FORM 1

603470

SPRUSON & FERGUSON

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

F Hoffmann-La Roche & Co Aktiengesellschaft, of Grenzacherstrasse 124-184, 4002 Basle, SWITZERLAND, hereby apply for the grant of a standard patent for an invention entitled:

Hydrocinnamic Acid Derivatives

which is described in the accompanying complete specification.

Details of basic application(s):-

Basic Applic. No:	Country:	Application Date:
2764/87	CH	21 July 1987

The address for service is:-

Spruson & Ferguson
Patent Attorneys
Level 33 St Martins Tower
31 Market Street
Sydney New South Wales Australia

DATED this FIFTEENTH day of JULY 1988

F Hoffmann-La Roche & Co Aktiengesellschaft

By:

Registered Patent Attorney

TO: THE COMMISSIONER OF PATENTS
OUR REF: 62841
S&F CODE: 55541

5845/2

COMMONWEALTH OF AUSTRALIA

THE PATENTS ACT 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

AUSTRALIA CONVENTION STANDARD & PETTY PATENT DECLARATION

In support of the Convention Application made for a patent for an invention entitled:

PAN 4083/12

Title of Invention

Hydrocinnamic Acid Derivatives

Full name(s) and address(es) of Declarant(s)

I Fridolin Klausner

of 187 Baselmattweg, 4123 Allschwil, Switzerland

do solemnly and sincerely declare as follows:—

Full name(s) of Applicant(s)

1. I am authorised by

F.HOFFMANN-LA ROCHE & CO. Aktiengesellschaft,

of 124-184 Grenzacherstrasse, Basle, Switzerland,

the applicant~~(s)~~ for the patent to make this declaration on its/~~their~~ behalf.

2. The basic application~~(s)~~ as defined by Section 141 of the Act was/~~were~~ made

Basic Country(ies)

in Switzerland

Priority Date(s)

on July 21, 1987

Basic Applicant(s)

by [X] F. HOFFMANN-LA ROCHE & CO., Aktiengesellschaft

[ ] the inventor(s) cited in paragraph 3.

Full name(s) and address(es) of inventor(s)

3.
1) Werner Aschwanden, 4 Grellingerstrasse, 4107 Ettingen, Switzerland
2) René Imhof, 3 Bleumatthöhe, 5264 Gipf-Oberfrick, Switzerland
3) Roland Jakob-Roetne, 26 Oberer Baselblick, 7854 Inzlingen, Germany
4) Emilio Kyburz, 127 Unterer Rebbergweg, 4153 Reinach, Switzerland

(respectively)

~~is~~/are the actual inventor(s) of the invention and the facts upon which the applicant~~(s)~~ is/~~are~~ entitled to make the application are as follows:

Set out how Applicant(s) derive title from actual inventor(s) e.g. The Applicant(s) is/are the assignee(s) of the invention from the inventor(s)

( ) the inventor(s) have assigned the invention to Hoffmann-La Roche Inc., Nutley, USA, who have re-assigned all their rights for Australia to the Applicant.

(x) the Applicant is the assignee of the invention from the inventor(s).

4. The basic application~~(s)~~ referred to in paragraph 2 of this Declaration was/~~were~~ the first application~~(s)~~ made in a Convention country in respect of the invention~~(s)~~ the subject of the application.

Declared at Basle, this 9th day of June, 1988

To:

The Commissioner of Patents,
COMMONWEALTH OF AUSTRALIA

Fridolin Klausner

Signature of Declarant(s)

(12) PATENT ABRIDGMENT (11) Document No. AU-B-19176/88
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 603470

(54) Title
HYDROCINNAMIC ACID DERIVATIVES

International Patent Classification(s)
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(71) Applicant(s)
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(74) Attorney or Agent
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(56) Prior Art Documents
US 4732979
EP 230967
DE 2141598

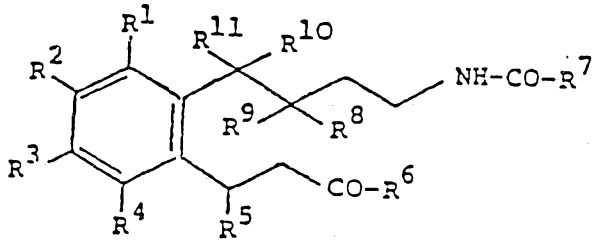
(57) Objects of the present invention are compounds of general formula I and pharmaceutically usable salts thereof per se and as pharmaceutically active substances, a process for the manufacture of these compounds and salts, medicaments containing these and the manufacture of such medicaments, as well as the use of compounds of general formula I and of pharmaceutically usable salts thereof in the control or prevention of illnesses or in the improvement of health, especially in the control or prevention of cerebral insufficiency or in the improvement of cognitive functions, and the use of compounds of general formula I and of pharmaceutically usable salts thereof for the manufacture of medicaments for the control or prevention of cerebral insufficiency or for the improvement of cognitive functions.

CLAIM

1. Hydrocinnamic acid derivatives of the general

.../2

formula



I

wherein

- one or two of the symbols R^1 to R^4 signify halogen or methoxy and the remainder signify hydrogen;
- R^5 signifies hydrogen or phenyl;
- R^6 signifies a residue of the formula

$$\underset{(a)}{-OR^{12}} \text{ or } \underset{(b)}{-NR^{13}R^{14}};$$

- R^7 signifies (C_1-C_4)-alkyl, (C_2-C_5)--alkanoylamino-(C_2-C_5)-alkyl, amino or (C_1-C_4)-alkoxyphenyl;
- R^8 and R^9 each signify hydrogen or (C_1-C_4)--alkyl;
- R^{10} signifies hydrogen and R^{11} signifies hydroxy or R^{10} and R^{11} together signify oxo;
- R^{12} signifies hydrogen, (C_1-C_{10})-alkyl, pyridylmethyl or carbamoylmethyl;
- R^{13} signifies hydrogen, (C_1-C_4)-alkyl and R^{14} signifies hydrogen, (C_1-C_4)-alkyl, pyridyl, phenyl-(C_1-C_4)-alkyl, carboxy-(C_1-C_4)-alkyl, carbamoyl-(C_1-C_4)-alkyl, (C_1-C_4)-alkoxycarbonyl-(C_1-C_4)-alkyl, di-(C_1-C_4)-alkoxycarbonyl-(C_2-C_5)-alkyl, piperidino-(C_2-C_4)--alkyl or halopyridinecarboxamido-(C_2-C_4)-alkyl or R^{13} and R^{14} together with the nitrogen atom signify 4-(C_1-C_4)-alkyl-piperazin-1-yl,

as well as pharmaceutically usable salts of basic

.../3

compounds of formula I with acids or of acidic compounds of formula I with bases.

S & F Ref: 62841

FORM 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

603470

FOR OFFICE USE:

Class Int Class

Complete Specification Lodged:
Accepted:
Published:

Priority:

Related Art:

This document contains the amendments made under Section 49 and is correct for printing.

Name and Address of Applicant: F Hoffmann-La Roche & Co Aktiengesellschaft
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SWITZERLAND

Address for Service: Spruson & Ferguson, Patent Attorneys
Level 33 St Martins Tower, 31 Market Street
Sydney, New South Wales, 2000, Australia

Complete Specification for the invention entitled:

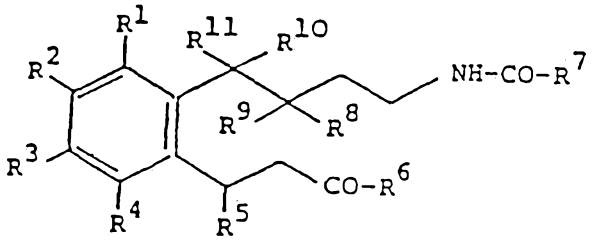
Hydrocinnamic Acid Derivatives

The following statement is a full description of this invention, including the best method of performing it known to me/us

5845/3

Abstract

Hydrocinnamic acid derivatives of the general formula



I

wherein

- one or two of the symbols R^1 to R^4 signify halogen or methoxy and the remainder signify hydrogen;
- R^5 signifies hydrogen or phenyl;
- R^6 signifies a residue of the formula

$$-OR^{12} \text{ (a)} \quad \text{or} \quad -NR^{13}R^{14} \text{ (b)};$$

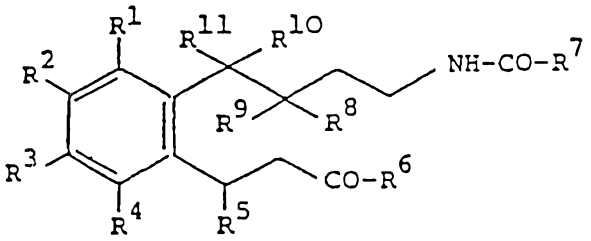
- R^7 signifies (C_1-C_4)-alkyl, (C_2-C_5)--alkanoylamino-(C_2-C_5)-alkyl, amino or (C_1-C_4)-alkoxyphenyl;
- R^8 and R^9 each signify hydrogen or (C_1-C_4)--alkyl;
- R^{10} signifies hydrogen and R^{11} signifies hydroxy or R^{10} and R^{11} together signify oxo;
- R^{12} signifies hydrogen, (C_1-C_{10})-alkyl, pyridylmethyl or carbamoylmethyl;
- R^{13} signifies hydrogen, (C_1-C_4)-alkyl and R^{14} signifies hydrogen, (C_1-C_4)-alkyl, pyridyl, phenyl-(C_1-C_4)-alkyl, carboxy-(C_1-C_4)-alkyl, carbamoyl-(C_1-C_4)-alkyl, (C_1-C_4)-alkoxycarbonyl-(C_1-C_4)-alkyl, di-(C_1-C_4)-alkoxy-

carbonyl-(C_2-C_5)-alkyl, piperidino-(C_2-C_4)-
-alkyl or halopyridinecarboxamido-(C_2-C_4)-alkyl or
R^{13} and R^{14} together with the nitrogen atom
signify 4-(C_1-C_4)-alkyl-piperazin-1-yl,

as well as pharmaceutically usable salts of basic compounds of formula I with acids or of acidic compounds of formula I with bases are suitable for the control or prevention of cerebral insufficiency or for the improvement of cognitive functions.

RAN 4083/12

The present invention is concerned with hydrocinnamic acid derivatives. In particular, it is concerned with hydrocinnamic acid derivatives of the general formula



I

wherein

- one or two of the symbols R^1 to R^4 signify halogen or methoxy and the remainder signify hydrogen;
- R^5 signifies hydrogen or phenyl;
- R^6 signifies a residue of the formula

$$-OR^{12} \text{ or } -NR^{13}R^{14};$$
(a) (b)

- R^7 signifies (C_1-C_4)-alkyl, (C_2-C_5)--alkanoylamino-(C_2-C_5)-alkyl, amino or (C_1-C_4)-alkoxyphenyl;
- R^8 and R^9 each signify hydrogen or (C_1-C_4)--alkyl;
- R^{10} signifies hydrogen and R^{11} signifies hydroxy or R^{10} and R^{11} together signify oxo;
- R^{12} signifies hydrogen, (C_1-C_{10})-alkyl, pyridyl-methyl or carbamoylmethyl;

- R^{13} signifies hydrogen, (C_1-C_4)-alkyl and R^{14} signifies hydrogen, (C_1-C_4)-alkyl, pyridyl, phenyl-(C_1-C_4)-alkyl, carboxy-(C_1-C_4)-alkyl, carbamoyl-(C_1-C_4)-alkyl, (C_1-C_4)-alkoxy-carbonyl-(C_1-C_4)-alkyl, di-(C_1-C_4)-alkoxy-carbonyl-(C_2-C_5)-alkyl, piperidino-(C_2-C_4)--alkyl or halopyridinecarboxamido-(C_2-C_4)-alkyl or R^{13} and R^{14} together with the nitrogen atom signify 4-(C_1-C_4)-alkyl-piperazin-1-yl,

as well as pharmaceutically usable salts of basic compounds of formula I with acids or of acidic compounds of formula I with bases.

These compounds and salts are novel and are distinguished by valuable pharmacodynamic properties.

Objects of the present invention are compounds of general formula I and pharmaceutically usable salts thereof per se and as pharmaceutically active substances, a process for the manufacture of these compounds and salts, medicaments containing these and the manufacture of such medicaments, as well as the use of compounds of general formula I and of pharmaceutically usable salts thereof in the control or prevention of illnesses or in the improvement of health, especially in the control or prevention of cerebral insufficiency or in the improvement of cognitive functions, and the use of compounds of general formula I and of pharmaceutically usable salts thereof for the manufacture of medicaments for the control or prevention of cerebral insufficiency or for the improvement of cognitive functions.

The term "alkyl" used in the present description denotes straight-chain or branched saturated hydrocarbon residues such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl, t-butyl and the like. The term

"alkoxy" denotes an alkyl residue in the sense of the previous definition which is attached via an oxygen atom. The term "alkanoyl" denotes residues which are derived from alkanecarboxylic acids by elimination of the hydroxyl group and accordingly embraces residues such as acetyl and the like. The term "di-alkoxycarbonylalkyl" denotes alkyl residues which are substituted by two alkoxycarbonyl groups, but not situated on the same carbon atom.

R^4 can conveniently signify hydrogen, in which case conveniently either R^1 signifies chlorine and R^2 and R^3 signify hydrogen or R^1 signifies hydrogen and R^2 and R^3 signify chlorine or R^1 and R^2 signify hydrogen and R^3 signifies fluorine, chlorine or methoxy. Preferably, R^3 signifies chlorine and R^1, R^2 and R^4 signify hydrogen.

