethyl group, in the manner described above, into a carboxy group and converting the latter further into an esterified or amidated carboxy group.

Conversely, esterified or amidated carboxy groups R_1 and R_2 can be converted into optionally acylated hydroxymethyl R_1 and R_2 , respectively, by first hydrolysing the esterified or amidated carboxy group R_1 and R_2 to carboxy in customary manner, for example in the presence of a basic or acidic hydrolysis agent, such as an alkali metal hydroxide or carbonate, for example sodium hydroxide or potassium carbonate, or a mineral acid, for example hydrochloric acid or sulphuric acid, and then reducing the resulting carboxy group in customary manner, for example in the presence of a reducing agent, for example of the kind mentioned above, to hydroxymethyl R_1 and R_2 , respectively, and, if desired, the latter can then be converted into acylated hydroxymethyl R_1 and R_2 , respectively, for example in the manner described above.

If the dotted line indicates the presence of a double

bond between the carbon atoms carrying the radicals R_1 and R_2 in the compounds according to the invention, this bond can be hydrogenated to a single bond, for example in a manner known per se using a reducing agent, for example of the kind mentioned in Variant f).

Furthermore, a compound according to the invention in which the dotted line indicates the presence of a double bond between the carbon atoms carrying the radicals R_1 and R_2 , and R_2 represents hydrogen can be converted into a corresponding piperidine compound according to the invention, for example in a manner known per se by the addition of a compound R_2 -H in which R_2 represents an optionally etherified or acylated hydroxy group or an optionally acylated amino group. The addition is carried out especially in the presence of a suitable base, for example of the kind mentioned under Variant a).

Conversely, compounds according to the invention in which the dotted line indicates the presence of a single bond between the carbon atoms carrying the radicals R_1 and R_2 can be converted in a manner known per se into corresponding tetrahydropyridine compounds according to the invention in which R_2 represents hydrogen, for example by elimination of a compound R_2 -H in which R_2 represents an optionally etherified or acylated hydroxy group or an optionally acylated amino group. Leaving groups R_2 that are less suitable for elimination, for example hydroxy, can first be converted, for example in situ, into more suitable leaving groups R_2 , for example lower alkane-sulphonyloxy, such as methanesulphonyloxy, or halogen, such as chlorine, bromine or iodine. The elimination is effected especially in the presence of a suitable base, for example of the kind mentioned under Variant a).

Salts of compounds of the formula I and of their tautomers can be manufactured in a manner known per se. Thus, for example, acid addition salts of compounds of the formula I are obtained by treatment with an acid or a suitable ion exchange reagent. Salts can be converted into the free compounds of the formula I in customary manner; for example acid addition salts can be converted by treatment with a suitable basic agent.

Depending upon the procedure and reaction conditions, the compounds of the formula I according to the invention having salt-forming, especially basic, properties may be obtained in free form or in the form of salts.

As a result of the close relationship between the novel compound of the formula I in free form and in the form of its salts, hereinbefore and hereinafter the free compound of the formula I or its salts should be understood as meaning optionally also the corresponding salts or the free compound of the formula I, respectively, where appropriate and expedient.

The novel compounds of the formula I, including the salts of salt-forming compounds, can also be obtained in the form of their hydrates or may include other solvents, for example those used for the crystallisation of compounds in solid form.

Depending upon the starting materials and procedures chosen, the novel compounds of the formula I may be in the form of one of the possible isomers or in the form of a mixture thereof. Depending upon the molecular symmetry, for example depending upon the number and the

absolute and relative configuration of the chiral centres, such as asymmetric carbon atoms, there may be obtained as pure isomers, for example, pure enantiomers and/or pure diastereoisomers, such as pure cis/trans-isomers or meso-compounds. Accordingly, as isomeric mixtures there may be obtained, for example, enantiomeric mixtures, such as racemates, diastereoisomeric mixtures or mixtures of racemates.

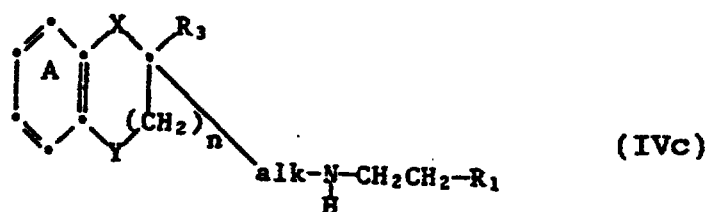
Resulting diastereoisomeric mixtures and mixtures of racemates can be separated into the pure diastereoisomers or racemates in known manner on the basis of the physico-chemical differences between the constituents, for example by fractional crystallisation.

Resulting enantiomeric mixtures, such as racemates, can be separated into the enantiomers according to known methods, for example by recrystallisation from an optically active solvent, by chromatography using chiral adsorbents, with the aid of suitable microorganisms, by cleaving with specific, immobilised enzymes, by means of the formation of inclusion compounds, for example using chiral Crown ethers, in which case only one enantiomer is complexed, or by conversion into diastereoisomeric salts, for example by reaction of a basic end product racemate with an optically active acid, such as a carboxylic acid, for example tartaric or malic acid, or a sulphonic acid, for example camphorsulphonic acid, and separation of the mixture of diastereoisomers obtained in this manner, for example on the basis of their different solubilities, into the diastereoisomers, from which the desired enantiomer can be freed by the action of suitable agents. Advantageously, the more active enantiomer is isolated.

The invention also relates to those forms of the process according to which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining steps are carried out, or a starting material is used in the form of a derivative or salt and/or its racemates or enantiomers or, especially, is formed under the reaction conditions.

In the process of the present invention it is preferable to use those starting materials which result in the compounds of the formula I described at the beginning as being especially valuable. The invention relates also to novel starting materials which were developed specifically for the manufacture of the compounds of the formula I according to the invention, to their use and to processes for their manufacture, the variables R_1 , R_2 , R_3 , X, Y, n and alk and the substituents of the ring A and the dotted line having the meanings indicated for the groups of compounds of the formula I that are preferred in each case.

In this connection, special mention should be made of compounds of the formula



and their salts. These likewise have nootropic properties in a degree of action comparable with that of the

corresponding compounds of the formulae I and I' and can likewise be used as nootropic active ingredients in medicaments.

Accordingly, the invention relates also to pharmaceutical, especially nootropic, preparations comprising as active ingredient a compound of the formula IVc in which R_1 represents carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, hydroxymethyl, C_2 - C_5 alkanoyloxymethyl, lower alkanesulphonyloxymethyl, benzoyloxymethyl or pyridoyloxymethyl, R_3 represents hydrogen or C_1 - C_7 alkyl, alk represents lower alkylene or lower alkylidene, the ring A is unsubstituted or is mono- or poly-substituted by hydroxy, lower alkoxy, C_2 - C_5 alkanoyloxy, halogen having an atomic number of up to and including 53, C_1 - C_7 alkyl and/or by trifluoromethyl, and either each of X and Y represents an oxygen atom and n represents 1, or X represents a methylene group, Y represents an oxygen atom and n represents 1, or X represents an oxygen atom, Y represents a methylene group and n represents 1, or X represents a direct bond, Y represents an oxygen atom and n represents 2, or a pharmaceutically acceptable salt thereof, to the use of the mentioned compounds of the formula IVc or their pharmaceutically acceptable salts for the manufacture of nootropic pharmaceutical preparations, to a method for the treatment of the symptoms of cerebral insufficiency, characterised in that one of the mentioned compounds of the formula IVc, or a pharmaceutically acceptable salt thereof, is administered, and to compounds of the formula IVc in which R_1 represents carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, hydroxymethyl, C_2 - C_5 alkanoyloxymethyl, lower alkanesulphonyloxy-

methyl, benzyloxymethyl or pyridoyloxymethyl, R_3 represents hydrogen or C_1 - C_7 alkyl, alk represents lower alkylene or lower alkylidene, the ring A is unsubstituted or is mono- or poly-substituted by hydroxy, lower alkoxy, C_2 - C_5 alkanoyloxy, halogen having an atomic number of up to and including 53, C_1 - C_7 alkyl and/or by trifluoromethyl, and either each of X and Y represents an oxygen atom and n represents 1, or X represents a methylene group, Y represents an oxygen atom and n represents 1, or X represents an oxygen atom, Y represents a methylene group and n represents 1, or X represents a direct bond, Y represents an oxygen atom and n represents 2, with the proviso that in compounds of the formula IVc in which the ring A is unsubstituted, each of X and Y represents oxygen, n represents 1 and R_3 represents hydrogen, alk is other than methylene if R_1 represents carbamoyl or N-methyl-, N-ethyl-, N,N-dimethyl- or N,N-diethyl-carbamoyl, and to their salts, and to a process for the manufacture of the latter, novel compounds of the formula IVc and their salts, radicals designated "lower" having from 1 up to and including 4 carbon atoms.

Accordingly, the invention relates, for example, also to pharmaceutical, especially nootropic, preparations comprising as active ingredient a compound of the formula IVc in which R_1 represents carboxy, lower alkoxy-carbonyl, carbamoyl, N-lower alkylcarbamoyl or N,N-di-lower alkylcarbamoyl, R_3 represents hydrogen or C_1 - C_7 alkyl, alk represents lower alkylene or lower alkylidene, the ring A is unsubstituted or is mono- or poly-substituted by hydroxy, lower alkoxy, C_2 - C_5 alkanoyloxy, halogen having an atomic number of up to and including 53, C_1 - C_7 alkyl and/or by trifluoromethyl, X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n

represents 1, or a pharmaceutically acceptable salt thereof, to the use of the mentioned compounds of the formula IVc or their pharmaceutically acceptable salts for the manufacture of nootropic pharmaceutical preparations, to a method for the treatment of the symptoms of cerebral insufficiency, characterised in that one of the mentioned compounds of the formula IVc, or a pharmaceutically acceptable salt thereof, is administered, and to compounds of the formula IVc in which R_1 represents carboxy, lower alkoxy carbonyl, carbamoyl, N-lower alkyl carbamoyl or N,N-di-lower alkyl carbamoyl, R_3 represents hydrogen or C_1 - C_7 alkyl, alk represents lower alkylene or lower alkylidene, the ring A is unsubstituted or is mono- or poly-substituted by hydroxy, lower alkoxy, C_2 - C_5 alkanoyloxy, halogen having an atomic number of up to and including 53, C_1 - C_7 alkyl and/or by trifluoromethyl, X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n represents 1, with the proviso that in compounds of the formula IVc in which the ring A is unsubstituted, each of X and Y represents oxygen, n represents 1 and R_3 represents hydrogen, alk is other than methylene if R_1 represents carbamoyl or N-methyl-, N-ethyl-, N,N-dimethyl- or N,N-diethyl-carbamoyl, and to their salts, and to a process for the manufacture of the latter, novel compounds of the formula IVc and their salts, radicals designated "lower" having from 1 up to and including 4 carbon atoms.

The variables in the formula IVc have, for example, the preferred meanings given under formula I.

The invention relates in this respect especially to pharmaceutical, especially nootropic, preparations and to the manufacture thereof and to methods of treatment,

characterised in that there is selected a compound of the formula IVc in which R₁ represents carboxy, lower alkoxy carbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, hydroxymethyl, C₂-C₅alkanoyloxy-methyl, lower alkanesulphonyloxymethyl, benzoyloxymethyl or pyridoyloxymethyl, R₃ represents hydrogen or C₁-C₇-alkyl, alk represents lower alkylene that links the ring system with the NH group shown in formula IVc by up to and including 3 carbon atoms, or alk represents lower alkylidene, the ring A is unsubstituted or is mono-, di- or poly-substituted by hydroxy, lower alkoxy, C₂-C₅-alkanoyloxy, halogen having an atomic number of up to and including 53, C₁-C₇alkyl and/or by trifluoromethyl, and either each of X and Y represents an oxygen atom and n represents 1, or X represents a methylene group, Y represents an oxygen atom and n represents 1, or X represents an oxygen atom, Y represents a methylene group and n represents 1, or X represents a direct bond, Y represents an oxygen atom and n represents 2, or one of the pharmaceutically acceptable salts thereof, and to compounds of the formula IVc in which R₁ represents carboxy, lower alkoxy carbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, hydroxymethyl, C₂-C₅alkanoyloxymethyl, lower alkanesulphonyloxymethyl, benzoyloxymethyl or pyridoyloxymethyl, R₃ represents hydrogen or C₁-C₇alkyl, alk represents lower alkylene that links the ring system with the NH group shown in formula IVc by up to and including 3 carbon atoms, or alk represents lower alkylidene, the ring A is unsubstituted or is mono-, di- or poly-substituted by hydroxy, lower alkoxy, C₂-C₅alkanoyloxy, halogen having an atomic number of up to and including 53, C₁-C₇alkyl and/or by trifluoromethyl, and either each of X and Y represents an oxygen atom and n represents 1, or X

represents a methylene group, Y represents an oxygen atom and n represents 1, or X represents an oxygen atom, Y represents a methylene group and n represents 1, or X represents a direct bond, Y represents an oxygen atom and n represents 2, with the proviso that in compounds of the formula IVc in which the ring A is unsubstituted, each of X and Y represents oxygen, n represents 1 and R_3 represents hydrogen, alk is other than methylene if R_1 represents carbamoyl or N-methyl-, N-ethyl-, N,N-dimethyl- or N,N-diethyl-carbamoyl, and to their salts, and to a process for the manufacture of the latter, novel compounds of the formula IVc and their salts, radicals designated "lower" having from 1 up to and including 4 carbon atoms, for example to pharmaceutical, especially nootropic, preparations and to the manufacture thereof and to methods of treatment, characterised in that there is selected a compound of the formula IVc in which R_1 represents carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl or N,N-di-lower alkylcarbamoyl, R_3 represents hydrogen or C_1 - C_7 alkyl, alk represents lower alkylene that links the ring system with the NH group shown in formula IVc by up to and including 3 carbon atoms, or alk represents lower alkylidene, the ring A is unsubstituted or is mono-, di- or poly-substituted by hydroxy, lower alkoxy, C_2 - C_5 alkanoyloxy, halogen having an atomic number of up to and including 53, C_1 - C_7 alkyl and/or by trifluoromethyl, X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n represents 1, or one of the pharmaceutically acceptable salts thereof, and to compounds of the formula IVc in which R_1 represents carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl or N,N-di-lower alkylcarbamoyl, R_3 represents hydrogen or C_1 - C_7 alkyl, alk represents lower alkylene that links the ring system

with the NH group shown in formula IVc by up to and including 3 carbon atoms, or alk represents lower alkylidene, the ring A is unsubstituted or is mono-, di- or poly-substituted by hydroxy, lower alkoxy, C₂-C₅alkanoyloxy, halogen having an atomic number of up to and including 53, C₁-C₇alkyl and/or by trifluoromethyl, X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n represents 1, with the proviso that in compounds of the formula IVc in which the ring A is unsubstituted, each of X and Y represents oxygen, n represents 1 and R₃ represents hydrogen, alk is other than methylene if R₁ represents carbamoyl or N-methyl-, N-ethyl-, N,N-dimethyl- or N,N-diethyl-carbamoyl, and to their salts, and to a process for the manufacture of the latter, novel compounds of the formula IVc and their salts, radicals designated "lower" having from 1 up to and including 4 carbon atoms.

In this respect the invention relates more especially to pharmaceutical, especially nootropic, preparations and to the manufacture thereof and to methods of treatment, characterised in that there is selected a compound of the formula IVc in which R₁ represents carboxy, hydroxymethyl, C₂-C₅alkanoyloxymethyl, such as acetoxymethyl, C₁-C₄alkoxycarbonyl, such as methoxycarbonyl, or carbamoyl, R₃ represents hydrogen or C₁-C₄alkyl, such as methyl, alk represents C₁-C₄alkylene that links the ring system with the NH group shown in formula IVc by up to and including 3 carbon atoms, such as methylene or ethylene, the ring A is unsubstituted or is substituted, especially in the 7-position, by C₁-C₄alkoxy, such as methoxy, and either each of X and Y represents an oxygen atom and n represents 1, or X represents a methylene group, Y represents an oxygen atom and n represents 1, or

X represents an oxygen atom, Y represents a methylene group and n represents 1, or X represents a direct bond, Y represents an oxygen atom and n represents 2, or one of the pharmaceutically acceptable salts thereof, and to compounds of the formula IVc in which R_1 represents carboxy, hydroxymethyl, C_2-C_5 alkanoyloxymethyl, such as acetoxymethyl, C_1-C_4 alkoxycarbonyl, such as methoxycarbonyl, or carbamoyl, R_3 represents hydrogen or C_1-C_4 -alkyl, such as methyl, alk represents C_1-C_4 alkylene that links the ring system with the NH group shown in formula IVc by up to and including 3 carbon atoms, such as methylene or ethylene, the ring A is unsubstituted or is substituted, especially in the 7-position, by C_1-C_4 -alkoxy, such as methoxy, and either each of X and Y represents an oxygen atom and n represents 1, or X represents a methylene group, Y represents an oxygen atom and n represents 1, or X represents an oxygen atom, Y represents a methylene group and n represents 1, or X represents a direct bond, Y represents an oxygen atom and n represents 2, with the proviso that in compounds of the formula IVc in which the ring A is unsubstituted, each of X and Y represents oxygen, n represents 1 and R_3 represents hydrogen, alk is other than methylene if R_1 represents carbamoyl, and to their salts, and to a process for the manufacture of the latter, novel compounds of the formula IVc and their salts, for example to pharmaceutical, especially nootropic, preparations and to the manufacture thereof, and to methods of treatment, characterised in that there is selected a compound of the formula IVc in which R_1 represents C_1-C_4 -alkoxycarbonyl, such as methoxycarbonyl, R_3 represents hydrogen or C_1-C_4 alkyl, such as methyl, alk represents C_1-C_4 alkylene that links the ring system with the NH group shown in formula IVc by up to and including 3

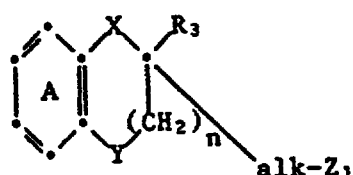
carbon atoms, such as methylene or ethylene, the ring A is unsubstituted, X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n represents 1, or one of the pharmaceutically acceptable salts thereof, and to compounds of the formula IVc in which R_1 represents C_1 - C_4 alkoxycarbonyl, such as methoxycarbonyl, R_3 represents hydrogen or C_1 - C_4 alkyl, such as methyl, alk represents C_1 - C_4 alkylene that links the ring system with the NH group shown in formula IVc by up to and including 3 carbon atoms, such as methylene or ethylene, the ring A is unsubstituted, X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n represents 1, and to their salts, and to a process for the manufacture of the latter, novel compounds of the formula IVc and their salts.

In this respect the invention relates most especially to pharmaceutical, especially nootropic, preparations and to the manufacture thereof, and to methods of treatment, characterised in that there is selected a compound of the formula IVc in which R_1 represents C_1 - C_4 alkoxycarbonyl, such as methoxycarbonyl, R_3 represents hydrogen, alk represents methylene or ethylene, the ring A is unsubstituted, X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n represents 1, or one of the pharmaceutically acceptable salts thereof, and to compounds of the formula IVc in which R_1 represents C_1 - C_4 alkoxycarbonyl, such as methoxycarbonyl, R_3 represents hydrogen, alk represents methylene or ethylene, the ring A is unsubstituted, X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n represents 1, and to their salts, and to a process for the manufacture of the latter, novel compounds of the formula IVc and their salts.

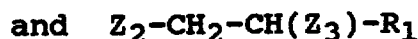
In this respect the invention relates specifically to pharmaceutical, especially nootropic, preparations and to the manufacture thereof and to methods of treatment, characterised in that there is selected one of the novel compounds of the formula IVc mentioned in the Examples, or one of the pharmaceutically acceptable salts thereof, and to the novel compounds of the formula IVc mentioned in the Examples and to their salts, and to processes for the manufacture of the latter, novel compounds of the formula IVc and their salts.

The present invention relates also to a process for the manufacture of compounds of the formula IVc and their salts, for example characterised in that

h) compounds of the formulae



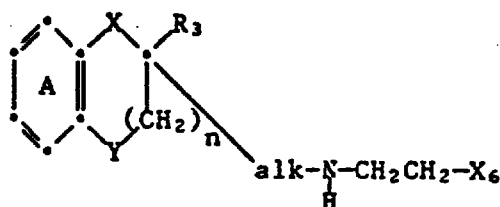
(VIIIa)



(VIIIb),

in which one of the radicals Z_1 and Z_2 represents reactive esterified hydroxy and the other represents amino and Z_3 represents hydrogen, or Z_1 represents amino and Z_2 and Z_3 together represent an additional bond, or optionally salts of these compounds, are reacted with one another, or

i) in a compound of the formula



(IX)

in which X_6 represents a radical that can be converted into R_1 , or in a salt thereof, X_6 is converted into R_1 , and, if desired, in the case of each of processes h) and i), a compound of the formula IVc obtainable in accordance with the process or by other means is converted into a different compound of the formula IVc, an isomeric mixture obtainable in accordance with the process is separated into the components, an enantiomeric or diastereoisomeric mixture obtainable in accordance with the process is separated into the enantiomers or diastereoisomers, respectively, and/or a free compound of the formula IVc obtainable in accordance with the process is converted into a salt or a salt obtainable in accordance with the process is converted into the free compound of the formula IVc or into a different salt.

Variant h):

Reactive esterified hydroxy Z_1 and Z_2 is especially hydroxy esterified by a strong inorganic acid or organic sulphonic acid, for example halogen, such as chlorine, bromine or iodine, sulphonyloxy, such as hydroxy-sulphonyloxy, halosulphonyloxy, for example fluoro-sulphonyloxy, lower alkanesulphonyloxy optionally substituted, for example, by halogen, for example methane- or trifluoromethane-sulphonyloxy, cycloalkane-sulphonyloxy, for example cyclohexanesulphonyloxy, or benzenesulphonyloxy optionally substituted, for example, by lower alkyl or by halogen, for example p-bromophenyl- or p-toluene-sulphonyloxy.

The reaction is in this case carried out especially in the presence of a condensation agent, such as a suitable base. Suitable bases are, for example, alkali metal

hydroxides, hydrides, amides, alkoxides, carbonates, triphenylmethylenes, di-lower alkylamides, amino-lower alkylamides or lower alkylsilylamides, or naphthalene-amines, lower alkylamines, basic heterocycles, ammonium hydroxides and carbocyclic amines. There may be mentioned by way of example: sodium hydroxide, hydride, amide or ethoxide, potassium tert.-butoxide or carbonate, lithium triphenylmethylenide, lithium diisopropylamide, potassium 3-(aminopropyl)-amide or bis-(trimethylsilyl)-amide, or dimethylaminonaphthalene, di- or tri-ethylamine, pyridine, benzyltrimethylammonium hydroxide, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU). The reaction of amines VIIIA (Z_1 = amino) with acrylic acid compounds VIIIB ($Z_2 + Z_3$ = bond) is effected, for example, while heating, for example at approximately 60-120°C.

The starting materials of the formulae VIIIA and VIIIB are known or they can be manufactured analogously to known methods.

Variant i):

A radical X_6 that can be converted into R_1 is, for example, functionally modified carboxy other than R_1 , such as cyano, anhydridised carboxy, optionally substituted amidino, optionally esterified or anhydridised carboximidoyl, esterified or amidated carboxy other than esterified or amidated carboxy R_1 , tri-lower alkoxymethyl or trihalomethyl.

Anhydridised carboxy is, for example, carboxy anhydridised with a mineral acid, such as a hydrohalic acid, or with a carboxylic acid, such as an optionally substituted lower alkanolic or benzoic acid, or with a carbonic acid

halide lower alkyl semiester. As examples there may be mentioned: halocarbonyl, such as chlorocarbonyl, lower alkanoyloxy carbonyl, such as acetoxycarbonyl, or lower alkoxy carbonyloxy carbonyl, such as ethoxycarbonyloxy carbonyl.

Substituted amidino is, for example, amidino substituted by an aliphatic radical, for example lower alkyl, such as lower alkylamidino, for example ethylamidino.

Esterified or anhydridised carboximidoyl is to be understood as being, for example, alkoxy- or halocarboximidoyl, for example lower alkoxy-, such as ethoxy-, or chloro-carboximidoyl, respectively.

Tri-lower alkoxy- or trihalo-methyl is, for example, trimethoxymethyl or trichloromethyl, respectively.

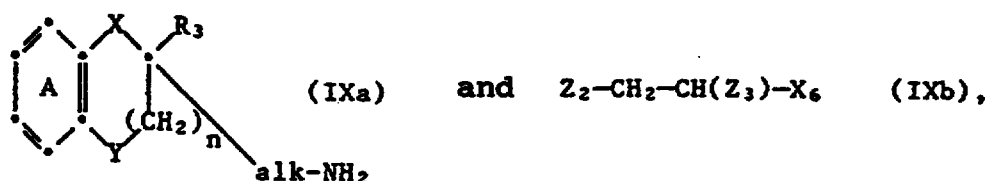
X₆ can be converted into R₁, for example, by solvolysis. Solvolysis agents are, for example, water, lower alkanols corresponding to the desired esterified carboxy R₁, ammonia, or amines corresponding to the desired amidated carboxy group R₁. The treatment with a corresponding solvolysis agent is optionally carried out in the presence of an acid or base. Suitable acids are, for example, inorganic or organic protonic acids, such as mineral acids, for example sulphuric acid or a hydrohalic acid, for example hydrochloric acid, sulphonc acids, for example lower alkanesulphonic or optionally substituted benzenesulphonic acid, for example methane- or p-toluenesulphonic acid, or carboxylic acids, for example lower alkanecarboxylic acids, for example acetic acid, whilst as bases there may be used, for example, those mentioned under Variant h), especially sodium or potassium

hydroxide.

In the solvolysis with water (hydrolysis), the cyano group, anhydridised carboxy, optionally substituted amidino, optionally esterified or anhydridised carboximidoyl, esterified or amidated carboxy other than esterified or amidated carboxy R_1 , tri-lower alkoxyethyl or trihalomethyl is hydrolysed to carboxy. Lower alkanoyloxy radicals which may be present at the ring A may be hydrolysed to hydroxy in the course of the hydrolysis.

Cyano, anhydridised carboxy, and esterified or amidated carboxy other than esterified or amidated carboxy R_1 are alcoholysed, for example with a suitable lower alkanol, to esterified carboxy R_1 , and cyano and anhydridised carboxy are ammonolysed or aminolysed, for example with ammonia or with an amine corresponding to the amidated carboxy R_1 , respectively.

The starting material of the formula IX can be obtained, for example, by reaction of compounds of the formulae



in which Z_2 represents reactive esterified hydroxy and Z_3 represents hydrogen, or Z_2 and Z_3 together represent an additional bond, or optionally salts of these compounds, the operation being carried out in a manner analogous to that described under Process Variant c), for example in the presence of a basic agent.

Subsequent operations which may, if desired, be carried out on compounds of the formula IVc obtainable in accordance with the process are especially conversions of R_1 and of substituents of the ring A, separations of enantiomers and diastereoisomers and conversions into one another of salts and free compounds, analogous to those indicated for the compounds of the formula I and are carried out in analogous manner.

The invention relates also to the use of compounds of the formula I or IVc and, where appropriate, their tautomers and/or pharmaceutically acceptable salts of such compounds having salt-forming properties, especially as pharmacological, especially nootropically active, active ingredients. They can be used, preferably in the form of pharmaceutically acceptable preparations, in a method for the prophylactic and/or therapeutic treatment of the animal or human body, especially as nootropics, for example for the treatment of the symptoms of cerebral insufficiency, especially memory disorders.

The invention relates also to pharmaceutical preparations that comprise as active ingredient a compound of the formula I or IVc or, where appropriate, a tautomer and/or pharmaceutically acceptable salt thereof, and to processes for their manufacture.

The pharmaceutical preparations according to the invention, which comprise a compound of the formula I or IVc or, where appropriate, a tautomer and/or pharmaceutically acceptable salt thereof, are for enteral, such as oral and also rectal, and parenteral administration to a warm-blooded animal, the preparations comprising the pharmacological active ingredient alone or together with

customary pharmaceutical adjuncts.

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

Suitable carriers are, especially, fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphate, for example tricalcium phosphate or calcium hydrogen phosphate, also binders, such as starch pastes using, for example, corn, wheat, rice or potato starch, gelatine, tragacanth, methylcellulose and/or polyvinylpyrrolidone, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Adjuncts are especially flow-regulating agents and lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable coatings

that may be resistant to gastric juices, there being used, inter alia, concentrated sugar solutions that may contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or 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. Colourings or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Further orally administrable pharmaceutical preparations are dry-filled capsules consisting of gelatine, and also soft, sealed capsules consisting of gelatine and a plasticiser, such as glycerine or sorbitol. The dry-filled capsules may contain the active ingredient in the form of a granulate, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and optionally stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, to which stabilisers may also 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. Suitable as suppository bases, are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. It is also possible to use gelatine rectal

capsules that comprise a combination of the active ingredient and a base material. Suitable base materials are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

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

The dosage of the active ingredient can depend upon various factors, such as the method of administration, the species of warm-blooded animal, age and/or individual condition. In normal cases, the estimated approximate daily dose for a warm-blooded animal weighing approximately 75 kg is, in the case of oral administration, from approximately 20 mg to approximately 500 mg, especially from approximately 25 mg to approximately 250 mg, advantageously in several equal partial doses.

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

As a result of the close relationship between a compound of the formula I and the corresponding tautomeric

compound of the formula I', in the Examples a compound of the formula I should be understood as meaning optionally also the tautomeric compound of the formula I' where appropriate and expedient. The same applies to a compound of the formula I' and to salts of compounds of the formulae I and I'.

Example 1: First 5.55 g (25 mmol) of 1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester hydrobromide (guvacoline hydrobromide) and then 11.31 g (87.5 mmol) of N-ethyl-N,N-diisopropylamine are added to a solution of 7.96 g (25 mmol) of 3-(p-toluenesulphonyloxymethyl)-chroman in 100 ml of dimethylformamide. The mixture is stirred for 15 hours at 50° and then concentrated by evaporation under a high vacuum. Water is added to the residue and extraction is carried out with diethyl ether. The organic phases are washed with water and extracted with 2N hydrochloric acid. The hydrochloric acid extracts are combined, rendered alkaline, while cold, with sodium hydroxide solution (30% strength) and extracted with dichloromethane. The combined organic phases are dried over sodium sulphate and concentrated by evaporation in vacuo. 5.92 g (83%) of 1-(chroman-3-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester are obtained in the form of a pale yellow oil. The 1-(chroman-3-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester hydrochloride produced therefrom using hydrochloric acid in diethyl ether melts at 158-159° after crystallisation from methanol/diethyl ether.

3-(p-toluenesulphonyloxymethyl)chroman can be manufactured, for example, as follows:

At room temperature and while stirring, a solution of 50.0 g (260 mmol) of 3-methoxycarbonylchroman (US 4,178,380) in 200 ml of absolute tetrahydrofuran is added dropwise within a period of 40 minutes to a suspension of 9.86 g (260 mmol) of lithium aluminium hydride in 300 ml of absolute diethyl ether. After stirring for 16 hours at room temperature, the reaction mixture is decomposed with 9.9 ml of water, 9.9 ml of sodium hydroxide solution (15% strength) and 30 ml of water. The precipitate formed is filtered off with suction and the filtrate is concentrated to dryness by evaporation in vacuo. The oily residue is dissolved in diethyl ether and the solution is washed with water, dried over sodium sulphate and concentrated to dryness by evaporation. 36.71 g (86%) of oily 3-hydroxymethylchroman, which crystallises from diethyl ether/pentane and melts at 60-61°, are obtained.