R^5 preferably signifies hydrogen.

When R^6 is a residue of formula (a) above, then R^{12} conveniently signifies hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, tert.-butyl, n-nonyl, 5-nonyl, 3-pyridylmethyl or carbamoylmethyl. When R^6 is a residue of formula (b) above, then conveniently either R^{13} and R^{14} both signify hydrogen or both signify ethyl or R^{13} and R^{14} together with the nitrogen atom signify 4-methylpiperazin-1-yl or R^{13} signifies hydrogen and R^{14} signifies 4-pyridyl, 2-phenylethyl, 2-piperidinoethyl, carboxymethyl, ethoxycarbonylmethyl, carbamoylmethyl, 1-ethoxycarbonylethyl, 1,4-bis-(ethoxycarbonyl)-2-butyl or 2-(5-chloro-2-pyridinecarboxamido)-ethyl. Preferably, R^{12} signifies ethyl, n-propyl, isopropyl, n-nonyl or carbamoylmethyl or R^{13} signifies hydrogen and R^{14} signifies hydrogen, ethoxycarbonylmethyl or 1,4-bis-(ethoxycarbonyl)-2-butyl.

R^7 conveniently signifies methyl, 3-acetylaminopropyl, amino or p-methoxyphenyl, preferably methyl or 3-acetylaminopropyl.

Conveniently, R^8 and R^9 both signify hydrogen or both signify methyl, preferably both signify hydrogen.

Preferably, R^{10} and R^{11} together signify oxo.

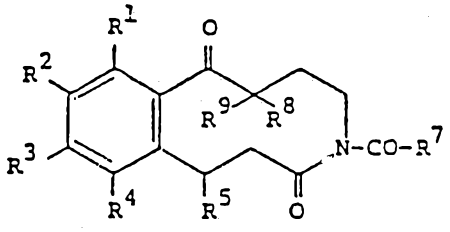
Particularly preferred compounds of general formula I are: ethyl N-[2-(4-acetamidobutyryl)-5 -chlorohydrocinnamoyl]glycinate, ethyl 2-[4-(4-acetamidobutyramido)-butyryl]-5-chlorohydrocinnamate, 2-[4-(4-acetamidobutyramido)butyryl]-5-chlorohydrocinnamide, nonyl 2-(4--acetamidobutyryl)-5-chlorohydrocinnamate, ethyl 2-(4--acetamidobutyryl)-5-chlorohydrocinnamate and 2-(4-acetamidobutyryl)-N-(carbamoylmethyl)-5-chlorohydrocinnamide.

Further especially preferred compounds of general formula I are: isopropyl 2-(4-acetamidobutyryl)-5-chlorohydrocinnamate, diethyl 2-[2-(4-acetamidobutyryl)-5--chlorohydrocinnamoyl]-L-glutamate and carbamoylmethyl 2-(4-acetamidobutyryl)-5-chlorohydrocinnamate.

Examples of further preferred compounds of general formula I are: 2-(4-acetamidobutyryl)-5-chlorohydrocinnamide and propyl 2-(4-acetamidobutyryl)-5-chlorohydrocinnamate.

The compounds of general formula I and pharmaceutically acceptable salts thereof can be manufactured in accordance with the invention by

a) treating a benzazecinedione of the general formula



II

wherein R^1, R^2, R^3, R^4, R^5, R^7, R^8 and R^9 have the above significance,

with an acid in the presence of a compound of the general formula

$$HOR^{12'} \qquad III$$

wherein $R^{12'}$ signifies hydrogen or (C_1-C_{10})--alkyl;

or

b) esterifying a compound of formula I in which R^6 signifies a residue of formula (a) and R^{12} signifies hydrogen, or a reactive derivative thereof, to give a corresponding compound of formula I in which R^6 signifies a residue of formula (a) and R^{12} is different from hydrogen; or

c) reacting a compound of formula I in which R^6 signifies a residue of formula (a) and R^{12} signifies hydrogen, or a reactive derivative thereof, with a compound of the general formula

$$HNR^{13}R^{14'} \qquad IV$$

wherein R^{13} has the above significance and $R^{14'}$ has the significance given above for R^{14}, but is not carboxy-(C_1-C_4)-alkyl,

or reacting a compound of formula I in which R^6 signifies a residue of formula (b) and R^{14} signifies carboxy-(C_1-C_4)-alkyl, or a reactive derivative thereof, with ammonia; or

d) reducing a compound of formula I in which R^{10} and R^{11} together signify oxo; or

e) hydrolyzing a compound of formula I in which R^6 signifies a residue of formula (b) and R^{14} signifies (C_1-C_4)-alkoxycarbonyl-(C_1-C_4)-alkyl to give a corresponding compound of formula I in which R^6 signifies a residue of formula (b) and R^{14} signifies carboxy-(C_1-C_4)-alkyl; or

f) converting a basic compound of formula I into a pharmaceutically usable salt by means of an acid or converting an acidic compound of formula I into a pharmaceutically usable salt by means of a base.

Compounds of formula I in which R^6 signifies a residue of formula (a) above, R^{12} signifies hydrogen or (C_1-C_{10})-alkyl and R^{10} and R^{11} together signify oxo are obtained in accordance with variant a) of the process in accordance with the invention.

If it is desired to convert a compound of formula II into a corresponding compound of formula I in which R^6 signifies a residue of formula (a) and R^{12} signifies (C_1-C_{10})-alkyl, then there is used a compound of formula III in which $R^{12'}$ signifies (C_1-C_{10})-alkyl, i.e. a corresponding alcohol. This alcohol can simultaneously serve as the solvent; it is, however, also possible

to add a different solvent, for example a halogenated hydrocarbon such as methylene chloride. A strong inorganic acid such as concentrated hydrochloric acid or the like is conveniently used as the acid. The reaction is conveniently effected at about room temperature and takes several (e.g. 10) hours to a few (e.g. 5) days.

If it is desired to convert a compound of formula II into a corresponding compound of formula I in which R^6 signifies a residue of formula (a) above and R^{12} signifies hydrogen, then there is used a compound of formula III in which $R^{12'}$ signifies hydrogen, i.e. water. In this case, the compound of formula II is conveniently dissolved in a polar aprotic solvent such as tetrahydrofuran, acetonitrile or the like and then aqueous acid, for example dilute (e.g. 2N) hydrochloric acid or the like, is added thereto. With respect to the reaction temperature and to the reaction duration, these are analogous to those described previously.

Aspect b) of the process in accordance with the invention is an esterification which can be carried out according to methods which are generally usual and which are familiar to any person skilled in the art.

The carboxylic acid to be esterified can be used conveniently in the form of one of its reactive derivatives, for example in the form of an acid halide (e.g. an acid chloride), an imidazolide etc, which is then reacted with the corresponding hydroxyl compound. In this case, the reactive functional derivative of the carboxylic acid, which can be prepared, for example, by means of thionyl chloride, carbonyldiimidazole etc, need not be isolated, but can be produced in situ. As reactive functional derivatives of the carboxylic acids to be esterified there can also be used silver salts; the

desired ester is obtained from such a silver salt by reaction with a corresponding halide. The reaction conditions such as temperature, duration, solvent etc vary according to the nature of the reactive carboxylic acid derivative which is used.

Free carboxylic acids can be used, for example, when the esterification is carried out by means of a component containing an olefinic double bond. Thus, a corresponding t-butyl ester is obtained by treating a free carboxylic acid with isobutylene in the presence of a small amount of a strong mineral acid (e.g. concentrated sulphuric acid).

In accordance with aspect c) of the process in accordance with the invention a carboxylic acid is converted into an amide which is optionally appropriately substituted on the nitrogen atom, which can be effected according to methods which are known per se and which are familiar to any person skilled in the art.

When a free carboxylic acid is used, then the reaction is effected with a compound of formula IV or with ammonia in the presence of a dehydrating agent such as dicyclohexylcarbodiimide. The reaction is conveniently effected in an organic solvent which is inert under the reaction conditions, e.g. in an ether such as tetrahydrofuran etc, it takes several (e.g. 10-20) hours and is conveniently carried out at about room temperature.

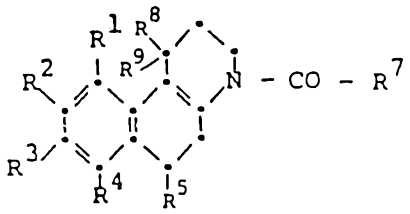
As reactive functional derivatives of the carboxylic acids used in this aspect of the process in accordance with the invention there are suitable, for example, their esters, their imidazolides etc, whereby the imidazolides need not be isolated, but can be produced in situ. The reaction conditions such as solvent, temperature, duration etc vary depending on the nature of the reactive functional carboxylic acid derivative which is used.

Compounds of formula I in which R^{10} signifies hydrogen and R^{11} signifies hydroxy are obtained in accordance with aspect d) of the process in accordance with the invention. The reduction is conveniently effected by means of a complex hydride in an organic solvent which is inert under the reaction conditions, for example by means of sodium borohydride in methanol etc. The reduction is conveniently effected at about room temperature and takes about 1 to a few hours.

The hydrolysis in accordance with aspect e) of the process in accordance with the invention is effected according to methods which are know per se and which are familiar to any person skilled in the art, conveniently under alkaline conditions, e.g. by means of an alkali metal hydroxide such as sodium hydroxide, in water or in a mixture of water and a water-miscible organic solvent such as tetrahydrofuran. It takes about 1 to a few hours and is conveniently effected at about room temperature.

The salt formation in accordance with aspect f) of the process in accordance with the invention is effected according to methods which are generally usual and which are familiar to any person skilled in the art. Basic compounds of formula I can be converted into pharmaceutically acceptable acid addition salts, for example with hydrogen chloride, hydrogen bromide, phosphoric acid, sulphuric acid, citric acid, p-toluenesulphonic acid and the like. Acidic compounds of formula I can form pharmaceutically acceptable salts with suitable bases, for example alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts as well as salts with amines such as triethanolamine, diethylaminoethanol, triethylamine, trimethylamine, diethylamine etc.

The starting materials of formula II can be prepared by oxidizing a benzoquinoline derivative of the general formula

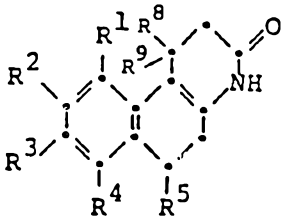


V

wherein R^1, R^2, R^3, R^4, R^5, R^7, R^8 and R^9 have the significance mentioned earlier.

Compounds of formula V can, in turn, be obtained by

aa) reducing a benzoquinolinone derivative of the general formula

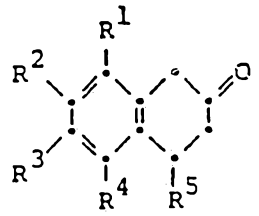


VI

wherein R^1, R^2, R^3, R^4, R^5, R^8 and R^9 have the significance mentioned earlier,

or

bb) reacting a compound of the formula



VII

wherein R^1, R^2, R^3, R^4 and R^5 have the significance mentioned earlier,

in the presence of a strong base with a compound of the general formula

$$X\text{-}(CH_2)_3\text{-}NH_2 \qquad \text{VIII}$$

wherein X signifies a leaving group,

and appropriately N-substituting the compound obtained.

The oxidation of benzoquinoline derivatives of general formula V to corresponding benzazecinediones of general formula II is conveniently effected by means of m-chloroperbenzoic acid in an inert organic solvent, for example in a halogenated hydrocarbon such as chloroform and the like, conveniently at temperatures of about -20°C to about 30°C, preferably between about -5°C and about room temperature.

Furthermore, this oxidation can also be carried out conveniently by means of potassium permanganate and sodium periodate, conveniently in a two-phase system consisting of water and an organic solvent which is not miscible therewith, e.g. a halogenated hydrocarbon such as methylene chloride and the like. In this case there is

preferably added a phase transfer catalyst, especially a quaternary ammonium salt such as benzyltriethylammonium chloride and the like. Again, the oxidation by means of potassium permanganate/sodium periodate can be carried out conveniently at temperatures between about 0°C and about 30°C, for example at about room temperature.

Furthermore, oxidation agents or oxidation systems such as peracetic acid, hydrogen peroxide and formic acid or p-toluenesulphonic acid, chromic acid, Jones reagent and the like are suitable for carrying out the oxidation in question.

The reduction of a benzoquinolinone derivative of general formula VI is conveniently effected by means of a complex hydride such as lithium aluminium hydride and the like in an organic solvent which is inert under the reaction conditions, conveniently in an ether such as tetrahydrofuran, dioxan and the like. The reduction can be effected at temperatures between about room temperature and about 120°C, conveniently at the reflux temperature.

The reaction of a compound of formula VII with a compound of formula VIII is effected in the presence of a strong base, conveniently in the presence of an inorganic base such as potassium or sodium hydroxide, a quaternary ammonium base such as benzyltrimethylammonium hydroxide and the like. The leaving group denoted by the symbol X in formula VIII is conveniently a halogen atom, especially a chlorine atom, but other equivalent leaving groups also come into consideration, e.g. alkylsulphonyloxy groups such as mesyloxy, arylsulphonyloxy groups such as benzene-sulphonyloxy, p-toluenesulphonyloxy, p-bromobenzene-sulphonyloxy and the like. The compound of formula VIII is conveniently used in the form of an acid addition salt, for example as the hydrochloride. The reaction is effected

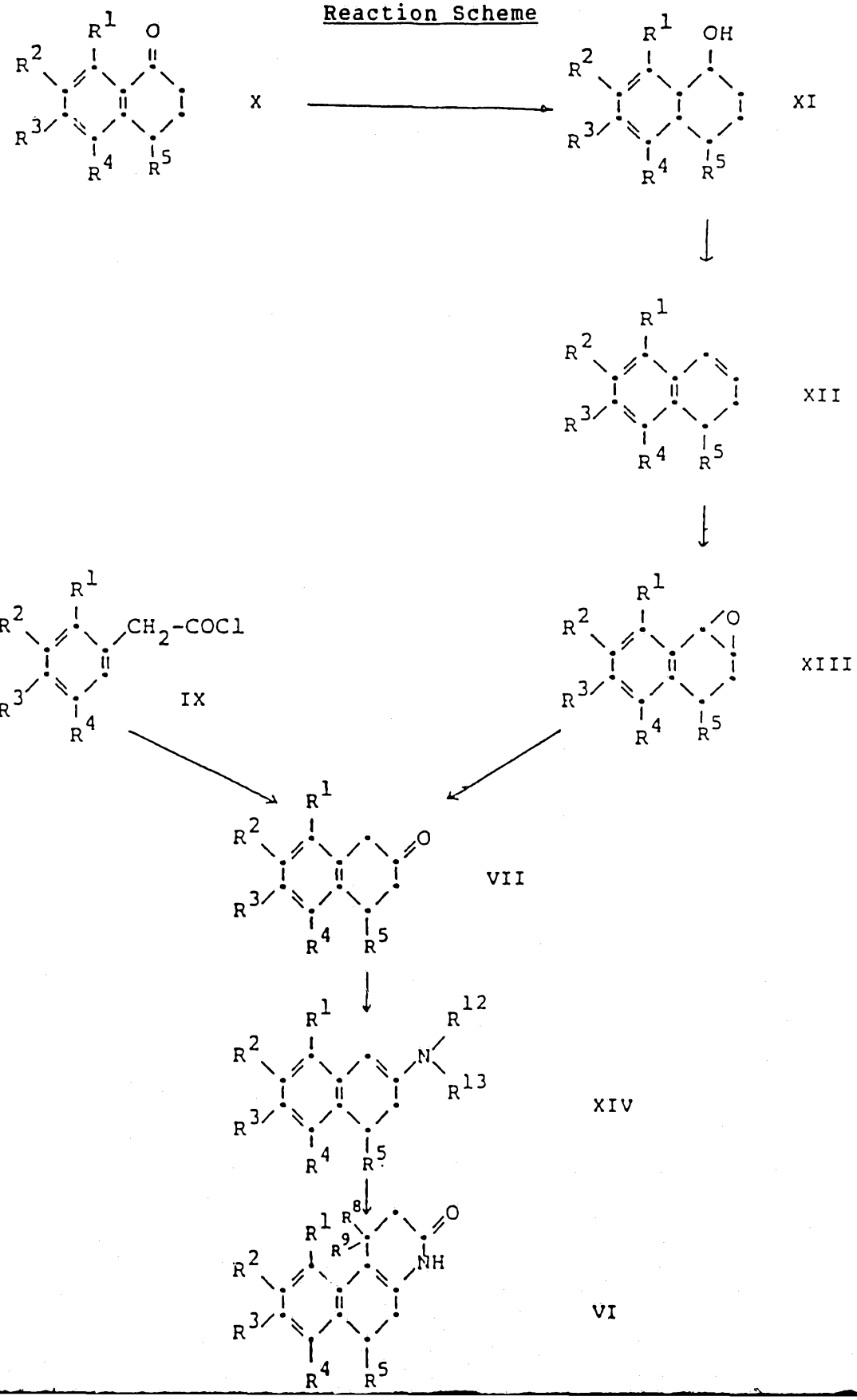
in the presence of an organic solvent which is inert under the reaction conditions, for example in an aromatic hydrocarbon such as toluene and the like. The reaction of the compounds of formulae VII and VIII can be effected conveniently at between temperatures of about 30°C and about 110°C, preferably at the reflux temperature.

Not only in the reduction of a benzoquinolinone derivative of general formula VI, but also in the reaction of compounds of formula VII and VIII, there are obtained compounds which are unsubstituted on the nitrogen and which subsequently must be N-acylated, and for the preparation of compounds of formula II in which R^7 signifies (C_1-C_4)-alkyl or (C_1-C_4)-alkoxyphenyl there are used as acylating agents reactive derivatives of the corresponding carboxylic acids, conveniently anhydrides such as acetic anhydride, carboxylic acid chlorides such as p-methoxybenzoyl chloride and the like. For the preparation of compounds of formula II in which R^7 signifies amino, the compound which is unsubstituted on the nitrogen can be reacted with α-chloroacetyl isocyanate and the compound obtained can be reacted with hydrazine hydrate. For the preparation of compounds of formula II in which R^7 signifies (C_2-C_5)-alkanoylamino-(C_2-C_5)-alkyl, the compound which is unsubstituted on the nitrogen can be reacted with a phthalimido-(C_2-C_5)-alkanoyl halide, the product obtained can be converted by means of hydrazine hydrate into the corresponding free amine and, finally, this can be acylated with a reactive derivative of the corresponding carboxylic acid such as acetyl chloride.

The preparation of compounds of general formulae VI and VII is conveniently effected in accordance with the following Reaction Scheme in which R^1, R^2, R^3, R^4, R^5, R^8 and R^9 have the significance mentioned

earlier and R^{12} and R^{13} each signify lower alkyl or together with the nitrogen atom signify a heterocyclic residue such as pyrrolin-1-yl, pyrrolidin-1-yl, piperidino, morpholino, 4-(C_1-C_4-alkyl)-piperazin-1-yl and the like.

Reaction Scheme



Compounds of formula VII can be prepared in one step from compounds of formula IX by reaction with ethylene or styrene in the presence of aluminium chloride or another Lewis acid which is suitable as a catalyst for such reactions. The reaction is effected in the presence of an organic solvent which is inert under the reaction conditions, conveniently in an halogenated hydrocarbon such as methylene chloride.

Compounds of formula VII can, however, also be prepared by a multi-step synthesis starting from compounds of formula X. Firstly, the compound of formula X is reduced to the corresponding compound of formula XI, conveniently with a complex hydride such as sodium borohydride or the like. The compound of formula XI obtained is then dehydrated to the corresponding compound of formula XII, conveniently under acidic conditions, e.g. by means of a strong acid such as p-toluenesulphonic acid or the like in a solvent which is not miscible with water but which distils azeotropically at the reflux temperature, whereby the water which results is removed continuously. The compound of formula XII is then oxidized to the corresponding compound of formula XIII, conveniently by means of m-chloroperbenzoic acid or the like in an organic solvent which is inert under the reaction conditions, for example in a chlorinated hydrocarbon such as methylene chloride. Compounds of formula VII are then obtained from corresponding compounds of formula XIII, for example by treatment with an ethereal solution of magnesium bromide or by treatment with an organic sulphonic acid such as p-toluenesulphonic acid or the like in an inert organic solvent such as toluene or the like.

For the preparation of a compound of formula XIV, a corresponding compound of formula VII is reacted with a secondary amine of the formula $HNR^{12}R^{13}$ such as e.g.

pyrrolidine in the presence of an acid, conveniently an organic sulphonic acid such as p-toluenesulphonic acid or the like, in an organic solvent which is inert under the reaction conditions, for example in an aromatic hydrocarbon such as benzene; the water which thereby results is removed from the reaction system, for example by the addition of molecular sieve or by azeotropic distillation. Compounds of formula VI are finally obtained by reacting a corresponding compound of formula XIV with acrylamide, 3,3-dimethylacrylamide or the like. The reaction with acrylamide is conveniently effected in the presence of an acid, e.g. an organic sulphonic acid such as p-toluenesulphonic acid, an acidic ion-exchanger or the like, at temperatures of about 100°C to about 200°C, conveniently of about 100-150°C, whereby (C_1-C_4)-alkanols such as ethanol or the like can be used as the solvent. The reaction with 3,3-dimethylacrylamide is conveniently effected in the presence of tetramethoxysilane and caesium fluoride in an aromatic hydrocarbon such as toluene at about the reflux temperature.

As mentioned above, the hydrocinnamic acid derivatives of formula I and their pharmaceutically usable salts are novel compounds with extremely valuable pharmacodynamic properties. They have only a low toxicity, and it has been shown that in the animal experiment described hereinafter they are capable of counteracting cerebral insufficiency produced experimentally.

The test apparatus is a "Skinner box" with an electrifiable grid floor (30 x 40 cm) and a grey plastic platform (15 x 15 x 0.8 cm) in the front right corner. Untrained male rats (100-120 g) are placed individually on the platform. As soon as they climb down on to the grid floor they receive an electric foot-shock (0.8 mA). The normal reaction of untrained rats is thereupon to jump back on to

the platform. Since, however, the rats still attempt to climb down again, the foot-shock procedure must by repeated three to five times for each animal. After these three to five repetitions per animal the rats have learnt a so-called "passive avoidance response", i.e. they no longer attempt to descend to the grid floor, as they know that they are punished when they do so.

Immediately thereafter three groups each comprising 30 animals are set up. The first group receives an injection (i.p.) of 0.3 mg/kg of scopolamine as well as distilled water (2 ml/kg p.o.). The second group receives an injection (i.p.) of 0.3 mg/kg of scopolamine and an oral dosage of the test substance. The third group receives only distilled water (p.o.).

2 hours later each rat is placed once on the platform in the "Skinner box". The criterion for the assessment of this test for the determination of the effect of a preparation on the short-term memory is whether the animal remains or does not remain for 60 seconds on the platform (the result can thus only read "yes" or "no" for each animal). The statistical significance of the difference between the results obtained in the first and in the second groups is determined by means of the Chi-Square test.

70-75% of the animals treated only with distilled water (p.o.) still remember 2-4 hours after learning the "passive avoidance response" that they should remain on the platform. In the case of 85-92% of the animals treated with scopolamine (0.3 mg/kg i.p.) and distilled water (p.o.) there can be established during 3-4 hours a retrograde effect on the short-term memory, i.e. they have forgotten that they must remain on the platform. A substance which is capable of counteracting cerebral

insufficiency can reverse the blocking of the short-term memory caused by the injection (i.p.) of 0.3 mg/kg of scopolamine. A dosage of a preparation is denoted as "active" against scopolamine if the number of positive results ("yes") is significantly different from those of control animals treated with scopolamine (0.3 mg/kg i.p.) and only distilled water (p.o.).

In the following Table there are given dosages in which certain compounds of formula I exhibit a significant activity in the test previously described. Moreover, the Table contains data for the acute toxicity (LD_{50} in mg/kg in the case of single oral administration to mice).

Table

R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}	Significant active dosage mg/kg p.o.	LD 50 mg/kg p.o.
H	H	Cl	H	H	$NHCH_2COOC_2H_5$	CH_3	H	H	Oxo		0.003 0.03 0.3 3 10	> 5000
H	H	Cl	H	H	OC_2H_5	$(CH_2)_3NHCOCH_3$	H	H	Oxo		0·003 0·03 0·3	> 5000
H	H	Cl	H	H	NH_2	$(CH_2)_3NHCOCH_3$	H	H	Oxo		0·00001 0·00003 0·0003 0·003 0·03	
H	H	Cl	H	H	$OCH(CH_3)_2$	CH_3	H	H	Oxo		0·01 0·03 0·1 0.3 1 3 10 30	> 4000
H	H	Cl	H	H	OC_2H_5	CH_3	H	H	Oxo		0·03 0·1 0·3 1 3	> 5000
H	H	Cl	H	H	$NH-CH-COOC_2H_5$ $(CH_2)-COOC_2H_5$	CH_3	H	H	Oxo		0·1 0·3 3	> 5000
H	H	Cl	H	H	OCH_2CONH_2	CH_3	H	H	Oxo		0·03 0·3 1	

Table (cont.)

R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}	Significant active dosage mg/kg p.o.	LD 50 mg/kg p.o.
H	H	Cl	H	H	NH_2	CH_3	H	H	Oxo		0·03 0·3	> 4000
H	H	Cl	H	H	$O-(CH_2)_2-CH_3$	CH_3	H	H	Oxo		0·1 0·3	> 5000
H	H	Cl	H	H	$O-(CH_2)_4-CH_3$	CH_3	H	H	Oxo		0·03 0·1 0·3 3	> 5000

The compounds of formula I and their pharmaceutically usable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragees, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

As mentioned earlier, medicaments containing a compound of formula I or a pharmaceutically usable salt thereof are also an object of the present invention, as is a process for the manufacture of such medicaments which comprises bringing one or more compounds of formula I and/or pharmaceutically usable salts thereof and, if desired, one or more other therapeutically active substances into a galenical administration form together with one or more therapeutically inert excipients.

For the manufacture of tablets, coated tablets, dragees and hard gelatine capsules there can be used as excipients e.g. lactose, maize starch or derivatives thereof, talc, stearic acid or its salts etc.

For soft gelatine capsules there are suitable as excipients e.g. vegetable oils, waxes, fats, semi-solid and liquid polyols etc.

For the manufacture of solutions and syrups there are suitable as excipients e.g. water, polyols, saccharose, invert sugar, glucose and the like.

For injection solutions there are suitable as excipients e.g. water, alcohols, polyols, glycerine, vegetable oils etc.

For suppositories there are suitable as excipients e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can contain, in addition, preserving agents, solubilizers, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, colouring agents, flavouring agents, salts for varying the osmotic pressure, buffers, coating agents or antioxidants. They can also contain other therapeutically valuable substances.