46.14 g (242 mmol) of p-toluenesulphonyl chloride are added while stirring at room temperature to a solution of 36.12 g (220 mmol) of 3-hydroxymethylchroman in 100 ml of absolute pyridine, the slightly exothermic reaction being maintained at room temperature by means of an ice bath. The reaction mixture is stirred for a further 3 hours at room temperature and then poured onto ice-water. The crystals formed are filtered off with suction, washed with water and dried in vacuo. 65.84 g (94%) of 3-(p-toluenesulphonyloxymethyl)chroman having a melting point of 86-87° are obtained.

Example 2: At room temperature and while stirring, 0.75 g (15.6 mmol) of sodium hydride dispersion in mineral oil (50%) is added within a period of 30 minutes to a solution of 4.36 g (13 mmol) of N,N-bis(2-methoxy-

carbonylethyl)-N-(chroman-3-ylmethyl)-amine in 50 ml of absolute dimethylformamide. The reaction mixture is stirred for a further 1 hour at room temperature and then concentrated by evaporation under a high vacuum. Diethyl ether is added to the resulting residue and extraction is carried out with cold 2N hydrochloric acid. The combined hydrochloric acid extracts are extracted by shaking with dichloromethane and the combined dichloromethane extracts are dried over sodium sulphate and concentrated by evaporation. There are obtained 3.8 g (85.8%) of crystalline 4-hydroxy-1-(chroman-3-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester hydrochloride or 1-(chroman-3-ylmethyl)-4-oxo-piperidine-3-carboxylic acid methyl ester hydrochloride which, after recrystallisation from methanol/diethyl ether, has a decomposition point of 167-168°.

N,N-bis(2-methoxycarbonylethyl)-N-(chroman-3-ylmethyl)-amine can be manufactured, for example, in the following manner:

First 1.77 g (13.32 mmol) of aluminium chloride in 50 ml of absolute diethyl ether are added dropwise while stirring at room temperature to a suspension of 3.04 g (80 mmol) of lithium aluminium hydride in 100 ml of absolute diethyl ether. Then 6.29 g (40 mmol) of 3-cyanochromene [R.C. Gupta *et al.*, Ind. J. Chem. 21B, 344 (1982)] in 50 ml of absolute tetrahydrofuran are added dropwise within a period of 20 minutes. The reaction mixture is boiled under reflux for 16 hours. After it has cooled, the reaction mixture is carefully decomposed with 3.1 ml of water, 3.1 ml of sodium hydroxide solution (15% strength) and 9.3 ml of water. The precipitate formed is filtered off with suction, the filtrate is

concentrated by evaporation in vacuo and the oily residue is dissolved in diethyl ether. The organic phase is washed with water and extracted with 2N hydrochloric acid. The combined hydrochloric acid extracts are rendered alkaline, while cold, with sodium hydroxide solution (30% strength) and extracted by shaking with dichloromethane. After drying the combined organic phases over sodium sulphate and concentrating in vacuo, 3.5 g (53.6%) of 3-aminomethylchroman are obtained in the form of a yellow oil. The 3-aminomethylchroman hydrochloride produced therefrom using hydrochloric acid in diethyl ether is recrystallised from methanol/diethyl ether and melts at 218-219°.

3.03 g (35.2 mmol) of acrylic acid methyl ester are added to a solution of 2.61 g (16 mmol) of 3-aminomethylchroman in 20 ml of methanol. The reaction solution is stirred for 16 hours at 50° and, after cooling, is concentrated by evaporation in vacuo. 5.1 g (95%) of N,N-bis(2-methoxycarbonylethyl)-N-(chroman-3-ylmethyl)-amine are obtained in the form of a reddish oil.

Example 3: A solution of 10.48 g (30 mmol) of N-[2-(chroman-3-yl)-ethyl]-N,N-bis(2-methoxycarbonylethyl)-amine in 35 ml of absolute dimethylformamide is added dropwise at room temperature and while stirring to a suspension of 2.16 g (40 mmol) of sodium methoxide in 25 ml of dimethylformamide within a period of 15 minutes. The reaction mixture is stirred for 16 hours at room temperature and then concentrated to dryness by evaporation under a high vacuum. Diethyl ether is added to the residue and extraction is carried out with cold 2N hydrochloric acid. The combined hydrochloric acid extracts are extracted by shaking with dichloromethane

and the dichloromethane phases are dried over sodium sulphate and concentrated by evaporation in vacuo. There are obtained 4.25 g (40%) of 1-[2-(chroman-3-yl)ethyl]-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester hydrochloride or 1-[2-(chroman-3-yl)ethyl]-4-oxopiperidine-3-carboxylic acid methyl ester hydrochloride which, after recrystallisation from methanol/-diethyl ether, has a decomposition point of 175-177°.

N-[2-(chroman-3-yl)ethyl]-N,N-bis(2-methoxycarbonyl-ethyl)-amine can be manufactured, for example, in the following manner:

12.53 g (192.5 mmol) of potassium cyanide are added at room temperature to a solution of 55.72 g (175 mmol) of 3-(p-toluenesulphonyloxymethyl)chroman (for manufacture see Example 1) in 300 ml of dimethyl sulphoxide and the whole is heated to 60° while stirring. After 3 hours, ice-water is added to the reaction mixture, the whole is extracted with diethyl ether and washed thoroughly with water. The combined organic phases are dried over sodium sulphate and concentrated by evaporation in vacuo.

26.75 g (88.3%) of 3-cyanomethylchroman are obtained in the form of a pale yellow oil which crystallises from diethyl ether/pentane. The crystals melt at 63°.

First 4.44 g (33.3 mmol) of aluminium chloride in 150 ml of absolute diethyl ether are added dropwise while stirring at room temperature to a suspension of 7.59 g (200 mmol) of lithium aluminium hydride in 300 ml of absolute diethyl ether. Then 17.32 g (100 mmol) of 3-cyanomethylchroman, dissolved in 200 ml of tetrahydrofuran, are added dropwise within a period of 15 minutes. The reaction mixture is stirred for 16 hours at room

temperature and then decomposed with 7.6 ml of water, 7.6 ml of sodium hydroxide solution (15% strength) and 22.8 ml of water. The precipitate formed is filtered off with suction and the filtrate is concentrated by evaporation in vacuo. The oily residue is dissolved in diethyl ether and washed with water. The organic phase is then extracted by shaking with 2N hydrochloric acid. The combined hydrochloric acid extracts are rendered alkaline, while cold, with sodium hydroxide solution (30% strength) and extracted with dichloromethane. The combined organic phases are dried over sodium sulphate and concentrated by evaporation in vacuo. 15.95 g (90%) of 3-(2-aminoethyl)chroman are obtained in the form of a colourless oil. The 3-(2-aminoethyl)chroman hydrochloride produced therefrom using hydrochloric acid in diethyl ether crystallises from methanol/diethyl ether and has a melting point of 244-245°.

6.63 g (77 mmol) of acrylic acid methyl ester are added at room temperature to a solution of 6.2 g (35 mmol) of 3-(2-aminoethyl)chroman in 50 ml of methanol and the whole is stirred for 16 hours at room temperature. The reaction mixture is then concentrated by evaporation in vacuo and yields 12.23 g (100%) of N-[2-(chroman-3-yl)ethyl]-N,N-bis(2-methoxycarbonyl)ethyl)-amine in the form of a reddish oil.

Example 4: In a manner analogous to that described in Example 3, by reacting 3-(2-aminoethyl)chroman with 1 equivalent of acrylic acid methyl ester, it is possible to manufacture the corresponding N-[2-(chroman-3-yl)-ethyl]-N-(2-methoxycarbonyl)ethyl)-amine whose hydrochloride melts at 190-192°.

Example 5: In a manner analogous to that described in Examples 3 and 4, by reacting 3-aminomethylchroman with 1 equivalent of acrylic acid methyl ester, it is possible to manufacture N-(2-methoxycarbonyl-ethyl)-N-(chroman-3-ylmethyl)-amine or its hydrochloride.

Example 6: First 3.3 g (14.8 mmol) of 1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester hydrobromide (guvacoline hydrobromide) and then 6.1 g (47.3 mmol) of N-ethyl-N,N-diisopropylamine are added to a solution of 4.5 g (13.5 mmol) of 3-[2-(p-toluenesulphonyloxy)ethyl]-chroman in 70 ml of absolute dimethylformamide. The mixture is stirred for 16 hours at 60° and, after cooling, is concentrated by evaporation under a high vacuum. Water is added to the oily residue and extraction is carried out with diethyl ether. The combined organic phases are extracted with 2N hydrochloric acid. The combined hydrochloric acid extracts are rendered alkaline, while cold, with sodium hydroxide solution (30% strength) and extracted with dichloromethane. The combined dichloromethane phases are dried over sodium sulphate and concentrated by evaporation in vacuo. 3.97 g (97.7%) of 1-[2-(chroman-3-yl)ethyl]-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester are obtained in the form of a yellow oil. The 1-[2-(chroman-3-yl)ethyl]-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester hydrochloride produced therefrom using hydrochloric acid in diethyl ether crystallises from methanol/diethyl ether and melts at 175-177°.

3-[2-(p-toluenesulphonyloxy)ethyl]chroman can be manufactured, for example, as follows:

50 ml of 2N sodium hydroxide solution are added to a

solution of 7.8 g (45 mmol) of 3-cyanomethylchroman in 150 ml of ethanol and the whole is boiled under reflux for 16 hours. After cooling, the reaction mixture is concentrated by evaporation in vacuo. The residue is dissolved in water and extracted with diethyl ether. The aqueous phase is acidified with hydrochloric acid (36% strength) and extracted by shaking with dichloromethane. The combined dichloromethane extracts are dried over sodium sulphate and concentrated by evaporation in vacuo. 8.3 g (96%) of 3-carboxymethylchroman are obtained in the form of colourless crystals which melt at 106-107°.

1.5 ml of sulphuric acid (100% strength) are added to a solution of 7.69 g (40 mmol) of 3-carboxymethylchroman in 150 ml of methanol and the whole is boiled under reflux for 3 hours. After cooling, the reaction mixture is concentrated by evaporation in vacuo. The residue is dissolved in diethyl ether and washed, while cold, with water, sodium hydrogen carbonate and again with water. The combined organic phases are dried over sodium sulphate and concentrated by evaporation in vacuo. 8.08 g (98%) of 3-methoxycarbonylmethylchroman are obtained in the form of a pale yellow oil.

At room temperature and while stirring, a solution of 7.22 g (35 mmol) of 3-methoxycarbonylmethylchroman in 50 ml of absolute tetrahydrofuran is added dropwise within a period of 30 minutes to a suspension of 1.33 g (35 mmol) of lithium aluminium hydride in 50 ml of absolute diethyl ether. Stirring is continued at room temperature for a further 16 hours and then the whole is carefully decomposed with 1.33 ml of water, 1.33 ml of sodium hydroxide solution (15% strength) and 4.0 ml of

water. The precipitate formed is filtered off with suction and the filtrate is concentrated by evaporation in vacuo. The oily residue is dissolved in diethyl ether. The solution is washed with water, dried over sodium sulphate and concentrated by evaporation in vacuo. 6.23 g (100%) of 3-(2-hydroxyethyl)chroman are obtained in the form of a yellow oil.

6.29 g (33 mmol) of p-toluenesulphonyl chloride are added while stirring at room temperature to a solution of 5.35 g (30 mmol) of 3-(2-hydroxyethyl)chroman in 30 ml of absolute pyridine, the slightly exothermic reaction being maintained at room temperature by means of an ice bath. After stirring for a further three hours at room temperature, the reaction mixture is poured onto ice-water. The crystals formed are filtered off with suction, washed with water and dried in vacuo. 5.9 g (59.2%) of 3-[2-(p-toluenesulphonyloxy)ethyl]chroman, which melts at 91-93°, are obtained.

Example 7: First 11.1 g (50 mmol) of 1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester hydrobromide (guvacoline hydrobromide) and then 22.6 g (175 mmol) of N-ethyl-N,N-diisopropylamine are added to a solution of 11.45 g (50 mmol) of 2-bromomethylbenzo-1,4-dioxan (US 2,366,102) in 100 ml of absolute dimethylformamide. The mixture is stirred for 16 hours at 50° and then concentrated by evaporation under a high vacuum. Water is added to the residue and extraction is carried out with diethyl ether. The organic phases are washed with water and extracted by shaking with 2N hydrochloric acid. The combined hydrochloric acid extracts are rendered alkaline, while cold, with sodium hydroxide solution (30% strength) and extracted with dichloromethane. The

combined dichloromethane phases are dried over sodium sulphate and concentrated by evaporation in vacuo. 10.75 g (74.4%) of 1-(benzo-1,4-dioxan-2-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester are obtained in the form of a yellow oil. The 1-(benzo-1,4-dioxan-2-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester hydrochloride produced therefrom using hydrochloric acid in diethyl ether crystallises from methanol/diethyl ether and decomposes at 215-217°.

Example 8: 0.5 g of palladium-on-carbon (5%) is added to a solution of 4.88 g (15 mmol) of 1-(benzo-1,4-dioxan-2-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester hydrochloride in 100 ml of methanol and the whole is hydrogenated for 6 hours at room temperature and at normal pressure. The catalyst is then filtered off with suction and the filtrate is concentrated by evaporation in vacuo. The oily residue is dissolved in hot acetone and diethyl ether is added until the solution becomes turbid. 4.08 g (83%) of 1-(benzo-1,4-dioxan-2-ylmethyl)-piperidine-3-carboxylic acid methyl ester hydrochloride having a melting point of 186-188° crystallise out.

Example 9: At room temperature and while stirring, a solution of 10.12 g (30 mmol) of N,N-bis(2-methoxycarbonylethyl)-N-(benzo-1,4-dioxan-2-ylmethyl)-amine in 25 ml of absolute dimethylformamide is added dropwise within a period of 15 minutes to a suspension of 2.16 g (40 mmol) of sodium methoxide in 25 ml of dimethylformamide. The reaction mixture is stirred for a further 3 hours at room temperature and then concentrated to dryness by evaporation under a high vacuum. Diethyl

ether is added to the residue and extraction by shaking is carried out with cold 2N hydrochloric acid. The combined hydrochloric acid extracts are extracted with dichloromethane and the dichloromethane phases are dried over sodium sulphate and concentrated by evaporation in vacuo. There are obtained 4.5 g (44.4%) of 4-hydroxy-1-(benzo-1,4-dioxan-2-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester hydrochloride or 1-(benzo-1,4-dioxan-2-ylmethyl)-4-oxopiperidine-3-carboxylic acid methyl ester hydrochloride which is recrystallised from methanol/diethyl ether and has a decomposition point of 185-187°.

N,N-bis(2-methoxycarbonyl-ethyl)-N-(benzo-1,4-dioxan-2-ylmethyl)-amine can be manufactured, for example, as follows:

7.57 g (88 mmol) of acrylic acid methyl ester are added to a solution of 6.61 g (40 mmol) of 2-aminomethylbenzo-1,4-dioxan [J. Augustin et al., J. Med. Chem. 8, 446 (1965)] in 80 ml of methanol and the whole is stirred for 16 hours at 50°. After cooling, the reaction mixture is concentrated by evaporation in vacuo. 12.82 g (95%) of N,N-bis(2-methoxycarbonyl-ethyl)-N-(benzo-1,4-dioxan-2-ylmethyl)-amine are obtained in the form of a reddish oil.

Example 10: In a manner analogous to that described in Example 9, by reacting 2-aminomethylbenzo-1,4-dioxan with 1 equivalent of acrylic acid methyl ester, it is possible to manufacture the corresponding N-(2-methoxycarbonyl-ethyl)-N-(benzo-1,4-dioxan-2-ylmethyl)-amine whose hydrochloride melts at 153-155°.

Example 11: In a manner analogous to that described in Example 9, it is also possible to manufacture 4-hydroxy-1-(2-methylbenzo-1,4-dioxan-2-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester hydrochloride or 1-(2-methylbenzo-1,4-dioxan-2-ylmethyl)-4-oxopiperidine-3-carboxylic acid methyl ester hydrochloride.

Example 12: In a manner analogous to that described in Examples 9 and 10, by reacting 2-(2-aminoethyl)-benzo-1,4-dioxan with 1 equivalent of acrylic acid methyl ester, it is possible to manufacture N-[2-(benzo-1,4-dioxan-2-yl)ethyl]-N-(2-methoxycarbonyl)ethyl)-amine and its hydrochloride, and by reacting 2-aminomethyl-2-methylbenzo-1,4-dioxan with 1 equivalent of acrylic acid methyl ester, it is possible to manufacture N-(2-methoxycarbonyl)ethyl)-N-(2-methylbenzo-1,4-dioxan-2-ylmethyl)-amine and its hydrochloride.

Example 13: A solution of 52.7 g (0.15 mol) of N,N-bis(2-methoxycarbonyl)ethyl)-N-[2-(benzo-1,4-dioxan-2-yl)ethyl]-amine in 150 ml of absolute dimethylformamide is added dropwise at room temperature while stirring to a suspension of 10.8 g (0.20 mol) of sodium methoxide in 100 ml of absolute dimethylformamide within a period of 10 minutes. The reaction mixture is stirred for a further 15 hours at room temperature and then concentrated to dryness by evaporation under a high vacuum. Diethyl ether is added to the resulting residue and extraction is carried out with cold 2N hydrochloric acid. The combined hydrochloric acid extracts are extracted by shaking with dichloromethane. The dichloromethane phases are dried over sodium sulphate and concentrated by evaporation in vacuo. There are obtained 34.0 g (63.7%)

of 1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester hydrochloride or 1-[2-(benzo-1,4-dioxan-2-yl)-ethyl]-4-oxopiperidine-3-carboxylic acid methyl ester hydrochloride which is recrystallised from methanol/diethyl ether and has a decomposition point of 165-166°.

N,N-bis(2-methoxycarbonyl-ethyl)-N-[2-(benzo-1,4-dioxan-2-yl)-ethyl]-amine can be manufactured, for example, in the following manner:

34.1 g (0.396 mol) of acrylic acid methyl ester are added at room temperature to a solution of 32.25 g (0.18 mol) of 2-(2-aminoethyl)-benzo-1,4-dioxan [J. Augustin *et al.*, J. Med. Chem. 8, 446 (1965)] in 250 ml of methanol. The reaction mixture is stirred for 6 hours at 50° and, after cooling, is concentrated by evaporation *in vacuo*. 57.9 g (91.5%) of N,N-bis(2-methoxycarbonyl-ethyl)-N-[2-(benzo-1,4-dioxan-2-yl)ethyl]-amine are obtained in the form of a red oil.

Example 14: 1.25 g of platinum oxide are added to a solution of 12.45 g (35 mmol) of 1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester hydrochloride or 1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-4-oxopiperidine-3-carboxylic acid methyl ester hydrochloride in 250 ml of methanol and the whole is hydrogenated at room temperature and at normal pressure. After the theoretically necessary amount of hydrogen has been taken up, the catalyst is separated off, the filtrate is concentrated by evaporation *in vacuo* and the oily residue is dissolved in hot acetone. After cooling, 4.87 g (38.9%) of *cis*-1-[2-(benzo-1,4-dioxan-2-yl)-ethyl]-4-hydroxypiperidine-3-

carboxylic acid methyl ester hydrochloride having a melting point of 182-185° crystallise out.

Example 15: At -15° and while stirring, 2.65 g (70 mmol) of sodium borohydride are added in portions over a period of one hour to a suspension of 12.45 g (35 mmol) of 1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester hydrochloride or 1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-4-oxopiperidine-3-carboxylic acid methyl ester hydrochloride in 250 ml of methanol. Stirring is continued for a further 4 hours at -10° and then the reaction mixture is concentrated by evaporation in vacuo and taken up in water/ethyl acetate. The ethyl acetate extracts are washed with water, dried over sodium sulphate and concentrated by evaporation. 11.2 g (100%) of crude product are obtained which are chromatographed on 560 g of silica gel (0.040-0.063 mm) using ethyl acetate as the eluant. 5.41 g (48.2%) of trans-1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-4-hydroxypiperidine-3-carboxylic acid methyl ester are obtained in the form of a pale yellow oil. The trans-1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-4-hydroxypiperidine-3-carboxylic acid methyl ester fumarate produced therefrom using fumaric acid crystallises from methanol/diethyl ether in the form of the hemihydrate having a melting point of 150-152°.

Example 16: First 19.03 g (125 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene and then, dropwise and while stirring at 0-5°, a solution of 3.44 g (30 mmol) of methanesulphonyl chloride in 20 ml of toluene are added to a solution of 8.03 g (25 mmol) of a mixture of cis- and trans-1-[2-(benzo-1,4-dioxan-2-yl)-ethyl]-4-hydroxypiperidine-3-carboxylic acid methyl ester in 100 ml of

toluene. The whole is then allowed to warm up to room temperature and is stirred for a further 16 hours. Ice-water is then added to the reaction mixture and the organic phase is extracted with 2N hydrochloric acid. The combined hydrochloric acid extracts are rendered alkaline, while cold, with sodium hydroxide solution (30% strength) and extracted by shaking with dichloromethane. The combined organic phases are washed with water, dried over sodium sulphate and concentrated by evaporation in vacuo. 5.8 g (76.5%) of crude product are obtained and are chromatographed on 300 g of silica gel (0.040-0.063 mm) using toluene/ethyl acetate (1:1) as the eluant. 4.13 g (54.5%) of 1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester are obtained in the form of a yellow oil. The 1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester hydrochloride produced therefrom using hydrochloric acid in diethyl ether crystallises from methanol/diethyl ether and decomposes at 205-206°.

Example 17: First 2.1 g (11 mmol) of 1,2,5,6-tetrahydropyridine-3-carboxylic acid ethyl ester hydrochloride and then 4.53 g (35 mmol) of N-ethyl-N,N-diisopropylamine are added to a solution of 3.32 g (10 mmol) of 3-[2-(p-toluenesulphonyloxy)ethyl]-chroman in 50 ml of absolute dimethylformamide. The mixture is stirred for 16 hours at 60° and, after cooling, is concentrated by evaporation under a high vacuum. Water is added to the oily residue and extraction is carried out with diethyl ether. The combined organic phases are extracted with 2N hydrochloric acid. The combined hydrochloric acid extracts are rendered alkaline, while cold, with sodium hydroxide solution (30% strength) and extracted with dichloro-

methane. The combined dichloromethane phases are dried over sodium sulphate and concentrated by evaporation in vacuo. 1.65 g (52.3%) of 1-[2-(chroman-3-yl)ethyl]-1,2,5,6-tetrahydropyridine-3-carboxylic acid ethyl ester are obtained in the form of a yellow oil. The 1-[2-(chroman-3-yl)ethyl]-1,2,5,6-tetrahydropyridine-3-carboxylic acid ethyl ester hydrochloride produced therefrom using hydrochloric acid in diethyl ether crystallises from acetone/diethyl ether and melts at 177-178°.

Example 18: 3.4 ml of sulphuric acid (100% strength) are added to a solution of 2.54 g (7.5 mmol) of 1-[2-(chroman-3-yl)ethyl]-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester hydrochloride in 170 ml of absolute ethanol and the whole is boiled under reflux for 35 hours. After cooling, the reaction mixture is concentrated by evaporation in vacuo. The residue is dissolved in water while cold and is extracted with diethyl ether. The aqueous phase is rendered alkaline, while cold, with sodium hydroxide solution (30% strength) and extracted with dichloromethane. The combined dichloromethane extracts are dried over sodium sulphate and concentrated by evaporation in vacuo. 2.30 g (97.4%) of 1-[2-(chroman-3-yl)ethyl]-1,2,5,6-tetrahydropyridine-3-carboxylic acid ethyl ester are obtained in the form of a yellow oil. The 1-[2-(chroman-3-yl)ethyl]-1,2,5,6-tetrahydropyridine-3-carboxylic acid ethyl ester hydrochloride produced therefrom using hydrochloric acid in diethyl ether crystallises from acetone/diethyl ether and melts at 177-178°.

Example 19: First 3.76 g (24 mmol) of piperidine-3-carboxylic acid ethyl ester and then 3.1 g (24 mmol) of

N-ethyl-N,N-diisopropylamine are added to a solution of 3.98 g (12 mmol) of 3-[2-(p-toluenesulphonyloxy)ethyl]-chroman in 50 ml of absolute dimethylformamide. The mixture is stirred for 16 hours at 60° and, after cooling, is concentrated by evaporation under a high vacuum. Water is added to the oily residue and extraction is carried out with diethyl ether. The combined organic phases are extracted with 2N hydrochloric acid. The combined hydrochloric acid extracts are rendered alkaline, while cold, with sodium hydroxide solution (30% strength) and extracted with dichloromethane. The combined dichloromethane phases are dried over sodium sulphate and concentrated by evaporation in vacuo. 3.7 g (97.3%) of 1-[2-(chroman-3-yl)ethyl]-piperidine-3-carboxylic acid ethyl ester are obtained in the form of a yellow oil. The 1-[2-(chroman-3-yl)ethyl]-piperidine-3-carboxylic acid ethyl ester hydrochloride produced therefrom using hydrochloric acid in diethyl ether crystallises from acetone/diethyl ether using 0.18 equivalent of water of crystallisation and melts at 140-143°.

Example 20: First 3.76 g (24 mmol) of piperidine-4-carboxylic acid ethyl ester and then 3.1 g (24 mmol) of N-ethyl-N,N-diisopropylamine are added to a solution of 3.98 g (12 mmol) of 3-[2-(p-toluenesulphonyloxy)-ethyl]-chroman in 50 ml of absolute dimethylformamide. The mixture is stirred for 16 hours at 60° and, after cooling, is concentrated by evaporation under a high vacuum. Water is added to the oily residue and extraction by shaking is carried out with diethyl ether. The combined organic phases are extracted with 2N hydrochloric acid. The combined hydrochloric acid extracts are rendered alkaline, while cold, with sodium hydroxide

solution (30% strength) and extracted with dichloromethane. The combined dichloromethane phases are dried over sodium sulphate and concentrated by evaporation in vacuo. 3.8 g (100%) of crude product are obtained which are chromatographed on 200 g of silica gel (0.040-0.063 mm) using ethyl acetate as the eluant. 3.7 g (97.3%) of 1-[2-(chroman-3-yl)ethyl]-piperidine-4-carboxylic acid ethyl ester are then obtained in the form of a colourless oil. The 1-[2-(chroman-3-yl)ethyl]-piperidine-4-carboxylic acid ethyl ester hydrochloride produced therefrom using hydrochloric acid in diethyl ether crystallises from ethanol/diethyl ether and melts at 182-186°.

Example 21: First 1.96 g (12.5 mmol) of piperidine-3-carboxylic acid ethyl ester and then 2.58 g (20 mmol) of N-ethyl-N,N-diisopropylamine are added to a solution of 3.34 g (10 mmol) of 2-[2-(p-toluenesulphonyloxy)ethyl]-benzo-1,4-dioxan in 50 ml of absolute dimethylformamide. The mixture is stirred for 16 hours at 60° and, after cooling, is concentrated by evaporation under a high vacuum. Water is added to the oily residue and extraction is carried out with diethyl ether. The combined organic phases are washed with water and extracted with 2N hydrochloric acid. The combined hydrochloric acid extracts are rendered alkaline, while cold, with sodium hydroxide solution (30% strength) and extracted with dichloromethane. The combined dichloromethane phases are dried over sodium sulphate and concentrated by evaporation in vacuo. 3.82 g (100%) of crude product are obtained which are filtered over 190 g of silica gel (0.040-0.063 mm) using ethyl acetate as the eluant. 3.70 g (96.6%) of 1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-piperidine-3-carboxylic acid ethyl ester are then

obtained in the form of a pale yellow oil. The 1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-piperidine-3-carboxylic acid ethyl ester hydrochloride produced therefrom using hydrochloric acid in diethyl ether crystallises from ethanol/diethyl ether and melts at 162-165°.

The 2-[2-(p-toluenesulphonyloxy)ethyl]-benzo-1,4-dioxan can be obtained, for example, in the following manner:

Hydrogen chloride is introduced at 5-10°, while stirring, into a solution of 15.76 g (90 mmol) of 2-cyanomethylbenzo-1,4-dioxan (BE 613,211) in 200 ml of absolute methanol until saturation is reached. The reaction mixture is then thawed to room temperature and is stirred for a further 16 hours at that temperature. The reaction mixture is then boiled under reflux for 2 hours. After cooling, the mixture is concentrated by evaporation in vacuo. Ice-water is added to the oily residue and extraction is carried out with diethyl ether. The combined organic phases are washed, while cold, with water, saturated sodium hydrogen carbonate solution and again with water, and then dried over sodium sulphate and concentrated by evaporation in vacuo. 18.2 g (97.3%) of 2-methoxycarbonylmethylbenzo-1,4-dioxan are obtained in the form of a pale yellow oil.

At room temperature and while stirring, a solution of 15.61 g (75 mmol) of 2-methoxycarbonylmethylbenzo-1,4-dioxan in 120 ml of absolute tetrahydrofuran is added dropwise within a period of 30 minutes to a suspension of 2.85 g (75 mmol) of lithium aluminium hydride in 120 ml of absolute diethyl ether. The reaction mixture is stirred for a further 2 hours at room temperature. It is then carefully decomposed with 2.85 ml of water, 2.85 ml

of sodium hydroxide solution (15% strength) and 8.55 ml of water. The precipitate formed is filtered off with suction and the filtrate is concentrated by evaporation in vacuo. The oily residue is dissolved in diethyl ether. The solution is washed thoroughly with water, dried over sodium sulphate and concentrated by evaporation in vacuo. 12.37 g (91.6%) of 2-(2-hydroxyethyl)-benzo-1,4-dioxan are obtained in the form of a colourless oil.

12.20 g (64 mmol) of p-toluenesulphonyl chloride are added at room temperature and while stirring to a solution of 10.81 g (60 mmol) of 2-(2-hydroxyethyl)benzo-1,4-dioxan in 35 ml of absolute pyridine, the slightly exothermic reaction being maintained at room temperature by means of an ice bath. The reaction mixture is stirred for a further 3 hours at room temperature and then poured onto ice-water. The crystals formed are filtered off with suction, washed with water and dried in vacuo. 15.50 g (77.2%) of 2-[2-(p-toluenesulphonyloxy)ethyl]-benzo-1,4-dioxan, which melts at 82-84°, are obtained.