In accordance with the invention the compounds of formula I and pharmaceutically usable salts thereof can be used in the control or prevention of cerebral insufficiency or in the improvement of cognitive functions (such as memory capacity, learning capability, interest in the surroundings and self-care), for example in geriatry, in the case of intoxications such as alcoholism and in the case of cerebro-vascular disorders; further possible fields of use are vestibular disorders (such as Meniere's disease) and development disorders (such as dyslexia). The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 1 to 2500 mg should be appropriate, whereby, however, the upper limit just given can be exceeded when this is shown to be indicated.

Finally, the use of the compounds of formula I and of pharmaceutically usable salts thereof for the manufacture of medicaments for the control or prevention of cerebral insufficiency or for the improvement of cognitive functions is also an object of the invention.

In the following Examples, which illustrate the present invention, but are not intended to limit its extent in any manner, all temperatures are given in degrees Celsuis.

Example 1

a) 1155 g (6.4 mol) of 6-chloro-3,4-dihydro-2(1H)--naphthalenone are dissolved in 5 l of toluene, 500 g (7.0 mol) of pyrrolidine and subsequently a solution of 26 g (0.14 mol) of p-toluenesulphonic acid monohydrate in toluene are added dropwise thereto and the mixture is boiled under reflux on a water separator. When about 120 ml of water have separated, 4 l of toluene are distilled off and the mixture is left to cool slowly. A solid thereby crystallizes out. Filtration and washing with acetone gives 1-(6-chloro-3,4-dihydro-2-naphthyl)-pyrrolidine with melting point 117-118°. Concentration of the mother liquor, suspension of the residue in ether, filtration and washing with acetone gives a further portion of the above product with melting point 117-118°.

b) 701 g (3 mol) of 1-(6-chloro-3,4-dihydro-2-naphthyl)-pyrrolidine and 640 g (19 mol) of acrylamide in 7 ml of ethanol are boiled under reflux for 3 days with the addition of 70 g of Amberlite IR200, the separated solid is filtered off, extractively crystallized with dioxan and there is obtained 8-chloro-1,4,5,6-tetrahydrobenzo[f]--quinolin-3(2H)-one with melting point 228-230°C.

c) 147 g (1.94 mol) of lithium aluminium hydride are suspended in 4 l of tetrahydrofuran under argon, 454 g (1.94 mol) of 8-chloro-1,4,5,6-tetrahydrobenzo[f]quinolin--3(2H)-one are slowly added thereto and the mixture is boiled under reflux for 2.5 hours. The mixture is then cooled, 470 ml of 18 percent sodium hydroxide solution are

added thereto, the resulting mixture is stirred at room temperature for 30 minutes, filtered and the filter residue is washed with tetrahydrofuran. Upon evaporation of the filtrate there is obtained 8-chloro-1,2,3,4,5,6--hexahydrobenzo[f]quinoline as a yellow oil.

d) 229 g (1.04 mol) of 8-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline are dissolved in 2 ml of methylene chloride, treated with 115 g (1.14 mol) of triethylamine and 89.5 g (1.14 mol) of acetyl chloride in 400 ml of methylene chloride are added dropwise thereto at 0°. After stirring at room temperature for 1 hour the mixture is poured into water, extracted with methylene chloride and the methylene chloride phase is dried with magnesium sulphate. Distillation of the solvent in a vacuum gives a crude product which is suspended in 500 ml of ether and filtered off. There is obtained 4-acetyl-8-chloro--1,2,3,4,5,6-hexahydrobenzo[f]quinoline with melting point 106-108°. Concentration of the mother liquor and chromatography (silica gel/chloroform) gives a further portion with melting point 106-108°.

4-Acetyl-8-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline can also be prepared from 6-chloro-3,4-dihydro-2(1H)--napthalenone as follows:

100 g (0.55 mol)of 6-chloro-3,4-dihydro-2(1H)--naphthalenone are dissolved under argon in 2 l of toluene, treated with 64.0 g of powdered potassium hydroxide, heated to boiling temperature, 165 g of 3-chloropropylamine hydrochloride are added portionwise thereto during 30 minutes and the mixture is boiled on a water separator until educt can no longer be detected in the thin-layer chromatogram. After cooling to room temperature the mixture is treated with 155 ml of triethylamine. While cooling with ice so that an internal temperature of 25° is not exceeded, the

mixture is treated dropwise with 60 ml of acetyl chloride dissolved in 450 ml of toluene. The mixture is stirred at room temperature for 1 hour, extracted with water/methylene chloride, dried with magnesium sulphate, the solvent is distilled off in a vacuum and there is obtained 4-acetyl-8-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline in the form of brown crystals which can be used as the crude product for the reaction described hereinafter.

e) 115 g (0.44 mol) of 4-acetyl-8-chloro-1,2,3,4,5,6--hexahydrobenzo[f]quinoline are dissolved in 1 l of methylene chloride and a suspension of 189 g (0.93 mol) of m-chloroperbenzoic acid (85%) in 500 ml of methylene chloride is added dropwise thereto at 0°. After stirring at room temperature for 1 hour the precipitate formed is filtered off and the filtrate is extracted with 2N sodium hydroxide solution and with water. Drying of the organic phase with magnesium sulphate, distillation of the solvent in vacuo and recrystallization of the residue from ethyl acetate-ether gives 4-acetyl-11-chloro-1,2,4,5,6,7--hexahydro-4-benzazecine-3,8-dione as white crystals with melting point 154-156°.

f) 1 ml of concentrated hydrochloric acid is added to a solution of 4.00 g (0.014 mol) of 4-acetyl-11-chloro--1,2,4,5,6,7-hexahydro-4-benzazecine-4,8-dione in 200 ml of methanol and the mixture is stirred at room temperature for 20 hours. The solution is concentrated, extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled in a vacuum. Chromatography on silica gel with ethyl acetate and then on aluminium oxide with ethyl acetate and crystallization from t-butyl methyl ether gives methyl 2-(4-acetamidobutyryl)-5-chlorohydrocinnamate as white crystals with melting point 46-48°.

Example 2

5 ml of concentrated hydrochloric acid are added to a solution of 4.00 g (0.014 mol) of 4-acetyl-11-chloro--1,2,4,5,6,7-hexahydro-4 -benzazecine-3,8-dione in 250 ml of ethanol and the mixture is stirred at room temperature for 30 hours. The solution is concentrated, extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with ethyl acetate-hexane (2:1) and crystallization from ether gives ethyl 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamate as beige crystals with melting point 64-66°.

Example 3

10 ml of concentrated hydrochloric acid are added to a solution of 7.35 g (0.025 mol) of 4-acetyl-11-chloro--1,2,4,5,6,7-hexahydro-4 -benzazecine-3,8-dione in 400 ml of n-propanol and the mixture is stirred at room temperature for 24 hours. The solution is concentrated, extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with ethyl acetate--hexane (2:1) and crystallization from ethyl acetate--hexane gives propyl 2-(4-acetamidobutyryl)-5-chlorohydrocinnamate as white crystals with melting point 60-62°.

Example 4

5 ml of concentrated hydrochloric acid are added to a solution of 4.00 g (0.014 mol) of 4-acetyl-11-chloro--1,2,4,5,6,7-hexahydro-4 -benzazecine-3,8-dione in 250 ml of isopropanol and the mixture is stirred at room temperature for 24 hours. The solution is concentrated, extracted with methylene chloride/water, dried with

magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with ethyl acetate--hexane (2:1) and crystallization from ether gives isopropyl 2-(4-acetamidobutyryl)-5-chlorohydrocinnamate as white crystals with melting point 35-37°.

Example 5

15 ml of concentrated hydrochloric acid are added to a solution of 10.00 g (0.034 mol) of 4-acetyl-11-chloro--1,2,4,5,6,7-hexahydro-4 -benzazecine-3,8-dione in 70 ml of n-butanol and 50 ml of methylene chloride and the mixture is stirred at room temperature for 18 hours. The solution is concentrated, extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with ethyl acetate and crystallization from ether gives butyl 2-(4-acetamidobutyryl)-5-chlorohydrocinnamate as white crystals with melting point 56-57°.

Example 6

15 ml of concentrated hydrochloric acid are added to a solution of 10.00 g (0.034 mol) of 4-acetyl-11-chloro--1,2,4,5,6,7-hexahydro-4 -benzazecine-3,8-dione in 90 ml of n-nonanol and 50 ml of methylene chloride and the mixture is stirred at room temperature for 15 hours. The solution is concentrated, extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with ethyl acetate-hexane (4:1) and crystallization from ether gives nonyl 2-(4-acetamidobutyryl)-5--chlorohydrocinnamate as white crystals with melting point 55-57°.

Example 7

15 ml of concentrated hydrochloric acid are added to a solution of 10.00 g (0.034 mol) of 4-acetyl-11-chloro--1,2,4,5,6,7-hexahydro-4 -benzazecine-3,8-dione in 90 ml of 5-nonanol and 50 ml of methylene chloride and the mixture is stirred at room temperature for 18 hours. The solution is concentrated, extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with ethyl acetate gives 1-butylpentyl 2-(4--acetamidobutyryl)-5-chlorohydrocinnamate as a yellow oil.

Example 8

a) 31.4 g (0.143 mol) of 8-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline dissolved in 300 ml of methylene chloride are added at 0° to a solution of 36.0 g (0.143 mol) of 4-phthalimidobutyryl chloride in 360 ml of methylene chloride and the mixture is stirred at room temperature for 1 hour. The solution is concentrated, extracted with methylene chloride and aqueous sodium hydrogen carbonate solution, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Extractive crystallization with acetone gives 8-chloro-1,2,3,4,5,6--hexahydro-4-(4-phthalimidobutyryl)benzo[f]quinoline as white crystals with melting point 182-183°.

b) A suspension of 10.9 g (0.025 mol) of 8-chloro--1,2,3,4,5,6-hexahydro-4-(4 -phthalimidobutyryl)benzo[f]-quinoline and 3.2 ml (0.065 mol) of hydrazine hydrate in 150 ml of ethanol is boiled at reflux temperature for 2 hours, the solution is concentrated, extracted with methylene chloride/water, dried with sodium sulphate and the solvent is distilled off in a vacuum. The residue is dissolved in 10 ml of 5.5N methanolic hydrochloric acid

and precipitated with ether. Recrystallization from methanol/ether gives 4-(4-aminobutyryl)-8-chloro--1,2,3,4,5,6 -hexahydrobenzo[f]quinoline hydrochloride as beige crystals with melting point 225°.

c) To a suspension of 5.09 g (0.015 mol) of 4-(4-aminobutyryl)-8-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline in 50 ml of methylene chloride are added 5 ml (0.036 mol) of triethylamine and then at 0° 1.33 ml (0.019 mol) of acetyl chloride dissolved in 15 ml of methylene chloride, and the mixture is stirred at room temperature for 1 hour. The mixture is extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Crystallization from methylene chloride/ether, chromatography on silica gel with ethyl acetate/methanol (9:1) and renewed crystallization from methylene chloride/ether gives N-[4-[8-chloro-2,3,5,6-tetrahydrobenzo[f]quinolin-4(1H)-yl]-4-oxobutyl]acetamide as white crystals with melting point 142-143°.

d) 4.80 g (0.024 mol) of 85 percent m-chloroperbenzoic acid dissolved in 50 ml of methylene chloride are added at 0° to a solution of 4.00 g (0.016 mol) of N-[4-[8-chloro--2,3,5,6-tetrahydrobenzo[f]quinolin-4(1H)-yl]-4--oxobutyl]acetamide in 40 ml of methylene chloride and the mixture is stirred at room temperature for 1 hour. The mixture is extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with ethyl acetate/methanol (9:1) and crystallization from ethyl acetate/hexane gives N-[3-[(11-chloro-2,3,5,6,7,8--hexahydro-3,8 -dioxo-4-benzazecin-4-(1H)-yl)carbonyl]-propyl]acetamide as white crystals with melting point 135-136°.

e) 1 ml of concentrated hydrochloric acid is added to a solution of 2.66 g (0.007 mol) of N-[3-[(11-chloro--2,3,5,6,7,8-hexahydro-3,8-dioxo -4-benzazecin-4-(1H)--yl)carbonyl]propyl]acetamide in 100 ml of ethanol and 30 ml of methylene chloride and the mixture is stirred at room temperature for 5 days. The solution is concentrated, extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on aluminium oxide with ethyl acetate/ethanol (19:1) and crystallization from methylene chloride/ether gives ethyl 2-[4-(4-acetamidobutyramido)-butyryl]-5-chlorohydrocinnamate as white crystals with melting point 95°.

Example 9

a) 15.0 g (0.06 mol) of 8-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline are dissolved in 150 ml of methylene chloride, treated with 6.68 g (0.066 mol) of triethylamine and 11.2 g (0.066 mol) of p-methoxybenzoyl chloride in 50 ml of methylene chloride are added dropwise thereto at 0°. After stirring at room temperature for 1 hour the mixture is extracted with water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Crystallization (methylene chloride-ether) gives 4-(p-methoxybenzoyl)-8 -chloro-1,2,3,4,5,6-hexahydrobenzo-[f]quinoline as white crystals with melting point 182-183°.

b) 8.80 g (0.025 mol) of 4-(p-methoxybenzoyl)-8-chloro--1,2,3,4,5,6-hexahydrobenzo[f]quinoline are dissolved in 100 ml of chloroform and a suspension of 10.3 g (0.051 mol) of 85% m-chloroperbenzoic acid in 100 ml of chloroform is added dropwise thereto at 0°. After stirring at room temperature for 1 hour the mixture is extracted with 2N sodium hydroxide solution and water, dried with magnesium sulphate and the solvent is distilled off in a

vacuum. Chromatography (silica gel, ether-hexane, 2:1) and crystallization (ether-hexane) gives 4-(p-methoxybenzoyl)--11-chloro-1,2,4,5,6,7 -hexahydro-4-benzazecine-3,8-dione as white crystals with melting point 143°.

c) 5 ml of concentrated hydrochloric acid are added to a solution of 3.60 g (0.009 mol) of 4-(p-methoxybenzoyl)-11--chloro-1,2,4,5,6,7 -hexahydro-4-benzazecine-3,8-dione in 200 ml of methanol and 50 ml of methylene chloride and the mixture is stirred at room temperature for 60 hours. The solution is concentrated, extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with hexane-ethyl acetate (1:1) and crystallization from methylene chloride/hexane gives methyl 2-[4--(p-methoxybenzoyl)amidobutyryl]-5 -chlorohydrocinnamate as white crystals with melting point 111°.

Example 10

500 ml of 2N hydrochloric acid are added to a solution of 103 g (0.35 mol) of 4-acetyl-11-chloro-1,2,4,5,6,7--hexahydro-4 -benzazecine-3,8-dione in 1 l of tetrahydrofuran and the mixture is stirred at room temperature overnight. The mixture is concentrated in a vacuum, treated with methylene chloride and extracted twice with 2N sodium hydroxide solution; the aqueous phase is then acidified with 6N hydrochloric acid and extracted with methylene chloride. Removal of the solvent by distillation in a vacuum and chromatography on silica gel with methylene chloride/methanol (20:1) yields 2-(4-acetamidobutyryl)-5--chlorohydrocinnamic acid with melting point 90-92°.

Example 11

a) 154.8 g of 2-chloro-phenylacetyl chloride dissolved in 290 ml of methylene chloride are added dropwise within 1 hour to 218 g of aluminium chloride in 1000 ml of methylene chloride while stirring at between 0° and 5°. Thereafter, ethylene is introduced at 0° and 5° during 40 minutes. The mixture is stirred at room temperature for 1 hour and treated at between 0° and 5° with 570 ml of water. The methylene chloride phase is washed with 2 x 500 ml of 2N hydrochloric acid, 2 x 500 ml of sodium hydrogen carbonate solution and 700 ml of water, dried with sodium sulphate and concentrated in a vacuum. The 8-chloro-3,4-dihydro-2(1H)-naphthalenone, crystallized from 400 ml of low-boiling petroleum ether, exhibits a melting point of 56-59°.

b) 70.0 g of 8-chloro-3,4-dihydro-2(1H)-naphthalenone are boiled at reflux for 2.5 hours in 550 ml of benzene and 33 ml of pyrrolidine in the presence of 1.4 g of p-toluenesulphonic acid. The crude 1-(8-chloro-3,4--dihydro-2-naphthyl)-pyrrolidine obtained is processed without purification.

c) 56.0 g of acrylamide and 3.0 g of anhydrous p-toluenesulphonic acid are added to 89.4 g of crude 1-(8-chloro--3,4-dihydro-2-naphthyl)-pyrrolidine. The mixture is heated under nitrogen at 100° for 2 hours and at 150° for 2 hours, extracted with methylene chloride-water and filtered through 500 g of silica gel and the solvent is distilled off in a vacuum. The 10-chloro-1,4,5,6-tetrahydrobenzo[f]quinolin -3(2H)-one obtained exhibits a melting point of 186-187° after recrystallization from ethyl acetate.

d) 20.0 g of 10-chloro-1,4,5,6-tetrahydrobenzo[f]-quinolin-3(2H)-one are added portionwise within 35 minutes at 20° to 25° to a stirred suspension of 6.49 g of lithium aluminium hydride in 240 ml of dry tetrahydrofuran. The reaction mixture is subsequently boiled under reflux for 150 minutes. The mixture is cooled, treated at 0° to 10° with 21.0 ml of 6.5N sodium hydroxide solution, filtered and rinsed several times with 20 ml of tetrahydrofuran each time. Distillation of the solvent in a vacuum gives 10-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline which is processed directly.

e) 20.1 g of crude 1-chloro-1,2,3,4,5,6-hexahydrobenzo-[f]quinoline are dissolved in 40 ml of pyridine and 36 ml of acetic anhydride, the reaction mixture is left to stand at room temperature for 20 hours, evaporated, the residue remaining behind is taken up twice in 150 ml of dry toluene each time and the solutions obtained are evaporated to dryness. Chromatography of the residue on silica gel with chloroform yields 4-acetyl-10-chloro-1,2,3,4,5,6--hexahydrobenzo[f]quinoline which exhibits a melting point of 117-118° after recrystallization from isopropyl ether.

f) 16.0 g of 85 percent m-chloroperbenzoic acid in 205 ml of chloroform are added at 0 to 5° to a solution of 8.50 g of 4-acetyl-10-chloro-1,2,3,4,5,6 -hexahydrobenzo[f]-quinoline in 205 ml of chloroform. After stirring at room temperature for 4 hours the mixture is treated with 4 g of potassium iodide and 70 ml of water and with sodium thiosulphate until decolorization occurs. The chloroform phase is washed with 70 ml of 2N sodium hydroxide solution and twice with 170 ml of water and evaporated in a vacuum. Chromatography on 100 g of silica gel with methylene chloride yields 4-acetyl-9-chloro-1,2,4,5,6,7-hexahydro--4-benzazecine-3,8-dione with a melting point of 115-116° after recrystallization from isopropyl ether.

g) 1 ml of 25 percent hydrochloric acid is added to a solution of 5.00 g (0.017 mol) of 4-acetyl-9-chloro--1,2,4,5,6,7-hexahydro-4-benzazecine -3,8-dione in 153 ml of methanol and the mixture is stirred at room temperature for 4 days. The solution is concentrated, extracted with methylene chloride and aqueous sodium hydrogen carbonate solution, dried with sodium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with methylene chloride and then with ethyl acetate and crystallization from petroleum ether gives methyl 2-(4--acetamidobutyryl)-3-chloro -hydrocinnamate as white crystals with melting point 51-52°.

Example 12

a) 149.4 g of 4-fluorophenylacetyl chloride in 300 ml of methylene chloride are added within 60 minutes to 230 g of aluminium chloride in 1050 ml of methylene chloride while stirring between 0° and 5°. Ethylene is conducted in at 0 to 5° for 30 minutes, the mixture is stirred at room temperature for a further 1 hour and treated at 0° to 5° within 30 minutes with 600 ml of ice-water. The methylene chloride phase is washed with 2N hydrochloric acid, water and saturated sodium hydrogen carbonate solution, dried with sodium sulphate and the solvent is distilled off in a vacuum. The residue is treated with 250 ml of low-boiling petroleum ether, left to stand in a refrigerator overnight and the 6-fluoro-3,4-dihydro-2(1H)-naphthalenone with melting point 50-60° is filtered off.

b) 16.7 g of 6-fluoro-3,4-dihydro-2(1H)-naphthalenone in 200 ml of benzene are boiled at reflux for 2.5 hours with 8.4 ml of pyrrolidine and 0.35 g of anhydrous p-toluene-sulphonic acid. The 1-(6-fluoro-3,4-dihydro-2-naphthyl)-pyrrolidine obtained is treated, without purification, with 10.8 g of acrylamide and 0.5 g of p-toluenesulphonic

acid. The mixture is heated under nitrogen at 100° for 2 hours and at 150° for 2 hours. The mixture is dissolved in 180 ml of chloroform, washed with water and chromatographed over 150 g of silica gel with chloroform. Recrystallization from ethyl acetate gives 8-fluoro--1,4,5,6-tetrahydrobenzo[f]quinolin-3(2H)-one with melting point 223-224°.

c) 6.20 g of 8-fluoro-1,4,5,6,-tetrahydrobenzo[f]-quinolin-3(2H)-one are added portionwise under nitrogen within 35 minutes at 20° to 25° to a stirred suspension of 2.17 g of lithium aluminium hydride in 60 ml of dry tetrahydrofuran. The reaction mixture is boiled for 150 minutes under reflux and then treated at 0° to 10° with 7.0 ml of 6.5N sodium hydroxide solution. The mixture is filtered, rinsed several times with 20 ml of tetrahydrofuran each time and the solvent is distilled off in a vacuum. The thus-obtained 8-fluoro-1,2,3,4,5,6-hexahydrobenzo[f]-quinoline obtained is processed directly.

d) A solution of 6.00 g of crude 8-fluoro-1,2,3,4,5,6--hexahydrobenzo[f]quinoline in 13 ml of pyridine and 12 ml of acetic anhydride is left to stand at room temperature for 20 hours, evaporated, the residue remaining behind is taken up twice in 50 ml of dry toluene each time and the solutions obtained are evaporated to dryness. The residue is chromatographed on 150 g of silica gel with methylene chloride. The 4-acetyl-8-fluoro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline obtained exhibits a melting point of 101-102° after recrystallization from isopropyl ether.

e) 2.48 g of 4-acetyl-8-fluoro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline in 60 ml of chloroform are treated at 0° to 5° with 5.24 g of 85 percent m-chloroperbenzoic acid in 40 ml of chloroform and the mixture is stirred at room temperature for 3 hours. 1.10 g of potassium iodide and

15 ml of water are then added thereto and sodium thiosulphate is added until decolorization occurs. The chloroform phase is separated and washed with 15 ml of 2N sodium hydroxide solution and 2 x 40 ml of water. Distillation of the chloroform in a vacuum and recrystallization from ethyl acetate yields 4-acetyl-11-fluoro-1,2,4,5,6,7-hexahydro-4-benzazecine-3,8-dione with a melting point of 161-162°.

f) 20 ml of 2N hydrochloric acid are added to a solution of 3.00 g (0.011 mol) of 4-acetyl-11-fluoro-1,2,4,5,6,7-hexahydro-4-benzazecine-3,8-dione in 40 ml of acetonitrile and the mixture is stirred at room temperature for 65 hours. Concentration of the solution, chromatography on silica gel with tetrahydrofuran and crystallization from ether gives 2-(4-acetamidobutyryl)-5-fluorohydrocinnamic acid as white crystals with melting point 100-101°.

Example 13

0.75 ml of 25 percent hydrochloric acid is added to a solution of 5.00 g (0.018 mol) of 4-acetyl-11-fluoro-1,2,4,5,6,7-hexahydro-4-benzazecine-3,8-dione in 163 ml of methanol and the mixture is stirred at room temperature for 99 hours. The solution is concentrated, extracted with toluene and saturated sodium hydrogen carbonate solution, dried with sodium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with chloroform/ethyl acetate and then on aluminium oxide with methylene chloride/ethyl acetate and subsequent trituration in petroleum ether gives methyl 2-(4-acetamidobutyryl)-5-fluorohydrocinnamate as light yellow crystals with melting point 39-40°.

Example 14

a) 12.0 g of 6-methoxy-2-tetralone in 200 ml of benzene are boiled at reflux for 2 hours with 5.6 ml of pyrrolidine in the presence of 0.5 g of anhydrous p-toluenesulphonic acid. The toluene is removed in a vacuum. 9.70 g of acrylamide and 0.5 g of p-toluenesulphonic acid are added to the crude 1-(6-methoxy-3,4-dihydro-2-naphthyl)pyrrolidine obtained. The mixture is heated under nitrogen at 100° for 2 hours and at 150° for 2 hours, extracted with chloroform/water, dried with sodium sulphate and the solvent is distilled off in a vacuum. Chromatography on 160 g of silica gel with methylene chloride and recrystallization from ethyl acetate gives 8-methoxy-1,4,5,8-tetrahydrobenzo[f]-quinolin-3(2H)-one with melting point 208-209°.

b) 5.10 g of 8-methoxy-1,4,5,8-tetrahydrobenzo[f]-quinolin-3(2H)-one are added portionwise at 20° under nitrogen within 35 minutes to a stirred suspension of 1.69 g of lithium aluminium hydride in 50 ml of dry tetrahydrofuran. The reaction mixture is boiled under reflux for 150 minutes and treated at 0° to 10° with 1.5 ml of 6.5N sodium hydroxide solution. The mixture is filtered, rinsed several times with tetrahydrofuran and the solvent is distilled off in a vacuum. The thus-obtained 8-methoxy-1,2,3,4,5,6-hexahydrobenzo[f]quinoline is processed directly.

c) A mixture of 4.70 g of 8-methoxy-1,2,3,4,5,6-hexahydrobenzo[f]quinoline in 15 ml of pyridine and 11 ml of acetic anhydride is left to stand at room temperature for 20 hours, evaporated, the residue remaining behind is taken up twice in 50 ml of dry toluene each time and the solutions obtained are evaporated to dryness. The residue is chromatographed on 50 g of silica gel with methylene

chloride and gives 4-acetyl-8-methoxy-1,2,3,4,5,6-hexahydrobenzo[f]quinoline with a melting point of 119-120° after recrystallization from ispropyl ether.

d) 38.0 g of 85 percent m-chloroperbenzoic acid in 250 ml of chloroform are added dropwise at 0° to 5° to a solution of 21.3 g of 4-acetyl-8-methoxy-1,2,3,4,5,6-hexahydrobenzo[f]quinoline in 200 ml of chloroform and the mixture is stirred at room temperature for 18 hours. The mixture is treated with sodium iodide and water and thereafter with sodium thiosulphate until decolorization occurs. The chloroform phase is washed with aqueous ammonia and sodium chloride solution, dried with sodium sulphate and evaporated in a vacuum. There is obtained 4-acetyl-11-methoxy--1,2,4,5,6,7-hexahydro-4 -benzazecine-3,8-dione with a melting point of 156-158° after recrystallization from ethyl acetate.

e) 5 ml of concentrated hydrochloric acid are added to a solution of 5.50 g (0.019 mol) of 4-acetyl-11-methoxy--1,2,4,5,6,7-hexahydro-4 -benzazecine-3,8-dione in 150 ml of ethanol and the mixture is stirred at room temperature overnight. The solution is concentrated, extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with ethyl acetate and crystallization from ethyl acetate/ether gives ethyl 2-(acetamidobutyryl)-5-methoxyhydrocinnamate as white crystals with melting point 59-61°.