Example 22: First 1.96 g (12.5 mmol) of piperidine-4-carboxylic acid ethyl ester and then 2.58 g (20 mmol) of N-ethyl-N,N-diisopropylamine are added to a solution of 3.34 g (10 mmol) of 2-[2-(p-toluenesulphonyloxy)ethyl]-benzo-1,4-dioxan in 50 ml of absolute dimethylformamide. The mixture is stirred for 16 hours at 60° and, after cooling, is concentrated by evaporation under a high vacuum. Water is added to the oily residue and extraction is carried out with diethyl ether. The combined organic phases are washed with water and extracted with 2N hydrochloric acid. The combined hydrochloric acid extracts are rendered alkaline, while cold, with sodium

hydroxide solution (30% strength) and extracted with dichloromethane. The combined dichloromethane phases are dried over sodium sulphate and concentrated by evaporation in vacuo. 3.80 g (99.2%) of crude product are obtained which are filtered over 190 g of silica gel (0.040-0.063 mm) using ethyl acetate as the eluant. 3.7 g (96.6%) of 1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-piperidine-4-carboxylic acid ethyl ester are then obtained in the form of a yellow oil. The 1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-piperidine-4-carboxylic acid ethyl ester hydrochloride produced therefrom using hydrochloric acid in diethyl ether crystallises from ethanol/diethyl ether and melts at 165-168°.

Example 23: 21 ml (42 mmol) of 2N sodium hydroxide solution are added at room temperature while stirring to a solution of 2.99 g (10 mmol) of N-[2-(chroman-3-yl)ethyl]-N-(2-methoxycarbonyl)ethyl)-amine hydrochloride in 60 ml of methanol. After 5 minutes, 40 ml of water are added to the reaction mixture which is then stirred for 30 minutes at 50-60°. After cooling, the mixture is concentrated by evaporation in vacuo. The residue is dissolved in 30 ml of water, and then 10 ml of hydrochloric acid (36% strength) are added and the whole is cooled in an ice bath. The crystals formed are filtered off with suction. 2.5 g (87.5%) of N-[2-(chroman-3-yl)ethyl]-N-(2-carboxyethyl)-amine hydrochloride are obtained (m.p. 186-188°).

The N-[2-(chroman-3-yl)ethyl]-N-(2-methoxycarbonyl)ethyl)-amine hydrochloride can be manufactured, for example, as described in Example 4.

Example 24: First 1.57 g (10 mmol) of piperidine-3-carboxylic acid ethyl ester and then 2.07 g (16 mmol) of N-ethyl-N,N-diisopropylamine are added to a solution of 2.66 g (8 mmol) of 2-[2-(p-toluenesulphonyloxy)ethyl]-chroman in 35 ml of absolute dimethylformamide. The mixture is stirred for 16 hours at 60° and, after cooling, is concentrated by evaporation under a high vacuum. Water is added to the oily residue and extraction is carried out with diethyl ether. The combined organic phases are washed with water and extracted with 2N hydrochloric acid. The combined hydrochloric acid extracts are rendered alkaline, while cold, with sodium hydroxide solution (30% strength) and extracted with dichloromethane. The combined dichloromethane phases are dried over sodium sulphate and concentrated by evaporation in vacuo. 2.28 g (90.1%) of crude product are obtained and are chromatographed on 120 g of silica gel (0.040-0.063 mm) using ethyl acetate as the eluant. 1.82 g (72.2%) of 1-[2-(chroman-2-yl)ethyl]-piperidine-3-carboxylic acid ethyl ester are then obtained in the form of a yellow oil. The 1-[2-(chroman-2-yl)ethyl]-piperidine-3-carboxylic acid ethyl ester hydrochloride produced therefrom using hydrochloric acid in diethyl ether crystallises from ethanol/diethyl ether and melts at 148-151°.

2-[2-(p-toluenesulphonyloxy)ethyl]chroman can be manufactured, for example, in the following manner:

14.2 ml of sulphuric acid (100% strength) are added to a solution of 70.34 g (0.39 mol) of 2-carboxychroman in 1400 ml of methanol and the whole is boiled under reflux for 4 hours. After cooling, the reaction mixture is concentrated by evaporation in vacuo and the residue is

dissolved in diethyl ether and washed with water, cold saturated sodium hydrogen carbonate solution and again with water. The ethereal phase is dried over sodium sulphate and concentrated by evaporation in vacuo. 72.8 g (96%) of 2-methoxycarbonylchroman are obtained in the form of a pale yellow oil.

At room temperature and while stirring, a solution of 36.4 g (0.19 mol) of 2-methoxycarbonylchroman in 400 ml of absolute tetrahydrofuran is added dropwise within a period of 1 hour to a suspension of 7.2 g (0.19 mol) of lithium aluminium hydride in 400 ml of absolute diethyl ether. After continuing to stir for a further 16 hours at room temperature, the reaction mixture is carefully decomposed with 7.2 ml of water, 7.2 ml of sodium hydroxide solution (15% strength) and 21.6 ml of water. The precipitate formed is filtered off with suction and the filtrate is concentrated by evaporation in vacuo. The oily residue is dissolved in diethyl ether. The ethereal solution is washed with water, dried over sodium sulphate and concentrated by evaporation in vacuo. 31 g (99.3%) of 2-hydroxymethylchroman are thus obtained in the form of a colourless oil.

38.16 g (0.2 mol) of p-toluenesulphonyl chloride are added at room temperature while stirring to a solution of 31 g (0.189 mol) of 2-hydroxymethylchroman in 110 ml of absolute pyridine, the slightly exothermic reaction being maintained at room temperature by means of an ice bath. The reaction mixture is stirred for a further 3 hours at room temperature and then poured onto ice-water. The oil which separates out is removed by decanting the aqueous phase, dissolved in diethyl ether and washed with ice-cold 2N hydrochloric acid and ice-water. The ethereal

phases are dried over sodium sulphate and concentrated by evaporation in vacuo. 58.15 g (96.6%) of 2-(p-toluene-sulphonyloxymethyl)chroman are obtained in the form of a colourless oil.

10.6 g (0.216 mol) of sodium cyanide are added to a solution of 57.31 g (0.18 mol) of 2-(p-toluene-sulphonyloxymethyl)chroman in 800 ml of absolute dimethylformamide and the whole is heated, while stirring, to 60°. After 10 hours, ice-water is added to the reaction mixture and extraction is carried out with diethyl ether. The combined ethereal phases are washed thoroughly with water, dried over sodium sulphate and concentrated by evaporation in vacuo. 30.0 g (96.2%) of crude product are obtained and are chromatographed on 1000 g of silica gel (0.040-0.063 mm) using toluene as the eluant. 18.16 g (58.2%) of 2-cyanomethylchroman are thus obtained in the form of a yellow oil.

Hydrogen chloride gas is introduced at 5-10° into a solution of 17.32 g (0.1 mol) of 2-cyanomethylchroman in 200 ml of absolute methanol until saturation is reached. The reaction mixture is then thawed to room temperature and is stirred for a further 16 hours at that temperature. The reaction mixture is then boiled under reflux for 2 hours. It is then cooled and the mixture is concentrated by evaporation in vacuo. Ice-water is added to the residue and extraction is carried out with diethyl ether. The combined organic phases are washed, while cold, with water, sodium hydrogen carbonate solution and again with water, and then dried over sodium sulphate and concentrated by evaporation in vacuo. 18.58 g (90.1%) of crude product are obtained and are filtered over 460 g of silica gel (0.040-0.063 mm) using toluene as the eluant.

17.80 g (86.3%) of 2-methoxycarbonylmethylchroman are obtained in the form of a pale yellow oil.

At room temperature and while stirring, a solution of 16.91 g (82 mmol) of 2-methoxycarbonylmethylchroman in 150 ml of absolute tetrahydrofuran is added dropwise within a period of 30 minutes to a suspension of 3.11 g (82 mmol) of lithium aluminium hydride in 150 ml of absolute diethyl ether. Stirring is continued for a further 16 hours at room temperature and then the whole is carefully decomposed with 3.1 ml of water, 3.1 ml of sodium hydroxide solution (15% strength) and 9.3 ml of water. The precipitate formed is filtered off with suction and the filtrate is concentrated by evaporation in vacuo. The oily residue is dissolved in diethyl ether. The ethereal solution is washed with water, dried over sodium sulphate and concentrated by evaporation in vacuo. 14.36 g (98.3%) of 2-(2-hydroxyethyl)chroman are obtained in the form of a colourless oil.

15.73 g (82.5 mmol) of *p*-toluenesulphonyl chloride are added at room temperature while stirring to a solution of 13.36 g (75 mmol) of 2-(2-hydroxyethyl)chroman in 90 ml of absolute pyridine, the slightly exothermic reaction being maintained at room temperature by means of an ice bath. After stirring for a further 3 hours at room temperature, the reaction mixture is poured onto ice-water. The crystals formed are filtered off with suction, washed with water and dried in vacuo. There are obtained 8.68 g (34.7%) of 2-[2-(*p*-toluenesulphonyloxy)-ethyl]chroman which melts at 57-59°.

Example 25: First 1.57 g (10 mmol) of piperidine-4-carboxylic acid ethyl ester and then 2.07 g (16 mmol) of

N-ethyl-N,N-diisopropylamine are added to a solution of 2.66 g (8 mmol) of 2-[2-(p-toluenesulphonyloxy)ethyl]-chroman in 35 ml of absolute dimethylformamide. The mixture is stirred for 16 hours at 60° and then, after cooling, is concentrated by evaporation under a high vacuum. Water is added to the oily residue and extraction is carried out with diethyl ether. The combined organic phases are washed with water and extracted with 2N hydrochloric acid. The combined hydrochloric acid extracts are rendered alkaline, while cold, with sodium hydroxide solution (30% strength) and extracted with dichloromethane. The combined dichloromethane phases are dried over sodium sulphate and concentrated by evaporation in vacuo. 2.17 g (85.7%) of crude product are obtained and are chromatographed on 110 g of silica gel (0.040-0.063 mm) using ethyl acetate as the eluant. 1.90 g (75.1%) of 1-[2-(chroman-2-yl)-ethyl]-piperidine-4-carboxylic acid ethyl ester are thus obtained in the form of a yellow oil. The 1-[2-(chroman-2-yl)ethyl]-piperidine-4-carboxylic acid ethyl ester hydrochloride produced therefrom using hydrochloric acid in diethyl ether crystallises from ethanol/diethyl ether and melts at 190-192°.

Example 26: 3.01 g (35 mmol) of acrylic acid methyl ester are added at 0-5°, while stirring, to a solution of 6.2 g (35 mmol) of 2-(2-aminoethyl)chroman in 200 ml of methanol. Stirring is continued for a further 16 hours at 0-5° and the mixture is then concentrated by evaporation in vacuo. 8.76 g (95.2%) of crude product are obtained and are chromatographed on 250 g of silica gel (0.040-0.063 mm) using ethyl acetate as the eluant. 5.10 g (55.4%) of N-[2-(chroman-2-yl)ethyl]-N-(2-methoxycarbonyl)ethyl)-amine are thus obtained in the form of a

yellow oil. The N-[2-(chroman-2-yl)ethyl]-N-(2-methoxycarbonyl)ethyl)-amine hydrochloride produced therefrom using hydrochloric acid in diethyl ether crystallises from methanol/diethyl ether and melts at 152-153°.

2-(2-aminoethyl)chroman can be manufactured, for example, in the following manner:

First, at room temperature and while stirring, 2.2 g (16.5 mmol) of aluminium chloride in 70 ml of absolute diethyl ether are added dropwise to a suspension of 3.8 g (100 mmol) of lithium aluminium hydride in 150 ml of absolute diethyl ether. Then 8.66 g (50 mmol) of 2-cyanomethylchroman in 70 ml of absolute tetrahydrofuran are added dropwise within a period of 20 minutes. The reaction mixture is stirred for a further 16 hours at room temperature and then carefully decomposed with 3.8 ml of water, 3.8 ml of sodium hydroxide solution (15% strength) and 11.4 ml of water. The precipitate formed is filtered off with suction and the filtrate is concentrated by evaporation in vacuo. The oily residue is dissolved in diethyl ether. The ethereal phase is washed with water, dried over sodium sulphate and concentrated by evaporation. 8.75 g (98.8%) of 2-(2-aminoethyl)chroman are obtained in the form of a colourless oil.

Example 27: 1.5 ml of concentrated hydrochloric acid are added to a solution of 4.81 g (0.015 mol) of 1-[2-(chroman-3-yl)-ethyl]-3-cyano-4-hydroxy-1,2,5,6-tetrahydropyridine hydrochloride or 1-[2-(chroman-3-yl)ethyl]-3-cyano-4-oxopiperidine hydrochloride in 100 ml of methanol (95% strength) and the whole is boiled under reflux for 15 hours. After cooling, the reaction

mixture is concentrated to a volume of approximately 30 ml under reduced pressure and the solution is poured into a mixture of 80 ml of 5N hydrochloric acid and 20 ml of toluene, whereupon, while stirring and cooling, 1-[2-(chroman-3-yl)ethyl]-4-hydroxy-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester hydrochloride or 1-[2-(chroman-3-yl)ethyl]-4-oxopiperidine-3-carboxylic acid methyl ester hydrochloride, respectively, having a melting point of 175-177° (decomposition) crystallises out.

The 1-[2-(chroman-3-yl)ethyl]-3-cyano-4-hydroxy-1,2,5,6-tetrahydropyridine hydrochloride or 1-[2-(chroman-3-yl)ethyl]-3-cyano-4-oxopiperidine hydrochloride can be manufactured, for example, in the following manner:

30 g (0.1 mol) of N-[2-(chroman-3-yl)ethyl]-N-(2-methoxycarbonyl)ethyl)-amine hydrochloride are dissolved in 100 ml of methanol, and then 10.5 g (0.1 mol) of triethylamine and 5.84 g (0.11 mol) of acrylonitrile are added to the solution and the whole is stirred for 15 hours at room temperature. The reaction mixture is then concentrated under a water-jet vacuum, the residue is taken up in diethyl ether and the ethereal solution is washed neutral with ice-water. The ethereal phase is dried over potassium carbonate and concentrated by evaporation. N-[2-(chroman-3-yl)-ethyl]-N-(2-cyanoethyl)-N-(2-methoxycarbonyl)ethyl)-amine is thus obtained in the form of a yellow oil.

A solution of 13.07 g (41.3 mmol) of N-[2-(chroman-3-yl)ethyl]-N-(2-cyanoethyl)-N-(2-methoxycarbonyl)ethyl)-amine in 200 ml of tetrahydrofuran is added dropwise under a nitrogen atmosphere to a suspension of 5.73 g of

sodium hydride (55% suspension in mineral oil) in 100 ml of tetrahydrofuran and the whole is stirred for 16 hours at room temperature. After adding 70 ml of 2N sulphuric acid, a yellow solution is obtained. 300 ml of diethyl ether and 100 ml of water are added thereto to form two phases. The aqueous phase is extracted three times with 100 ml of diethyl ether each time. The combined organic phases are dried over sodium sulphate, concentrated to approximately 100 ml under reduced pressure and then poured into a mixture of 80 ml of 5N hydrochloric acid and 20 ml of toluene, whereupon, while stirring and cooling, 1-[2-(chroman-3-yl)ethyl]-3-cyano-4-hydroxy-1,2,5,6-tetrahydropyridine hydrochloride or 1-[2-(chroman-3-yl)ethyl]-3-cyano-4-oxopiperidine hydrochloride crystallises out.