Example 15

a) 9.00 g (0.042 mol) of 6,7-dichloro-3,4-dihydro-2(1H)-naphthalenone and 0.3 g of p-toluenesulphonic acid are dissolved in 200 ml of pyridine, 3.5 ml (0.042 mol) of pyrrolidine are added dropwise thereto and the mixture is

boiled under reflux for 2 hours. Distillation of the solvent in a vacuum, addition of 200 ml of ether and filtering off the crystals formed yields 1-(6,7--dichloro-3,4-dihydro-2-naphthyl)pyrrolidine with melting point 141-142°.

b) A melt of 10.1 g (0.038 mol) of 1-(6,7-dichloro-3,4--dihydro-2-naphthyl)pyrrolidine, 5.36 g (0.075 mol) of acrylamide and 0.3 g of p-toluenesulphonic acid is stirred under nitrogen at 100° for 2 hours and at 150° for 2 hours. Recrystallization of the melt cake from ethanol yields 8,9-dichloro-1,4,5,6-tetrahydrobenzo[f]quinolin--3(2H)-one with melting point 260-261°.

c) 1.57 g (0.042 mol) of lithium aluminium hydride are suspended in 60 ml of tetrahydrofuran under argon, 5.56 g (0.021 mol) of 8,9-dichloro-1,4,5,6-tetrahydrobenzo[f]-quinolin-3(2H)-one are slowly added thereto and the mixture is boiled under reflux for 2.5 hours. The mixture is then cooled to 0°, 5.2 ml of 18 percent sodium hydroxide solution are added dropwise thereto and the precipitate formed is filtered off. On evaporation of the filtrate there is obtained 8,9-dichloro-1,2,3,4,5,6-hexa-hydrobenzo[f]quinoline as a yellow oil which is processed directly.

d) 6.17 g (0.024 mol) of 8,9-dichloro-1,2,3,4,5,6-hexa-hydrobenzo[f]quinoline are dissolved in 10 ml of pyridine, 9 ml (0.09 mol) of acetic anhydride are added dropwise thereto and the mixture is stirred at room temperature for 17 hours. Chromatography on silica gel with chloroform yields a product which is suspended in ether and filtered off. There is obtained 4-acetyl-8,9-dichloro-1,2,3,4,5,6--hexahydrobenzo[f]quinoline with melting point 146-148°.

e) 4.14 g (0.014 mol) of 4-acetyl-8,9-dichloro--1,2,3,4,5,6-hexahydrobenzo[f]quinoline are dissolved in 70 ml of chloroform and a suspension of 7.28 g (0.036 mol) of m-chloroperbenzoic acid (85 percent) in 100 ml of chloroform is added dropwise thereto at 0°. After stirring at room temperature for 3 hours the mixture is filtered off from the precipitate formed and extracted with potassium iodide and sodium thiosulphate solution. Chromatography on silica gel with chloroform and recrystallization from isopropyl ether gives 4-acetyl-10,11--dichloro-1,2,4,5,6,7-hexahydro-4-benzazecine-3,8-dione as white crystals with melting point 163-165°.

f) 2 ml of concentrated hydrochloric acid are added to a solution of 1.75 g (0.005 mol) of 4-acetyl-10,11-dichloro--1,2,4,5,6,7-hexahydro-4-benzazecine-3,8-dione in 60 ml of ethanol and the mixture is stirred at room temperature for 20 hours. The solution is concentrated, extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with methylene chloride and crystallization from t-butyl methyl ether gives ethyl 2-(4--acetamidobutyryl)-4,5-dichloro-hydrocinnamate as white crystals with melting point 63-65°.

Example 16

a) A suspension of 127 g (0.7 mol) of 6-chloro-2--tetralone, 70.0 g (0.7 mol) of 3,3-dimethylacrylamide, 63.6 ml (0.42 mol) of tetramethoxysilane and 85.3 g (0.56 mol) of caesium fluoride in 400 ml of toluene is boiled under reflux for 18 hours. Distillation of the solvent in a vacuum, extraction with methylene chloride/water, chromatography on silica gel with ethyl acetate/hexane (1:1) and recrystallization from methylene chloride/hexane yields 8-chloro-1,1-dimethyl-1,2,5,6-

-tetrahydrobenzo[f]quinolin-3-one as white crystals with melting point 213°.

b) 3.36 g (0.089 mol) of lithium aluminium hydride are suspended in 100 ml of tetrahydrofuran under argon, 11.6 g (0.044 mol) of 8-chloro-1,1-dimethyl-1,2,5,6-tetrahydrobenzo[f]quinolin-3-one are slowly added thereto and the mixture is boiled under reflux for 2.5 hours. The mixture is then cooled to 0°, 12 ml of 18 percent sodium hydroxide solution are added dropwise thereto and the mixture is filtered. On evaporation of the filtrate there is obtained 8-chloro-1,1-dimethyl-1,2,3,4,5,6-hexahydrobenzo[f]quinoline as a yellow oil which is processed directly.

c) 10.6 g (0.043 mol) of 8-chloro-1,1-dimethyl--1,2,3,4,5,6-hexahydrobenzo[f]quinoline and 6.6 ml (0.047 mol) of triethylamine are dissolved in 100 ml of methylene chloride and 3.5 ml (0.047 mol) of acetyl bromide dissolved in 20 ml of methylene chloride are added dropwise thereto at 0°. After stirring for 1 hour the mixture is extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Recrystallization from methylene chloride/hexane gives 4-acetyl-8-chloro-1,1-dimethyl-1,2,3,4,5,6--hexahydrobenzo[f]quinoline as white crystals with melting point 126-127°.

d) 5.30 g (0.018 mol) of 4-acetyl-8-chloro-1,1-dimethyl--1,2,3,4,5,6 -hexahydrobenzo[f]quinoline are dissolved in 100 ml of methylene chloride and a suspension of 8.20 g (0.04 mol) of m-chloroperbenzoic acid (85 percent) in 50 ml of methylene chloride is added dropwise thereto at 0°. After stirring at room temperature for 1.5 hours one filters off from the precipitate formed and extracts with methylene chloride/water. Chromatography on silica gel with ethyl acetate/hexane (1:1) and recrystallization from

ether/hexane gives 4-acetyl-11-chloro-7,7-dimethyl--1,2,4,5,6,7-hexahydro-4-benzazecine-3,8-dione as white crystals with melting point 113-115°.

e) 3 ml of concentrated hydrochloric acid are added to a solution of 2.40 g (0.008 mol) of 4-acetyl-11-chloro-7,7--dimethyl-1,2,4,5,6,7-hexahydro -4-benzazecine-3,8-dione in 150 ml of methanol and the mixture is stirred at room temperature for 24 hours. The solution is concentrated, extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with hexane-ethyl acetate (2:1) and then on aluminium oxide with ethyl acetate gives methyl 2-(4-acetamido-2,2-dimethylbutyryl)--5-chloro -hydrocinnamate as a yellow oil.

Example 17

0.3 ml of concentrated sulphuric acid is added to a solution of 10.00 g (0.032 mol) of 2-(4-acetamidobutyryl)--5-chlorohydrocinnamic acid in 40 ml of tetrahydrofuran in a steel autoclave and about 60 ml of isobutylene are condensed in. The mixture is stirred at room temperature for 30 days, the solution is concentrated, extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography with ethyl acetate on aluminium oxide and then on silica gel gives t-butyl 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamate as a colourless oil.

Example 18

2.00 g (0.006 mol) of 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid and 0.5 ml (0.006 mol) of thionyl chloride in 20 ml of methylene chloride are stirred at room temperature for 5 minutes and then a solution of

2.2 ml (0.023 mol) of 3-hydroxymethylpyridine in 20 ml of methylene chloride is added thereto at 0°. After stirring at room temperature for 1 hour the solution is concentrated, extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on aluminium oxide with ethyl acetate gives 3-pyridylmethyl 2-(4-acetamidobutyryl)-5--chlorohydrocinnamate as a beige oil.

Example 19

8.15 g (0.025 mol) of methyl 2-(4-acetamidobutyryl)-5--chlorohydrocinnamate are stirred at room temperature for 30 hours in 200 ml of a solution of ammonia in methanol. After concentration of the solution the residue is extracted with methylene chloride/water, dried with magnesium sulphate, the solvent is distilled off in a vacuum and the residue is chromatographed on silica gel with chloroform-methanol (9:1). Recrystallization from methanol/ether yields 2-(4-acetamidobutyryl)-5-chloro--hydrocinnamide as white crystals with melting point 149-151°.

Example 20

1.00 g (0.002 mol) of ethyl 2-[4-(4-acetamidobutyramido)butyryl]-5-chlorohydrocinnamate is stirred at room temperature for 6 days in 20 ml of a solution of ammonia in methanol. After concentration of the solution the residue is extracted with methylene chloride/water, dried with magnesium sulphate, the solvent is distilled off in a vacuum and the residue is chromatographed on aluminium oxide with ethyl acetate. Recrystallization from methanol/t-butyl methyl ether yields 2-[4-(4-acetamidobutyramido)butyryl]-5-chloro -hydrocinnamide as white crystals with melting point 126-127°.

Example 21

2.50 g (0.008 mol) of methyl 2-(4-acetamidobutyryl)-3--chloro-hydrocinnamate are stirred at room temperature for 2 days in 100 ml of a solution of ammonia in methanol. After concentration of the solution the residue is extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Recrystallization from methanol/ether yields 2-(4--acetamidobutyryl)-3-chloro-hydrocinnamide as white crystals with melting point 148-150°.

Example 22

9.30 g (0.03 mol) of methyl 2-(4-acetamidobutyryl)-5--fluoro-hydrocinnamate are stirred at room temperature for 6 days in 200 ml of a solution of ammonia in methanol. After concentration of the solution the residue is extracted with methylene chloride/water, dried with magnesium sulphate, the solvent is distilled off in a vacuum and the residue is chromatographed on silica gel with methylene chloride-methanol (20:1). Recrystallization from methanol/ether yields 2-(4-acetamidobutyryl)-5--fluoro-hydrocinnamide as white crystals with melting point 125-127°.

Example 23

3.10 g (0.01 mol) of 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid and 1.70 g (0.015 mol) of 1,1'--carbonyldiimidazole are stirred at room temperature for 1 hour in 30 ml of tetrahydrofuran, 1.1 ml (0.015 mol) of diethylamine are added thereto at -70° and the mixture is left to warm to room temperature overnight. After concentration of the solution the residue is extracted with methylene chloride/water, dried with magnesium sulphate

and the solvent is distilled off in a vacuum. Chromatography on silica gel with ethyl acetate gives 2-(4--acetamidobutyryl)-5-chloro-N,N-diethylhydrocinnamide as a yellow oil.

Example 24

3.10 g (0.01 mol) of 2-(4-acetamidobutyryl)-5-chlorohydrocinnamic acid and 1.70 g (0.011 mol) of 1,1'--carbonyldiimidazole are stirred at room temperature for 1 hour in 30 ml of tetrahydrofuran, 1.2 ml (0.011 mol) of 1-methylpiperazine are added thereto at -70° and the mixture is left to warm to room temperature overnight. After concentration of the solution the residue is extracted firstly with methylene chloride/2N hydrochloric acid and then with methylene chloride/concentrated aqueous ammonia solution, dried with sodium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with methylene chloride-methanol (20:1) and crystallization from ethyl acetate/hexane gives N-[3-[4--chloro-2-[2-[(4-methyl-piperazin-1-yl)carbonyl]ethyl]-benzoyl]propyl]acetamide as white crystals with melting point 126-128°.

Example 25

3.75 g (0.012 mol) of 2-(4-acetamidobutyryl)-5-chlorohydrocinnamic acid and 2.05 g (0.013 mol) of 1,1'--carbonyldiimidazole are stirred at reflux for 1 hour in 40 ml of tetrahydrofuran and then 1.67 ml (0.013 mol) of 2-piperidinoethylamine are added thereto. After stirring at reflux temperature for 2 hours the solution is concentrated, extracted with ethyl acetate/water (pH 14), dried with sodium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with chloroform--methanol (4:2) and then on aluminium oxide with ethyl

acetate-methanol (98:2) and subsequent crystallization from ethyl acetate/cyclohexane gives 2-(4-acetamidobutyryl)-5-chloro-N-(2-piperidinoethyl)hydrocinnamide as white crystals with melting point 103-105°.

Example 26

3.10 g (0.01 mol) of 2-(4-acetamidobutyryl)-5-chlorohydrocinnamic acid and 1.70 g (0.015 mol) of 1,1'-carbonyldiimidazole are stirred at room temperature for 1 hour in 30 ml of tetrahydrofuran and 1.35 g (0.015 mol) of 2-phenylethylamine are then added thereto. After stirring at room temperature for 2 hours the solution is concentrated, extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Crystallization from ethyl acetate/hexane gives 2-(4-acetamidobutyryl)-5-chloro-N-phenethyl-hydrocinnamide as white crystals with melting point 127-128°.

Example 27

5.00 g (0.016 mol) of 2-(4-acetamidobutyryl)-5-chlorohydrocinnamic acid, 1.26 g (0.013 mol) of 4-aminopyridine and 4.16 g of N,N'-dicyclohexylcarbodiimide are stirred at room temperature for 18 hours in 100 ml of tetrahydrofuran, the solution is concentrated, extracted with ethyl acetate/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with ethyl acetate-methanol (4:1) and crystallization from methanol/t-butyl methyl ether gives 2-[4-acetamidobutyryl]-5-chloro-N-(4-pyridyl)hydrocinnamide as white crystals with melting point 170-171°.

Example 28

2.00 g (0.006 mol) of 2-(4-acetamidobutyryl)-5-chlorohydrocinnamic acid and 1.09 g (0.007 mol) of 1,1'-carbonyldiimidazole are stirred at room temperature for 1.5 hours in 20 ml of tetrahydrofuran and 1.04 g (0.007 mol) of ethyl L-alaninate hydrochloride and 0.94 ml (0.007 mol) of triethylamine are then added thereto. After stirring at room temperature for 2 hours the mixture is extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with ethyl acetate-methanol (9:1) and then on aluminium oxide with ethyl acetate and subsequent crystallization from ethyl acetate/hexane gives ethyl N-[2-(4-acetamidobutyryl)-5-chlorohydrocinnamoyl] -L-alaninate as white crystals with melting point 106°.

Example 29

3.10 g (0.01 mol) of 2-(4-acetamidobutyryl)-5-chlorohydrocinnamic acid and 1.70 g (0.015 mol) of 1,1'-carbonyldiimidazole are stirred at room temperature for 1 hour in 50 ml of tetrahydrofuran and 2.51 g (0.011 mol) of diethyl L-glutamate hydrochloride and 1.8 ml (0.011 mol) of N-ethyldiisopropylamine are then added thereto. After stirring at room temperature for 2 hours the solution is concentrated, extracted with methylene chloride/water, dried with sodium sulphate and the solvent is distilled off in a vacuum. Chromatography on aluminium oxide with methylene chloride-methanol (97:3) and crystallization from ethyl acetate/hexane gives diethyl N-[2-(4-acetamidobutyryl)-5-chlorohydrocinnamoyl]-L-glutamate as white crystals with melting point 109-111°.

Example 30

1.75 g (0.006 mol) of 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid and 0.95 g (0.006 mol) of 1,1'--carbonyldiimidazole are stirred at room temperature in 15 ml of tetrahydrofuran and 1.0 ml (0.006 mol) of N-ethyldiisopropylamine and 0.82 g (0.006 mol) of ethyl glycinate hydrochloride are then added thereto. After stirring at room temperature for 1 hour the solution is concentrated, extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on aluminium oxide with ethyl acetate-ethanol (9:1) and crystallization from methylene chloride/t-butyl methyl ether gives ethyl N-[2-(4-acetamidobutyryl)-5-chlorohydrocinnamoyl]-glycinate as white crystals with melting point 96°.

Example 31

3.00 g (0.008 mol) of ethyl N-[2-(4-acetamidobutyryl)--5-chlorohydrocinnamoyl]glycinate are stirred at room temperature for 3 days in 30 ml of a solution of ammonia in methanol. After concentration of the solution the residue is extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Recrystallization from methanol/t-butyl methyl ether yields 2-(4-acetamidobutyryl)-N-(carbamoyl-methyl)-5-chlorohydrocinnamide as white crystals with melting point 148-149°.

Example 32

0.38 g (0.01 mol) of sodium borohydride is added to a solution of 3.25 g (0.01 mol) of methyl 2-(4-acetamido-butyryl)-5-chloro-hydrocinnamate in 35 ml of methanol and the mixture is stirred at room temperature for 1 hour. The

solution is concentrated, extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with chloroform-methanol (20:1) gives methyl 2-(4-acetamido-1-hydroxybutyl)-5-chlorohydrocinnamate as a yellow oil.

Example 33

A suspension of 15.5 g (0.05 mol) of 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid and 8.50 g (0.052 mol) of 1,1'-carbonyldiimidazole in 350 ml of tetrahydrofuran is stirred at room temperature for 2 hours and 4.00 g (0.052 mol) of glycolamide are added thereto. After stirring at room temperature overnight the solution is concentrated, extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with methylene chloride-methanol (20:1) and crystallization from ethyl acetate/ether gives carbamoylmethyl 2-(4--acetamidobutyryl)-5-chlorohydrocinnamate as white crystals with melting point 114-116°.

Example 34

3.10 g (0.01 mol) of 2-(4-acetamidobutyryl)-5-chlorohydrocinnamic acid and 1.70 g (0.01 mol) of 1,1'-carbonyldiimidazole are suspended in 30 ml of tetrahydrofuran, stirred at room temperature for 1 hour and treated with 2.50 g (0.01 mol) of N-(2-aminoethyl)-5-chloro-2-pyridinecarboxamide hydrochloride and 1.8 ml (0.01 mol) of ethyldiisopropylamine. After 2 hours the mixture is concentrated, extracted with ethyl acetate/water and recrystallized from methanol/ether. The 2-(4-acetamidobutyryl)-5--chloro-N-[2-(5-chloro-2-pyridinecarboxamido)ethyl]hydrocinnamide obtained melts at 163-165°.

Example 35

a) 8.00 g (0.06 mol) of aluminium chloride are suspended in 600 ml of methylene chloride, treated at 0° with 7.56 g (0.04 mol) of 4-chlorophenylacetyl chloride in 250 ml of methylene chloride and a solution of 4.17 g (0.04 mol) of styrene in 400 ml of methylene chloride is added dropwise thereto at -40° to -50°. After warming to room temperature the mixture is poured on to ice, extracted with methylene chloride, dried with magnesium sulphate, filtered over Dicalit and the solvent is distilled off in a vacuum. Chromatography on silica gel with ethyl acetate-hexane (1:4) and recrystallization from ether/hexane gives 6-chloro-3,4-dihydro-4-phenyl-2(1H)-naphthalenone as beige crystals with melting point 61-62°.

b) A solution of 73.3 g (0.23 mol) of 6-chloro-3,4--dihydro-4-phenyl-2(1H)-naphthalenone in 1.5 l of toluene is treated with 32.4 g (0.58 mol) of potassium hydroxide and 83.7 g (0.64 mol) of 3-chloropropylamine hydrochloride and boiled on a water separator for 42 hours. After cooling to room temperature there are added thereto 79 ml (0.56 mol) of triethylamine and dropwise 29.7 ml (0.42 mol) of acetyl chloride in 250 ml of toluene, the mixture is stirred for 1 hour, extracted with ethyl acetate/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography over silica gel with hexane-ethyl acetate (4:1) and then with hexane-ethyl acetate (1:1) and recrystallization from ethyl acetate gives 4-acetyl-8-chloro-1,2,3,4,5,6--hexahydro-6-phenylbenzo[f]quinoline as beige crystals with melting point 167-168°.

c) 8.13 g (0.04 mol) of m-chlorcperbenzoic acid (85 percent) in 80 ml of methylene chloride are added to a solution of 6.60 g (0.02 mol) of 1-acetyl-8-chloro-

-1,2,3,4,5,6-hexahydro-6-phenylbenzo[f]quinoline in 70 ml of methylene chloride and the mixture is stirred at room temperature for 1 hour. The mixture is filtered, extracted with methylene chloride/saturated sodium hydrogen carbonate solution, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Crystallization from methylene chloride/hexane gives 4-acetyl-11-chloro-1--phenyl-1,2,4,5,6,7-hexahydro-4-benzazecine-3,8-dione as white crystals with melting point 184-185°.

d) A solution of 3.30 g (0.009 mol) of 4-acetyl-11--chloro-1-phenyl-1,2,4,5,6,7-hexahydro-4-benzazecine-3,8--dione in 40 ml of tetrahydrofuran and 20 ml of 2N hydrochloric acid is stirred at room temperature for two days, the solution is concentrated, extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with hexane-ethyl acetate (1:1) and crystallization from ethyl acetate/hexane gives 2-(4-acetamidobutyryl)-5-chloro-ß-phenylhydrocinnamic acid as white crystals with melting point 114-116°.

Example 36

5.2 ml (0.005 mol) of 1N sodium hydroxide solution are added to a suspension of 2.00 g (0.005 mol) of 2-(4--acetamidobutyryl)-5-chloro-ß-phenylhydrocinnamic acid in 120 ml of water, the mixture is treated slowly with 0.88 g (0.005 mol) of silver nitrate in 1 ml of water and stirred at room temperature overnight. The precipitate formed is filtered off and stirred overnight with 50 ml of ethyl iodide. The mixture is extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with hexane-ethyl acetate (1:1) and on aluminium oxide with hexane-ethyl acetate (1:1) gives ethyl 2-(4-

-acetamidobutyryl)-5-chloro-ß-phenylhydrocinnamate as a colourless oil.

Example 37

120 ml of 2N hydrochloric acid are added to a solution of 23.8 g (0.06 ml) of N-[3-[(11-chloro-2,3,5,6,7,8-hexahydro-3,8-dioxo-4-benzazecin-4(1H)-yl)-carbonyl]propyl]-acetamide in 240 ml of tetrahydrofuran and the mixture is stirred at room temperature for 8 days. The solution is concentrated, extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Recrystallization from methanol/ether gives 2-[4-(4-acetamidobutyramido)butyryl]-5-chlorohydrocinnamic acid as beige crystals with melting point 108°.

Example 38

6.00 g (0.015 mol) of 2-[4-(4-acetamidobutyramido)-butyryl]-5-chlorohydrocinnamic acid and 2.57 g (0.016 mol) of 1,1'-carbonyldiimidazole are stirred at room temperature for 1.5 hours in 60 ml of tetrahydrofuran and 2.22 g (0.016 mol) of ethyl glycinate hydrochloride and 2.2 ml (0.016 mol) of triethylamine are added thereto. After stirring at room temperature for 1 hour the solution is concentrated, extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with ethyl acetate-ethanol (9:1) and crystallization from methanol--ether gives ethyl N-[2-[4-(4-acetamidobutyramido)--butyryl]-5-chlorohydrocinnamoyl]glycinate as white crystals with melting point 94-96°.

Example 39

2.50 g (0.005 mol) of ethyl N-[2-[4-(4-acetamidobutryamido)butyryl]-5-chlorohydrocinnamoyl]glycinate are stirred at room temperature overnight in 50 ml of a solution of ammonia in methanol. After concentration of the solution the residue is extracted with methylene chloride/ water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Two-fold recrystallization from methanol/ether gives 2-[4-(4-acetamidobutyramido)butyryl]-N-(carbamoylmethyl)-5-chlorohydrocinnamide as white crystals with melting point 172-174°.

Example 40

15 ml of 2N sodium hydroxide solution are added to a solution of 1.50 g (0.004 mol) of ethyl N-[2-(4-acetamidobutyryl)-5-chlorohydrocinnamoyl]glycinate in 15 ml of tetrahydrofuran and the mixture is stirred at room temperature for 1 hour. After acidification with 17 ml of 2N hydrochloric acid the mixture is extracted with ethyl acetate/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Recrystallization from ethyl acetate/ether yields N-[2-(4-acetamidobutyryl)--5-chlorohydrocinnamoyl]glycine as white crystals with melting point 88-89°.

Example 41

a) 25.0 g (0.115 mol) of 8-chloro-1,2,3,4,5,6-hexhydrobenzo[f]quinoline are dissolved in 145 ml of methylene chloride, 21.8 g (0.182 mol) of α-chloroacetyl isocyanate in 30 ml of methylene chloride are added dropwise thereto at 0° and the mixture is stirred at room temperature overnight. After the addition of 200 ml of methanol the mixture is again stirred for 24 hours and the

resulting 8-chloro-N-(chloroacetyl)-2,3,5,6-tetrahydrobenzo[f]quinoline-4(1H)-carboxamide which exhibits a melting point of 158-161° after recrystallization from ethyl acetate/ether, is filtered off. A further amount of the above product can be obtained from the filtrate and the mother liquor.

b) A suspension of 11.85 g (0.035 mol) of 8-chloro-N--(chloroacetyl)-2,3,5,6-tetrahydrobenzo[f]quinoline-4(1H)--carboxamide and 4.4 ml (0.091 mol) of hydrazine hydrate in 250 ml of ethanol is stirred at room temperature for 3 hours, concentrated in a vacuum and extracted with methylene chloride/water. Drying with magnesium sulphate and distillation of the solvent in a vacuum yields 8-chloro-2,3,5,6-tetrahydrobenzo[f]quinoline-4(1H)-carboxamide as white crystals which exhibit a melting point of 169-171° after recrystallization from methylene chloride.

c) 9.20 g (0.035 mol) of 8-chloro-2,3,5,6-tetrahydrobenzo[f]quinoline-4(1H)-carboxamide are suspended in 100 ml of methylene chloride and 14.1 g (0.071 mol) of m-chloroperbenzoic acid (85 percent) in 150 ml of methylene chloride are added dropwise thereto at 10-15°. After stirring at room temperature for 1.5 hours the mixture is poured into saturated sodium hydrogen carbonate solution, extracted with methylene chloride, dried with magnesium sulphate and the solvent is distilled off in a vacuum. The solid obtained is washed with hot ethyl acetate. Recrystallization from dioxan/ether yields 11-chloro-2,3,5,6,7,8-hexahydro-3,8-dioxo-4-benzazecine--4(1H)-carboxamide as white crystals with melting point 182-184°.

d) 7 ml of concentrated hydrochloric acid are added to a solution of 6.80 g (0.023 mol) of 11-chloro-2,3,5,6,7,8--hexahydro-3,8-dioxo-4-benzazecine-4(1H)-carboxamide in

5 l of ethanol and the mixture is stirred at room temperature for 13 days. The solution is concentrated, extracted with methylene chloride/water, dried with magnesium sulphate and the solvent is distilled off in a vacuum. Chromatography on silica gel with methylene chloride/methanol (97:3) and crystallization from ethyl acetate/hexane gives ethyl 5-chloro-2-(4-ureidobutyryl)hydrocinnamate as white crystals with melting point 127-129°.