Example 28: 17.4 ml of n-butyllithium in hexane are added at 0-5° to a solution of 2.81 g of diisopropylamine in 30 ml of dry tetrahydrofuran. The whole is stirred for 30 minutes at room temperature, then cooled to -15° and a solution of 6.24 g (25 mmol) of 1-[2-(chroman-3-yl)ethyl]-4-oxopiperidine in 30 ml of tetrahydrofuran is added. After 15 minutes, a solution of 3.05 g (28 mmol) of chlorotrimethylsilane in 15 ml of tetrahydrofuran is added dropwise. The whole is stirred overnight at room temperature, the solution is filtered and the filtrate is concentrated to dryness by evaporation under reduced pressure. 1-[2-(chroman-3-yl)ethyl]-4-trimethylsilyloxy-1,2,5,6-tetrahydropyridine is thus obtained in the form of a pale yellow oil. 6.63 g (20 mmol) of the 1-[2-(chroman-3-yl)-ethyl]-4-trimethylsilyloxy-1,2,5,6-tetrahydropyridine obtained are dissolved in 50 ml of dichloromethane and the solution is added dropwise to a solution, cooled to 0°, of 2.3 g (24 mmol) of chloro-

formic acid methyl ester and 60 mg (2.4 mmol) of anhydrous zinc bromide in 50 ml of absolute dichloromethane. After warming up to room temperature, the reaction solution is stirred for one hour and then poured onto 150 ml of saturated sodium hydrogen carbonate solution. Extraction is carried out with dichloromethane, and the combined organic phases are dried over sodium sulphate and then concentrated by evaporation. The residue is dissolved in 70 ml of ethanol and the solution is acidified with ethanolic hydrochloric acid. After adding diethyl ether and after cooling, 1-[2-(chroman-3-yl)ethyl]-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester hydrochloride or 1-[2-(chroman-3-yl)-ethyl]-4-oxopiperidine-3-carboxylic acid methyl ester hydrochloride having a melting point of 175-177° crystallises out.

The 1-[2-(chroman-3-yl)ethyl]-4-oxopiperidine can be manufactured, for example, in the following manner:

First 8.45 g (55 mmol) of piperidone hydrochloride monohydrate and then 22.62 g (175 mmol) of N-ethyl-N,N-diisopropylamine are added to a solution of 16.62 g (50 mmol) of 3-[2-(p-toluenesulphonyloxy)ethyl]chroman in 100 ml of dimethylformamide. The mixture is stirred for 18 hours at 80° and, after cooling, is concentrated to dryness by evaporation under reduced pressure. The residue is dissolved in diethyl ether and washed with water. The organic phase is separated off and extracted with 2N hydrochloric acid. The hydrochloric acid extracts are combined, rendered alkaline, while cold, with concentrated sodium hydroxide solution and extracted with dichloromethane. The dichloromethane phases are combined, dried over sodium sulphate and concentrated to

dryness by evaporation under reduced pressure. A dark brown resin is obtained which is purified by chromatography on 350 g of silica gel (0.040-0.063 mm) using toluene/ethyl acetate (1:1) as the eluant. 1-[2-(chroman-3-yl)ethyl]-4-oxopiperidine is obtained in the form of a pale yellow oil.

Example 29: A solution of 2.7 g (25 mmol) of benzyl alcohol in 25 ml of tetrahydrofuran is added to a suspension of 1.2 g of sodium hydride (50% suspension in mineral oil) in 25 ml of dry tetrahydrofuran and, when the evolution of gas has subsided, the whole is heated under reflux for 30 minutes. After cooling, a solution of 8.5 g (25 mmol) of 1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester in 50 ml of tetrahydrofuran is added dropwise and the whole is heated under reflux again for 5 hours. After cooling, the solvent is removed. A mixture of cis- and trans-1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-4-benzyloxypiperidine-3-carboxylic acid methyl ester is obtained in the form of an oil.

Example 30: At -10° and while stirring, 1.41 g of sodium borohydride are introduced within a period of 90 minutes into a suspension of 8.45 g (18 mmol) of 1-[2-(chroman-3-yl)ethyl]-3-methoxycarbonylpyridinium p-toluenesulphonate in 43 ml of methanol. Stirring is continued for 1 hour at 0° and for 2 hours at room temperature and then 50 ml of water are added to the reaction mixture and extraction by shaking is carried out twice with 100 ml of dichloromethane each time. The dichloromethane phases are combined, dried over magnesium sulphate and concentrated to dryness by evaporation. The crude product is purified by chromatography on 150 g of silica gel (0.063-0.2 mm)

using ethyl acetate as the eluant. The main eluate, which is concentrated by evaporation, is treated with ethereal hydrochloric acid to yield 1-[2-(chroman-3-yl)ethyl]-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester hydrochloride having a melting point of 175-177°.

The 1-[2-(chroman-3-yl)ethyl]-3-methoxycarbonylpyridinium p-toluenesulphonate can be manufactured, for example, in the following manner:

16.6 g (50 mmol) of 3-[2-(p-toluenesulphonyloxy)ethyl]-chroman and 9.3 g (67.5 mmol) of pyridine-3-carboxylic acid methyl ester are suspended in 50 ml of butan-2-one and the suspension is boiled for 72 hours while stirring. It is cooled, the reaction mixture is concentrated under reduced pressure, and 1-[2-(chroman-3-yl)ethyl]-3-methoxycarbonylpyridinium p-toluenesulphonate is thus obtained in the form of a white foam.

Example 31: 33.2 g (0.1 mol) of 3-[2-(p-toluenesulphonyloxy)ethyl]chroman, 14.0 g of N-(2-methoxycarbonylethyl)-amine hydrochloride and 39 g of N-ethyl-N,N-diisopropylamine are dissolved under nitrogen in 750 ml of dimethylformamide and the solution is stirred for 16 hours at room temperature. The reaction mixture is subsequently concentrated to approximately 200 ml under reduced pressure, 500 ml of water are then added and the whole is extracted by shaking three times with 150 ml of dichloromethane each time. The combined organic phases are dried over sodium sulphate and concentrated to dryness by evaporation. By adding ethanolic hydrochloric acid and cooling, N-[2-(chroman-3-yl)ethyl]-N-(2-methoxycarbonylethyl)-amine hydrochloride

having a melting point of 190-192° is obtained.

Example 32: 6 ml of concentrated hydrochloric acid are added to a solution of 11.5 g (0.05 mmol) of N-[2-(chroman-3-yl)ethyl]-N-(2-cyanoethyl)-amine in 100 ml of methanol. The reaction mixture is boiled under reflux for 15 hours. After cooling, the solvent is removed under reduced pressure and the residue is crystallised from methanol/acetone. After recrystallisation from methanol/acetone, N-[2-(chroman-3-yl)ethyl]-N-(2-methoxycarbonyl)ethyl)-amine hydrochloride having a melting point of 190-192° is obtained (yield: 82%).

The N-[2-(chroman-3-yl)ethyl]-N-(2-cyanoethyl)-amine can be manufactured, for example, in the following manner:

17.7 g (0.1 mol) of 3-(2-aminoethyl)chroman are dissolved in 100 ml of methanol, and then 10.5 g (0.1 mol) of triethylamine and 5.84 g (0.11 mol) of acrylonitrile are added to the solution. The reaction mixture is stirred for 15 hours at room temperature and then concentrated under a water-jet vacuum. The residue is taken up in diethyl ether and washed neutral with ice-water. The ethereal phase is dried over potassium carbonate and concentrated by evaporation. N-[2-(chroman-3-yl)ethyl]-N-(2-cyanoethyl)amine is thus obtained in the form of a pale yellow oil.

Example 33: 5.2 g of a mixture of cis- and trans-1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-4-benzyloxypiperidine-3-carboxylic acid methyl ester are dissolved in 100 ml of methanol, and then 2 g of palladium-on-carbon (10%) are added and the whole is hydrogenated in a Parr apparatus for 12 hours at room temperature. The reaction mixture

is then filtered over diatomaceous earth and the filtrate is concentrated to dryness by evaporation. The crude oily residue is chromatographed on silica gel using toluene/ethyl acetate (9:1) as the eluant. First the trans-1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-4-hydroxypiperidine-3-carboxylic acid methyl ester and then the cis-1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-4-hydroxypiperidine-3-carboxylic acid methyl ester is eluted. In each case the purified fractions are combined and concentrated by evaporation. The residue that contains the trans product is treated with fumaric acid in methanol/diethyl ether and thus yields trans-1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-4-hydroxypiperidine-3-carboxylic acid methyl ester fumarate which crystallises out in the form of the hemihydrate and melts at 150-152°. The residue that contains the cis product is treated with ethereal hydrochloric acid and thus yields cis-1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-4-hydroxypiperidine-3-carboxylic acid methyl ester hydrochloride which has a melting point of 182-185°.

Example 34: 6.8 g (20 mmol) of a mixture of cis- and trans-1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-4-chloropiperidine-3-carboxylic acid methyl ester are dissolved in 20 ml of methanol. 40 ml (140 mmol) of a 3.5N solution of ammonia in methanol are added dropwise at room temperature. The mixture is left to stand at room temperature for 24 hours. The solvent is then removed under reduced pressure. The resulting residue is dissolved in dichloromethane, the solution is extracted by shaking with 2N hydrochloric acid and the acidic aqueous phase is separated off, rendered alkaline with sodium hydrogen carbonate and extracted with diethyl ether/dichloromethane (2:1). The organic extracts are

washed with saturated sodium chloride solution, dried over magnesium sulphate and freed of the solvent under reduced pressure. The resulting residue is chromatographed on basic silica gel using dichloromethane/-methanol (99:1) as the eluant. The eluates are combined and concentrated to dryness by evaporation. The oily residue consists of pure 4-amino-1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-piperidine-3-carboxylic acid amide (cis/trans mixture).

A mixture of cis- and trans-1-[2-(benzo-1,4-dioxan-2-yl)-ethyl]-4-chloropiperidine-3-carboxylic acid methyl ester can be obtained, for example, as follows:

9.7 g (30 mmol) of a mixture of cis- and trans-1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-4-hydroxypiperidine-3-carboxylic acid methyl ester (for manufacture see Example 33) and 3.6 g (36 mmol) of triethylamine are dissolved in 100 ml of dichloromethane. 3.92 g (33 mmol) of thionyl chloride are added dropwise while stirring at room temperature. The mixture is stirred for 4 hours at room temperature. The triethylamine hydrochloride formed is then filtered off and the filtrate, while cold, is extracted by shaking with saturated sodium hydrogen carbonate solution. The organic phase is washed with saturated sodium chloride solution, dried over magnesium sulphate and freed of the solvent under reduced pressure. The resulting mixture of cis- and trans-1-[2-(benzo-1,4-dioxan-2-yl)ethyl]-4-chloropiperidine-3-carboxylic acid methyl ester is used further in the crude state.

Example 35: At room temperature and while stirring, a solution of 11.94 g (30 mmol) of N-(3-ethoxycarbonylpropyl)-N-(2-bromoethyl)-N-[2-(chroman-3-yl)ethyl]-amine

in 40 ml of absolute dimethylformamide is added dropwise within a period of 20 minutes to a suspension of 2.72 g (40 mmol) of sodium ethoxide in 30 ml of dimethylformamide. The reaction mixture is stirred for 16 hours at room temperature and then concentrated to dryness by evaporation under a high vacuum. Diethyl ether is added to the residue and extraction is carried out with cold 2N hydrochloric acid. The combined hydrochloric acid extracts are extracted by shaking with dichloromethane and the dichloromethane phases are dried over sodium sulphate and concentrated by evaporation in vacuo. The crude product is obtained as the residue and is chromatographed on 500 g of silica gel (0.040-0.063 mm) using ethyl acetate as the eluant. The eluate is concentrated by evaporation to yield 1-[2-(chroman-3-yl)ethyl]-piperidine-4-carboxylic acid ethyl ester in the form of a colourless oil. The 1-[2-(chroman-3-yl)ethyl]-piperidine-4-carboxylic acid ethyl ester hydrochloride produced therefrom using hydrochloric acid in diethyl ether crystallises from ethanol/diethyl ether and melts at 182-186°.

The N-(3-ethoxycarbonylpropyl)-N-(2-bromoethyl)-N-[2-(chroman-3-yl)ethyl]-amine can be manufactured, for example, in the following manner:

17.7 g (0.1 mol) of 3-(2-aminoethyl)chroman are dissolved in 100 ml of methanol, and then 10.5 g (0.1 mol) of triethylamine and 19.5 g (0.1 mol) of 4-bromobutyric acid ethyl ester are added to the solution. The reaction mixture is stirred for 15 hours at room temperature and is then concentrated under a water-jet vacuum. The residue is taken up in diethyl ether and washed neutral with ice-water. The ethereal phase is dried over

potassium carbonate and concentrated by evaporation. Oily N-(3-ethoxycarbonylpropyl)-N-[2-(chroman-3-yl)-ethyl]-amine is thus obtained and can be used further in crude form.

29.1 g (0.1 mol) of N-(3-ethoxycarbonylpropyl)-N-[2-(chroman-3-yl)ethyl]-amine are dissolved in 200 ml of methanol, and then 10.5 g (0.1 mol) of triethylamine and 18.8 g (0.1 mol) of 1,2-dibromoethane are added to the solution. The reaction mixture is stirred for 16 hours at room temperature and then concentrated under a water-jet vacuum. The residue is taken up in diethyl ether and washed neutral with ice-water. The ethereal phase is dried over potassium carbonate and concentrated by evaporation. N-(3-ethoxycarbonylpropyl)-N-(2-bromoethyl)-N-[2-(chroman-3-yl)ethyl]-amine is thus obtained in the form of an oil which can be used further in the crude state.

Example 36: In a manner analogous to that described in Examples 4, 5, 10, 12, 23, 26, 31 and 32, it is also possible to obtain N-[2-(chroman-4-yl)ethyl]-N-(2-methoxycarbonylethyl)-amine and its hydrochloride.

Example 37: In a manner analogous to that described in Examples 1 to 3, 6 to 9, 11, 13 to 22, 24, 25, 27 to 30 and 33 to 35 it is also possible to obtain 1-[2-(chroman-4-yl)ethyl]-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester and its hydrochloride and 1-[2-(chroman-4-yl)ethyl]-piperidine-3-carboxylic acid ethyl ester and its hydrochloride.

Example 38: Tablets, each comprising 25 mg of active ingredient, for example 1-(benzo-1,4-dioxan-2-ylmethyl)-piperidine-3-carboxylic acid methyl ester hydrochloride, can be manufactured in the following manner:

Constituents (for 1000 tablets):

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

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

Example 39: Tablets, each comprising 50 mg of the active ingredient, for example 1-(benzo-1,4-dioxan-2-ylmethyl)-piperidine-3-carboxylic acid methyl ester hydrochloride, are manufactured as follows:

Composition (for 10,000 tablets):

active ingredient	500.00 g
lactose	140.80 g
potato starch	274.70 g
stearic acid	10.00 g
talc	50.00 g
magnesium stearate	2.50 g
colloidal silica	32.00 g
ethanol	q.s.

A mixture of the active ingredient, the lactose and 194.70 g of the potato starch is moistened with an ethanolic solution of the stearic acid and granulated through a sieve. After drying, the remainder of the potato starch, the talc, the magnesium stearate and the colloidal silica are admixed and the mixture is compressed to form tablets that each weigh 0.1 g and that may, if desired, be provided with dividing notches for finer adjustment of the dosage.

100 mg of active ingredient can be incorporated in an analogous manner.

Example 40: Capsules, each comprising 0.025 g of the active ingredient, for example 1-(benzo-1,4-dioxan-2-ylmethyl)-piperidine-3-carboxylic acid methyl ester hydrochloride, can be manufactured as follows:

Composition (for 1000 capsules):

active ingredient	25.00 g
lactose	249.00 g
gelatine	2.00 g
corn starch	10.00 g
talc	15.00 g
water	q.s.

The active ingredient is mixed with the lactose and the mixture is moistened uniformly with an aqueous solution of the gelatine and is granulated by being passed through a sieve having a mesh width of from 1.2 to 1.5 mm. The granulate is mixed with the dried corn starch and the talc and 300 mg portions are filled into hard gelatine capsules (size 1).

Example 41: In a manner analogous to that described in Examples 38 to 40, it is also possible to manufacture pharmaceutical preparations that comprise N-[2-(chroman-3-yl)ethyl]-N-(2-methoxycarbonyl)ethyl)-amine hydrochloride as active ingredient.

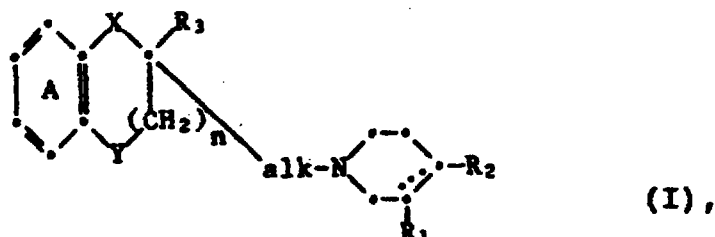
Example 42: In a manner analogous to that described in Examples 38 to 41, it is also possible to manufacture pharmaceutical preparations that comprise as active ingredient a different compound of the formula I or a tautomer and/or a pharmaceutically acceptable salt thereof or a different compound of the formula IVc or a

pharmaceutically acceptable salt thereof, for example according to Examples 1 to 37.



Patent claims for Contracting States: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE.

1. A compound of the formula



in which either R_1 represents carboxy, lower alkoxy-carbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, hydroxymethyl, C_2 - C_5 alkanoyloxymethyl, lower alkanesulphonyloxymethyl, benzoyloxymethyl or pyridoyloxymethyl and R_2 represents hydrogen, hydroxy, lower alkoxy, benzyloxy, C_2 - C_5 alkanoyloxy, lower alkane-sulphonyloxy, benzoyloxy, pyridoyloxy, amino, C_2 - C_5 -alkanoylamino, lower alkanesulphonylamino, benzoylamino or pyridoylamino, or R_1 represents hydrogen and R_2 represents carboxy, lower alkoxy-carbonyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, hydroxy-methyl, C_2 - C_5 alkanoyloxymethyl, lower alkanesulphonyloxy-methyl, benzoyloxymethyl or pyridoyloxymethyl, R_3 represents hydrogen or C_1 - C_7 alkyl, alk represents lower alkylene that bridges the two ring systems by up to and including 3 carbon atoms, or alk represents lower alkylidene, the ring A is unsubstituted or is mono-, di- or poly-substituted by hydroxy, lower alkoxy, C_2 - C_5 -alkanoyloxy, halogen having an atomic number of up to and including 53, C_1 - C_7 alkyl and/or by trifluoromethyl, the dotted line is intended to indicate the presence of a single or a double bond between the carbon atoms carrying the radicals R_1 and R_2 , and either each of X and Y represents an oxygen atom and n represents 1, or X represents a methylene group, Y represents an oxygen atom and n represents 1, or X represents an oxygen atom, Y



represents a methylene group and n represents 1, or X represents a direct bond, Y represents an oxygen atom and n represents 2, radicals designated "lower" containing from 1 up to and including 4 carbon atoms, or a tautomer and/or salt thereof.

2. A compound of the formula I according to claim 1 in which R_1 represents carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl or N,N-di-lower alkylcarbamoyl, R_2 represents hydrogen, hydroxy, lower alkoxy, benzyloxy, C_2 - C_5 alkanoyloxy, lower alkane-sulphonyloxy, benzoyloxy, pyridoyloxy, amino, C_2 - C_5 -alkanoylamino, benzoylamino or pyridoylamino, R_3 represents hydrogen or C_1 - C_7 alkyl, alk represents lower alkylene that bridges the two ring systems by up to and including 3 carbon atoms, or alk represents lower alkylidene, the ring A is unsubstituted or is mono-, di- or poly-substituted by hydroxy, lower alkoxy, C_2 - C_5 -alkanoyloxy, halogen having an atomic number of up to and including 53, C_1 - C_7 alkyl and/or by trifluoromethyl, the dotted line is intended to indicate the presence of a single or a double bond between the carbon atoms carrying the radicals R_1 and R_2 , X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n represents 1, radicals designated "lower" containing from 1 up to and including 4 carbon atoms, or a tautomer and/or salt thereof.

3. A compound of the formula I according to claim 1 in which either R_1 represents C_1 - C_4 alkoxycarbonyl, carbamoyl, hydroxymethyl or C_2 - C_5 alkanoyloxymethyl and R_2 represents hydrogen or hydroxy, or R_1 represents hydrogen and R_2 represents C_1 - C_4 alkoxycarbonyl, R_3 represents hydrogen or C_1 - C_4 alkyl, alk represents C_1 - C_4 alkylene that bridges the two ring systems by up to and including 3 carbon atoms, the ring A is unsubstituted or is sub-



stituted, especially in the 7-position, by C₁-C₄alkoxy, the dotted line is intended to indicate the presence of a single or a double bond between the carbon atoms carrying the radicals R₁ and R₂, and either each of X and Y represents an oxygen atom and n represents 1, or X represents a methylene group, Y represents an oxygen atom and n represents 1, or X represents an oxygen atom, Y represents a methylene group and n represents 1, or X represents a direct bond, Y represents an oxygen atom and n represents 2, or a tautomer and/or salt thereof.

4. A compound of the formula I according to claim 1 in which R₁ represents C₁-C₄alkoxycarbonyl, R₂ represents hydrogen or hydroxy, R₃ represents hydrogen or C₁-C₄-alkyl, alk represents C₁-C₄alkylene that bridges the two ring systems by up to and including 3 carbon atoms, the ring A is unsubstituted, the dotted line is intended to indicate the presence of a single or a double bond between the carbon atoms carrying the radicals R₁ and R₂, X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n represents 1, or a tautomer and/or salt thereof.

5. A compound of the formula I according to claim 1 in which R₁ represents C₁-C₄alkoxycarbonyl, R₂ represents hydrogen or hydroxy, R₃ represents hydrogen, alk represents methylene or ethylene, the ring A is unsubstituted, the dotted line is intended to indicate the presence of a single or a double bond between the carbon atoms carrying the radicals R₁ and R₂, X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n represents 1, or a tautomer and/or salt thereof.

6. 4-Hydroxy-1-(chroman-3-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester or 1-(chroman-3-ylmethyl)-4-oxo-piperidine-3-carboxylic acid methyl



ester, 1-[2-(chroman-3-yl)-ethyl]-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester, 1-(benzo-1,4-dioxan-2-ylmethyl)-piperidine-3-carboxylic acid methyl ester or 4-hydroxy-1-(benzo-1,4-dioxan-2-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester or 1-(benzo-1,4-dioxan-2-ylmethyl)-4-oxopiperidine-3-carboxylic acid methyl ester or, respectively, a salt thereof.

7. 1-[2-(Chroman-3-yl)-ethyl]-1,2,5,6-tetrahydropyridine-3-carboxylic acid ethyl ester or a salt thereof.

8. 1-(Chroman-3-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester, 1-[2-(chroman-3-yl)-ethyl]-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester or 1-[2-(chroman-3-yl)-ethyl]-4-oxopiperidine-3-carboxylic acid methyl ester, 1-(benzo-1,4-dioxan-2-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester, 4-hydroxy-1-(2-methylbenzo-1,4-dioxan-2-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester or 1-(2-methylbenzo-1,4-dioxan-2-ylmethyl)-4-oxopiperidine-3-carboxylic acid methyl ester, 1-[2-(benzo-1,4-dioxan-2-yl)-ethyl]-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester or 1-[2-(benzo-1,4-dioxan-2-yl)-ethyl]-4-oxopiperidine-3-carboxylic acid methyl ester, cis-1-[2-(benzo-1,4-dioxan-2-yl)-ethyl]-4-hydroxypiperidine-3-carboxylic acid methyl ester, trans-1-[2-(benzo-1,4-dioxan-2-yl)-ethyl]-4-hydroxypiperidine-3-carboxylic acid methyl ester or 1-[2-(benzo-1,4-dioxan-2-yl)-ethyl]-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester or, respectively, a salt thereof.

9. 1-[2-(Chroman-3-yl)-ethyl]-piperidine-3-carboxylic acid ethyl ester, 1-[2-(chroman-3-yl)-ethyl]-piperidine-4-carboxylic acid ethyl ester, 1-[2-(benzo-1,4-dioxan-2-



yl)-ethyl]-piperidine-3-carboxylic acid ethyl ester, 1-[2-(benzo-1,4-dioxan-2-yl)-ethyl]-piperidine-4-carboxylic acid ethyl ester, 1-[2-(chroman-2-yl)-ethyl]-piperidine-3-carboxylic acid ethyl ester, 1-[2-(chroman-2-yl)-ethyl]-piperidine-4-carboxylic acid ethyl ester, cis-1-[2-(benzo-1,4-dioxan-2-yl)-ethyl]-4-benzyloxy-piperidine-3-carboxylic acid methyl ester, trans-1-[2-(benzo-1,4-dioxan-2-yl)-ethyl]-4-benzyloxy-piperidine-3-carboxylic acid methyl ester, cis-4-amino-1-[2-(benzo-1,4-dioxan-2-yl)-ethyl]-piperidine-3-carboxylic acid amide, trans-4-amino-1-[2-(benzo-1,4-dioxan-2-yl)-ethyl]-piperidine-3-carboxylic acid amide, 1-[2-(chroman-4-yl)-ethyl]-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester or 1-[2-(chroman-4-yl)-ethyl]-piperidine-3-carboxylic acid ethyl ester or, respectively, a salt thereof.

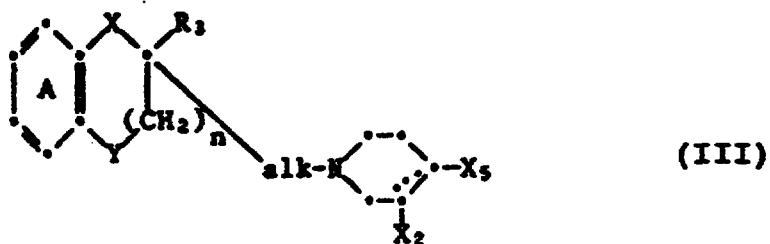
10. A process for the manufacture of a compound of the formula I, or a tautomer and/or salt thereof, according to any one of claims 1 to 9, characterised in that
a) a compound of the formula



or a salt thereof, in which X_1 represents hydroxy or reactive esterified hydroxy, is reacted with a compound of the formula

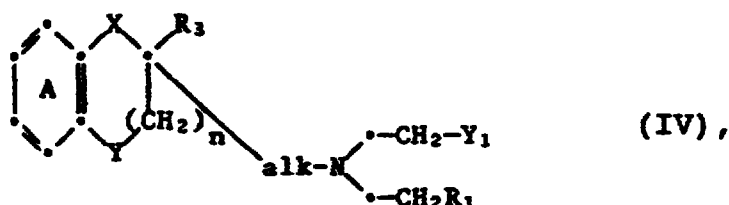


or a tautomer and/or salt thereof, or
b) in a compound of the formula



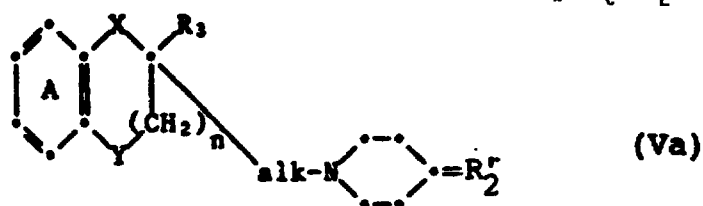
or a tautomer and/or salt thereof, in which X_2 represents a radical that can be converted into R_1 that is other than hydrogen, and X_5 represents a radical R_a , and R_a represents hydrogen, hydroxy, lower alkoxy, benzyloxy, C_2 - C_5 alkanoyloxy, lower alkanesulphonyloxy, benzoyloxy, pyridoyloxy, amino, C_2 - C_5 alkanoylamino, lower alkane-sulphonylamino, benzoylamino or pyridoylamino, X_2 is converted into R_1 that is other than hydrogen, or in a compound of the formula III in which X_2 represents hydrogen and X_5 represents a radical that can be converted into R_b , and R_b represents a radical R_2 other than a radical R_a , X_5 is converted into R_b , or

c) for the manufacture of a compound of the formula I or a tautomer and/or salt thereof, in which R_2 represents hydroxy or amino and R_1 is other than hydrogen and represents especially lower alkoxycarbonyl, a compound of the formula



in which Y_1 represents a group of the formula $-CH=R_2^1$, $-C(Y_2)=R_2^1$, $-CH(Y_2)-R_2$ or cyano, wherein R_2^1 represents oxo or imino and Y_2 represents a removable radical, or a salt thereof, is cyclised, or

d) for the manufacture of a compound of the formula I' or a tautomer and/or salt thereof, in which R_2^1 represents oxo or imino and R_1 is other than hydrogen and represents especially lower alkoxycarbonyl, a compound of the formula

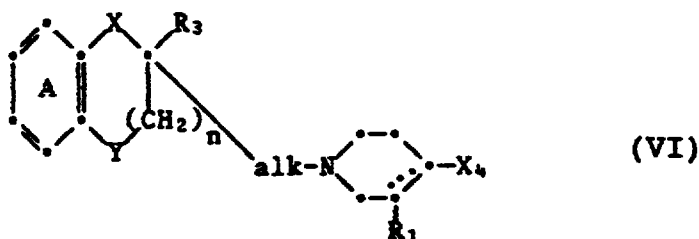


or a tautomer, or in each case a salt thereof, is reacted with a compound of the formula



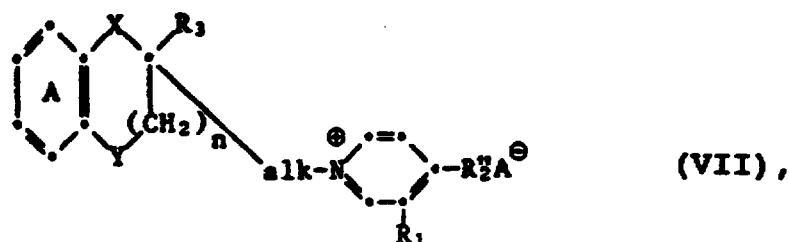
or a salt thereof, in which R_1 is other than hydrogen and X_3 represents halogen or lower alkoxy, or

e) for the manufacture of a compound of the formula I or a tautomer and/or salt thereof, in which R_2 represents hydroxy, lower alkoxy, benzyloxy, C_2 - C_5 alkanoyloxy, lower alkanesulphonyloxy, benzoyloxy, pyridoyloxy, amino, C_2 - C_5 alkanoylamino, lower alkanesulphonylamino, benzoylamino or pyridoylamino, in a compound of the formula



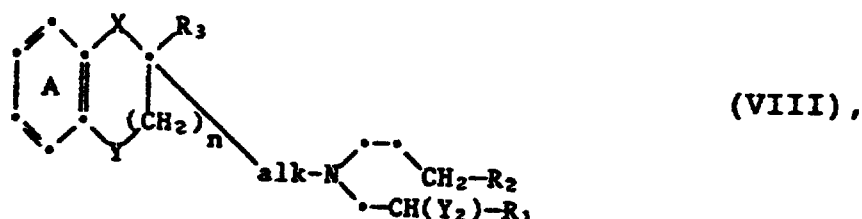
or in a salt thereof, in which X_4 represents a radical that can be converted into R_2 , X_4 is converted into R_2 , or

f) especially for the manufacture of a compound of the formula I or a tautomer and/or salt thereof, in which R_2 is hydrogen, hydroxy, amino, carboxy, lower alkoxy-carbonyl, N-lower alkylcarbamoyl, N,N-di-lower alkyl-carbamoyl or hydroxymethyl, in a compound of the formula



in which $A^{\ominus}$ represents the anion of an acid and R_2 represents hydrogen, lower alkoxy, benzyloxy, C_2 - C_5 -alkanoyloxy, lower alkanesulphonyloxy, benzoyloxy, pyridoyloxy, protected hydroxy, C_2 - C_5 alkanoylamino, lower alkanesulphonylamino, benzoylamino, pyridoylamino, protected amino, carboxy, lower alkoxycarbonyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, C_2 - C_5 -alkanoyloxymethyl, lower alkanesulphonyloxymethyl, benzoyloxymethyl, pyridoyloxymethyl or etherified or protected hydroxymethyl, the excess double bonds are reduced to single bonds, or

g) for the manufacture of a compound of the formula I or a tautomer and/or salt thereof, in which R_2 represents carboxy, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl or especially lower alkoxycarbonyl, a compound of the formula

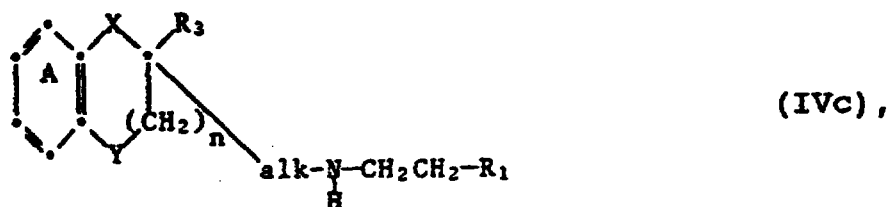


in which Y_2 represents a removable radical, or a salt thereof, is cyclised, and in the case of each of processes a) to g), a protecting group which may be present is removed, and, if desired, a compound of the formula I obtainable in accordance with the process or by other means is converted into a different compound of the formula I, an isomeric mixture obtainable in accordance with the process is separated into the components, an enantiomeric or diastereoisomeric mixture obtainable in



accordance with the process is separated into the enantiomers or diastereoisomers, respectively, and/or a free compound of the formula I obtainable in accordance with the process is converted into a salt or a salt obtainable in accordance with the process is converted into the free compound of the formula I or into a different salt, radicals designated "lower" containing from 1 up to and including 4 carbon atoms.