Example A

Tablets of the following composition, which contain ethyl N-[2-(4-acetamidobutyryl)-5-chlorohydrocinnamoyl]-glycinate as the active substance, are manufactured.

		Per tablet
1.	Active substance (micronized)	50 mg
2.	Lactose	120 mg
3.	Maize starch	50 mg
4.	Polyvinylpyrrolidone	8 mg
5.	Sodium carboxymethylstarch	20 mg
6.	Magnesium stearate	2 mg
		250 mg

The active substance is mixed homogeneously with a mixture of lactose and maize starch. The mixture is sieved, moistened with an aqueous polyvinylpyrrolidone solution, granulated and dried. The dried granulate is mixed with sodium carboxymethylstarch and magnesium stearate and the thus-obtained mixture is pressed to tablets of suitable size with a break-bar.

Example B

Tablets of the following composition, which contain ethyl N-[2-(4-acetamidobutyryl)-5-chlorohydrocinnamoyl]-glycinate as the active substance, are manufactured.

		Per tablet
1.	Active substance (micronized)	10 mg
2.	Lactose	88 mg
3.	Microcrystalline cellulose	60 mg
4.	Maize starch	20 mg
5.	Sodium carboxymethylstarch	20 mg
6.	Magnesium stearate	2 mg
		200 mg

The active substance is mixed homogeneously with lactose. The mixture is sieved, then a mixture of microcrystalline cellulose, maize starch and sodium carboxymethylstarch is admixed therewith and the resulting mixture is blended with the magnesium stearate. The thus-obtained ready-to-press mixture is processed to tablets of suitable size with a break-bar.

Example C

Tablets of the following composition, which contain ethyl N-[2-(4-acetamidobutyryl)-5-chlorohydrocinnamoyl]-glycinate as the active substance, are manufactured.

		Per tablet
1.	Active substance (micronized)	0.10 mg
2.	Lactose	126.90 mg
3.	Maize starch	50.00 mg
4.	Polyvinylpyrrolidone	6.00 mg

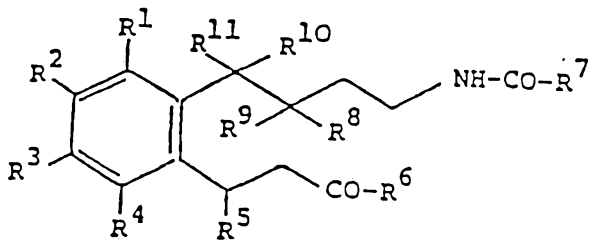
5.	Sodium carboxymethylstarch	15.00 mg
6.	Magnesium stearate	2.00 mg
		200.00 mg

The active substance is mixed homogeneously with a mixture of lactose and maize starch. The mixture is sieved, moistened with an aqueous polyvinylpyrrolidone solution, granulated and dried. The dried granulate is mixed with sodium carboxymethylstarch and magnesium stearate and the thus-obtained mixture is pressed to tablets of suitable size with a break-bar.

~~Claims~~

The claims defining the invention are as follows:

1. Hydrocinnamic acid derivatives of the general formula



I

wherein

- one or two of the symbols R^1 to R^4 signify halogen or methoxy and the remainder signify hydrogen;
- R^5 signifies hydrogen or phenyl;
- R^6 signifies a residue of the formula

$$\underset{(a)}{-OR^{12}} \quad \text{or} \quad \underset{(b)}{-NR^{13}R^{14}};$$

- R^7 signifies (C_1-C_4)-alkyl, (C_2-C_5)--alkanoylamino-(C_2-C_5)-alkyl, amino or (C_1-C_4)-alkoxyphenyl;
- R^8 and R^9 each signify hydrogen or (C_1-C_4)--alkyl;
- R^{10} signifies hydrogen and R^{11} signifies hydroxy or R^{10} and R^{11} together signify oxo;
- R^{12} signifies hydrogen, (C_1-C_{10})-alkyl, pyridylmethyl or carbamoylmethyl;
- R^{13} signifies hydrogen, (C_1-C_4)-alkyl and R^{14} signifies hydrogen, (C_1-C_4)-alkyl, pyridyl, phenyl-(C_1-C_4)-alkyl, carboxy-(C_1-C_4)-alkyl, carbamoyl-(C_1-C_4)-alkyl, (C_1-C_4)-alkoxy-

carbonyl-(C_1-C_4)-alkyl, di-(C_1-C_4)-alkoxy-carbonyl-(C_2-C_5)-alkyl, piperidino-(C_2-C_4)--alkyl or halopyridinecarboxamido-(C_2-C_4)-alkyl or R^{13} and R^{14} together with the nitrogen atom signify 4-(C_1-C_4)-alkyl-piperazin-1-yl,

as well as pharmaceutically usable salts of basic compounds of formula I with acids or of acidic compounds of formula I with bases.

2. Compounds in accordance with claim 1, wherein R^4 signifies hydrogen and either R^1 signifies chlorine and R^2 and R^3 signify hydrogen or R^1 signifies hydrogen and R^2 and R^3 signify chlorine or R^1 and R^2 signify hydrogen and R^3 signifies fluorine, chlorine or methoxy.

3. Compounds in accordance with claim 2, wherein R^3 signifies chlorine and R^1, R^2 and R^4 signify hydrogen.

4. Compounds in accordance with any one of claims 1 to 3, wherein R^5 signifies hydrogen.

5. Compounds in accordance with any one of claims 1 to 4, wherein R^6 signifies a residue of formula (a) or (b) defined in claim 1 in which R^{12} signifies hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, tert.-butyl, n-nonyl, 5-nonyl, 3-pyridylmethyl or carbamoylmethyl or either R^{13} and R^{14} both signify hydrogen or both signify ethyl or R^{13} and R^{14} together with the nitrogen atom signify 4-methylpiperazin-1-yl or R^{13} signifies hydrogen and R^{14} signifies 4-pyridyl, 2-phenylethyl, 2-piperidinoethyl, carboxymethyl, ethoxy-carbonylmethyl, carbamoylmethyl, 1-ethoxycarbonylethyl, 1,4-bis-(ethoxycarbonyl)-2-butyl or 2-(5-chloro-2--pyridinecarboxamido)ethyl.

6. Compounds in accordance with claim 5, wherein R^{12} signifies ethyl, n-propyl, isopropyl, n-nonyl or carbamoylmethyl or R^{13} signifies hydrogen and R^{14} signifies hydrogen, ethoxycarbonylmethyl or 1,4-bis--(ethoxycarbonyl)-2-butyl.

7. Compounds in accordance with any one of claims 1 to 6, wherein R^7 signifies methyl, 3-acetylaminopropyl, amino or p-methoxyphenyl.

8. Compounds in accordance with claim 7, wherein R^7 signifies methyl or 3-acetylaminopropyl.

9. Compounds in accordance with any one of claims 1 to 8, wherein R^8 and R^9 both signify hydrogen or both signify methyl.

10. Compounds in accordance with claim 9, wherein R^8 and R^9 both signify hydrogen.

11. Compounds in accordance with any one of claims 1 to 10, wherein R^{10} and R^{11} together signify oxo.

12. Ethyl N-[2-(4-acetamidobutyryl)-5-chlorohydrocinnamoyl]glycinate.

13. Ethyl 2-[4-(4-acetamidobutyramido)butyryl]-5--chlorohydrocinnamate.

14. 2-[4-(4-Acetamidobutyramido)butyryl]-5-chlorohydrocinnamide.

15. Isopropyl 2-(4-acetamidobutyryl)-5-chlorohydrocinnamate.

16. Ethyl 2-(4-acetamidobutyryl)-5-chlorohydrocinnamate.

17. Diethyl 2-[2-(4-acetamidobutyryl)-5-chlorohydrocinnamoyl]-L-glutamate.

18. Carbamoylmethyl 2-(4-acetamidobutyryl)-5-chlorohydrocinnamate.

19. 2-(4-Acetamidobutyryl)-5-chlorohydrocinnamide.

20. Propyl 2-(4-acetamidobutyryl)-5-chlorohydrocinnamate.

21. 2-(4-Acetamidobutyryl)-N-(carbamoylmethyl)-5--chlorohydrocinnamide.

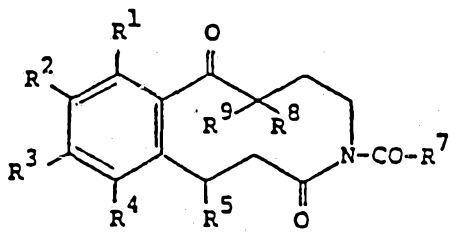
22. Nonyl 2-(4-acetamidobutyryl)-5-chlorohydrocinnamate.

23. Compounds in accordance with any one of claims 1 to 22 for use as therapeutically active substances.

24. Compounds in accordance with any one of claims 1 to 22 for use as therapeutically active substances counteracting cerebral insufficiency or improving cognitive functions.

25. A process for the manufacture of compounds in accordance with any one of claims 1 to 22, which process comprises

a) treating a benzazecinedione of the general formula



II

wherein R^1, R^2, R^3, R^4, R^5, R^7, R^8 and R^9 have the significance given in claim 1,

with an acid in the presence of a compound of the general formula

$$HOR^{12'} \qquad III$$

wherein $R^{12'}$ signifies hydrogen or (C_1-C_{10})--alkyl;

or

b) esterifying a compound of formula I defined in claim 1 in which R^6 signifies a residue of formula (a) and R^{12} signifies hydrogen, or a reactive derivative thereof, to give a corresponding compound of formula I in which R^6 signifies a residue of formula (a) and R^{12} is different from hydrogen; or

c) reacting a compound of formula I in which R^6 signifies a residue of formula (a) and R^{12} signifies hydrogen, or a reactive derivative thereof, with a compound of the general formula

$$HNR^{13}R^{14'} \qquad IV$$

wherein R^{13} has the significance given in claim 1 and $R^{14'}$ has the significance given in claim 1 for R^{14}, but is not carboxy-(C_1-C_4)-alkyl,

or reacting a compound of formula I in which R^6 signifies a residue of formula (b) and R^{14} signifies carboxy-

-(C_1-C_4)-alkyl, or a reactive derivative thereof, with ammonia; or

d) reducing a compound of formula I in which R^{10} and R^{11} together signify oxo; or

e) hydrolyzing a compound of formula I in which R^6 signifies a residue of formula (b) and R^{14} signifies (C_1-C_4)-alkoxycarbonyl-(C_1-C_4)-alkyl to give a corresponding compound of formula I in which R^6 signifies a residue of formula (b) and R^{14} signifies carboxy-(C_1-C_4)-alkyl; or

f) converting a basic compound of formula I into a pharmaceutically usable salt by means of an acid or converting an acidic compound of formula I into a pharmaceutically usable salt by means of a base.

26. A medicament containing a compound in accordance with any one of claims 1 to 22 and a therapeutically inert excipient.

27. A medicament counteracting cerebral insufficiency or improving cognitive functions, containing a compound in accordance with any one of claims 1 to 22 and a therapeutically inert excipient.

28. The use of compounds in accordance with any one of claims 1 to 22 in the control or prevention of illnesses or in the improvement of health.

29. The use of compounds in accordance with any one of claims 1 to 22 in the control or prevention of cerebral insufficiency or in the improvement of cognitive functions.

30. The use of compounds in accordance with any one of claims 1 to 22 for the manufacture of medicaments for the control or prevention of cerebral insufficiency or for the improvement of cognitive functions.

31. Compounds in accordance with any one of claims 1 to 22, whenever manufactured according to the process as claimed in claim 25 or by an obvious chemical equivalent thereof.

32. A method for counteracting cerebral insufficiency and/or improving cognitive functions in a mammal which comprises administering to said mammal in an amount sufficient to counteract cerebral insufficiency and/or to improve cognitive functions a compound in accordance with any one of claims 1 to 22 or a medicament in accordance with claim 26 or claim 27.

33. A hydrocinnamic acid derivative substantially as hereinbefore described with reference to any one of Examples 1 to 41.

34. A process for the manufacture of a hydrocinnamic derivative, substantially as hereinbefore described with reference to any one of Examples 1 to 41.

35. A medicament counteracting cerebral insufficiency or improving cognitive functions, substantially as hereinbefore described with reference to any one of Examples A, B or C.

36. A method for the treatment or prophylaxis of cerebral insufficiency in a patient requiring said treatment or prophylaxis, which method comprises administering to said patient an effective amount of at least one derivative according to claim 33 or of a medicament according to claim 35.

DATED this NINTH day of AUGUST 1990
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