11. A compound of the formula



in which R_1 represents carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, hydroxymethyl, C_2 - C_5 alkanoyloxymethyl, lower alkanesulphonyloxymethyl, benzoyloxymethyl or pyridoyloxymethyl, R_3 represents hydrogen or C_1 - C_7 alkyl, alk represents lower alkylene or lower alkylidene, the ring A is unsubstituted or is mono- or poly-substituted by hydroxy, lower alkoxy, C_2 - C_5 alkanoyloxy, halogen having an atomic number of up to and including 53, C_1 - C_7 alkyl and/or by trifluoromethyl, and either each of X and Y represents an oxygen atom and n represents 1, or X represents a methylene group, Y represents an oxygen atom and n represents 1, or X represents an oxygen atom, Y represents a methylene group and n represents 1, or X represents a direct bond, Y represents an oxygen atom and n represents 2, with the proviso that in compounds of the formula IVc in which the ring A is unsubstituted, each of X and Y represents oxygen, n represents 1 and R_3 represents hydrogen, alk is other than methylene if R_1 represents carbamoyl or N-methyl-, N-ethyl-, N,N-dimethyl- or N,N-diethyl-carbamoyl, radicals designated



"lower" containing from 1 up to and including 4 carbon atoms, or a salt thereof.

12. A compound of the formula IVc according to claim 11 in which R_1 represents carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl or N,N-di-lower alkylcarbamoyl, R_3 represents hydrogen or C_1 - C_7 alkyl, alk represents lower alkylene or lower alkylidene, the ring A is unsubstituted or is mono- or poly-substituted by hydroxy, lower alkoxy, C_2 - C_5 alkanoyloxy, halogen having an atomic number of up to and including 53, C_1 - C_7 alkyl and/or by trifluoromethyl, X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n represents 1, with the proviso that in compounds of the formula IVc in which the ring A is unsubstituted, each of X and Y represents oxygen, n represents 1 and R_3 represents hydrogen, alk is other than methylene if R_1 represents carbamoyl or N-methyl-, N-ethyl-, N,N-dimethyl- or N,N-diethyl-carbamoyl, radicals designated "lower" containing from 1 up to and including 4 carbon atoms, or a salt thereof.

13. A compound of the formula IVc according to claim 11 in which R_1 represents carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, hydroxymethyl, C_2 - C_5 alkanoyloxymethyl, lower alkanesulphonyloxymethyl, benzoyloxymethyl or pyridoyloxymethyl, R_3 represents hydrogen or C_1 - C_7 alkyl, alk represents lower alkylene that links the ring system with the NH group shown in formula IVc by up to and including 3 carbon atoms, or alk represents lower alkylidene, the ring A is unsubstituted or is mono-, di- or poly-substituted by hydroxy, lower alkoxy, C_2 - C_5 alkanoyloxy, halogen having an atomic number of up to and including 53, C_1 - C_7 alkyl and/or by trifluoromethyl, and either each of X and Y represents an oxygen atom and n repre-



sents 1, or X represents a methylene group, Y represents an oxygen atom and n represents 1, or X represents an oxygen atom, Y represents a methylene group and n represents 1, or X represents a direct bond, Y represents an oxygen atom and n represents 2, with the proviso that in compounds of the formula IVc in which the ring A is unsubstituted, each of X and Y represents oxygen, n represents 1 and R_3 represents hydrogen, alk is other than methylene if R_1 represents carbamoyl or N-methyl-, N-ethyl-, N,N-dimethyl- or N,N-diethyl-carbamoyl, radicals designated "lower" containing from 1 up to and including 4 carbon atoms, or a salt thereof.

14. A compound of the formula IVc according to claim 11 in which R_1 represents carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl or N,N-di-lower alkylcarbamoyl, R_3 represents hydrogen or C_1 - C_7 alkyl, alk represents lower alkylene that links the ring system with the NH group shown in formula IVc by up to and including 3 carbon atoms, or alk represents lower alkylidene, the ring A is unsubstituted or is mono-, di- or poly-substituted by hydroxy, lower alkoxy, C_2 - C_5 alkanoyloxy, halogen having an atomic number of up to and including 53, C_1 - C_7 alkyl and/or by trifluoromethyl, X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n represents 1, with the proviso that in compounds of the formula IVc in which the ring A is unsubstituted, each of X and Y represents oxygen, n represents 1 and R_3 represents hydrogen, alk is other than methylene if R_1 represents carbamoyl or N-methyl-, N-ethyl-, N,N-dimethyl- or N,N-diethyl-carbamoyl, radicals designated "lower" containing from 1 up to and including 4 carbon atoms, or a salt thereof.

15. A compound of the formula IVc according to claim 11 in which R_1 represents carboxy, hydroxymethyl, C_2 - C_5 -



alkanoyloxymethyl, C_1 - C_4 alkoxycarbonyl or carbamoyl, R_3 represents hydrogen or C_1 - C_4 alkyl, alk represents C_1 - C_4 alkylene that links the ring system with the NH group shown in formula IVc by up to and including 3 carbon atoms, the ring A is unsubstituted or is substituted, especially in the 7-position, by C_1 - C_4 alkoxy, and either each of X and Y represents an oxygen atom and n represents 1, or X represents a methylene group, Y represents an oxygen atom and n represents 1, or X represents an oxygen atom, Y represents a methylene group and n represents 1, or X represents a direct bond, Y represents an oxygen atom and n represents 2, with the proviso that in compounds of the formula IVc in which the ring A is unsubstituted, each of X and Y represents oxygen, n represents 1 and R_3 represents hydrogen, alk is other than methylene if R_1 represents carbamoyl, or a salt thereof.

16. A compound of the formula IVc according to claim 11 in which R_1 represents C_1 - C_4 alkoxycarbonyl, R_3 represents hydrogen or C_1 - C_4 alkyl, alk represents C_1 - C_4 alkylene that links the ring system with the NH group shown in formula IVc by up to and including 3 carbon atoms, the ring A is unsubstituted, X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n represents 1, or a salt thereof.

17. A compound of the formula IVc according to claim 11 in which R_1 represents C_1 - C_4 alkoxycarbonyl, R_3 represents hydrogen, alk represents methylene or ethylene, the ring A is unsubstituted, X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n represents 1, or a salt thereof.

18. N-[2-(Chroman-3-yl)-ethyl]-N-(2-methoxycarbonyl-ethyl)-amine or a salt thereof.



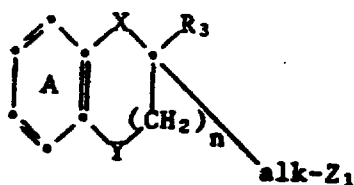
19. N-(2-Methoxycarbonyl-ethyl)-N-(benzo-1,4-dioxan-2-ylmethyl)-amine or a salt thereof.

20. N-(2-Methoxycarbonyl-ethyl)-N-(chroman-3-ylmethyl)-amine, N-[2-(benzo-1,4-dioxan-2-yl)-ethyl]-N-(2-methoxycarbonyl-ethyl)-amine or N-(2-methoxycarbonyl-ethyl)-N-(2-methylbenzo-1,4-dioxan-2-ylmethyl)-amine or, respectively, a salt thereof.

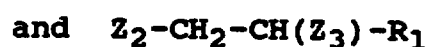
21. N-[2-(Chroman-3-yl)-ethyl]-N-(2-carboxyethyl)-amine, N-[2-(chroman-2-yl)-ethyl]-N-(2-methoxycarbonyl-ethyl)-amine or N-[2-(chroman-4-yl)-ethyl]-N-(2-methoxycarbonyl-ethyl)-amine or, respectively, a salt thereof.

22. A process for the manufacture of a compound of the formula IVc, or a salt thereof, according to any one of claims 11 to 21, characterised in that

h) compounds of the formulae



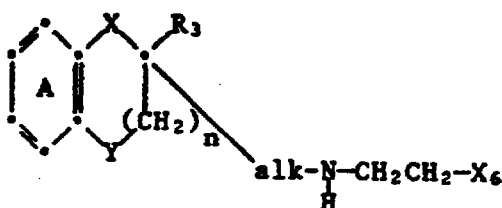
(VIIIa)



(VIIIb),

in which one of the radicals Z_1 and Z_2 represents reactive esterified hydroxy and the other represents amino and Z_3 represents hydrogen, or Z_1 represents amino and Z_2 and Z_3 together represent an additional bond, or optionally salts of these compounds, are reacted with one another, or

i) in a compound of the formula

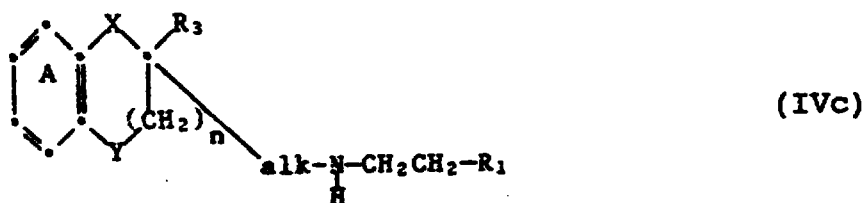


(IX)



in which X_6 represents a radical that can be converted into R_1 , or in a salt thereof, X_6 is converted into R_1 , and, if desired, in the case of each of processes h) and i), a compound of the formula IVc obtainable in accordance with the process or by other means is converted into a different compound of the formula IVc, an isomeric mixture obtainable in accordance with the process is separated into the components, an enantiomeric or diastereoisomeric mixture obtainable in accordance with the process is separated into the enantiomers or diastereoisomers, respectively, and/or a free compound of the formula IVc obtainable in accordance with the process is converted into a salt or a salt obtainable in accordance with the process is converted into the free compound of the formula IVc or into a different salt.

23. A compound of the formula

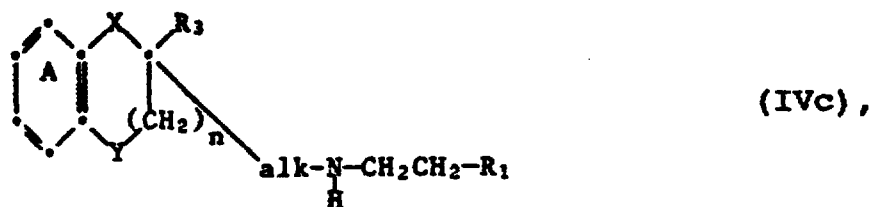


in which R_1 represents carboxy, lower alkoxy carbonyl, carbamoyl, N-lower alkyl carbamoyl, N,N-di-lower alkyl carbamoyl, hydroxymethyl, C_2 - C_5 alkanoyloxymethyl, lower alkanesulphonyloxymethyl, benzoyloxymethyl or pyridoyloxymethyl, R_3 represents hydrogen or C_1 - C_7 alkyl, alk represents lower alkylene or lower alkylidene, the ring A is unsubstituted or is mono- or poly-substituted by hydroxy, lower alkoxy, C_2 - C_5 alkanoyloxy, halogen having an atomic number of up to and including 53, C_1 - C_7 alkyl and/or by trifluoromethyl, and either each of X and Y represents an oxygen atom and n represents 1, or X represents a methylene group, Y represents an oxygen atom and n represents 1, or X represents an oxygen atom, Y represents a methylene group and n represents 1, or X



represents a direct bond, Y represents an oxygen atom and n represents 2, radicals designated "lower" containing from 1 up to and including 4 carbon atoms, or a pharmaceutically acceptable salt thereof, for use in a method for the therapeutic and/or prophylactic treatment of the human or animal body.

24. A compound of the formula



in which R_1 represents carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl or N,N-di-lower alkylcarbamoyl, R_3 represents hydrogen or C_1 - C_7 alkyl, alk represents lower alkylene or lower alkylidene, the ring A is unsubstituted or is mono- or poly-substituted by hydroxy, lower alkoxy, C_2 - C_5 alkanoyloxy, halogen having an atomic number of up to and including 53, C_1 - C_7 alkyl and/or by trifluoromethyl, X represents an oxygen atom or a methylene group, Y represents an oxygen atom and n represents 1, radicals designated "lower" containing from 1 up to and including 4 carbon atoms, or a pharmaceutically acceptable salt thereof, for use in a method for the therapeutic and/or prophylactic treatment of the human or animal body.

25. A compound according to any one of claims 1 to 9 and 11 to 21 or if appropriate a tautomer and/or a pharmaceutically acceptable salt thereof for use in a method for the therapeutic and/or prophylactic treatment of the human or animal body.

26. A compound according to any one of claims 2, 4, 6, 8, 12, 14 and 16 to 20 or if appropriate a tautomer and/or a



pharmaceutically acceptable salt thereof for use in a method for the therapeutic and/or prophylactic treatment of the human or animal body.

27. A compound of the formula IVc according to claim 23 in which R_1 represents carbamoyl or N-methyl-, N-ethyl-, N,N-dimethyl- or N,N-diethyl-carbamoyl, R_3 represents hydrogen, alk represents methylene, the ring A is unsubstituted, each of X and Y represents an oxygen atom and n represents 1, or a pharmaceutically acceptable salt thereof, for use in a method for the therapeutic and/or prophylactic treatment of the human or animal body.

28. A pharmaceutical preparation comprising as active ingredient a compound according to any one of claims 1 to 9, 11 to 21, 23 and 25 or if appropriate a tautomer and/or a pharmaceutically acceptable salt thereof, optionally together with customary pharmaceutical adjuncts.

29. A pharmaceutical preparation comprising as active ingredient a compound according to any one of claims 2, 4, 6, 8, 12, 14, 16 to 20, 24, 26 and 27 or if appropriate a tautomer and/or a pharmaceutically acceptable salt thereof, optionally together with customary pharmaceutical adjuncts.

30. The use of a compound according to any one of claims 1 to 9, 11 to 21, 23 and 25, or if appropriate a tautomer and/or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical preparation, for example a nootropic.