FORM 1

627203

SPRUSON & FERGUSON

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

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

Ethylenediamine Monoamide Derivatives

which is described in the accompanying complete specification.

Details of basic application(s):-

Basic Applic. No:	Country:	Application Date:
2871/88	CH	28 July 1988

The address for service is:-

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

DATED this TWENTY FOURTH day of JULY 1989

F Hoffmann-La Roche AG

By: J. Ferguson

Registered Patent Attorney

TO: THE COMMISSIONER OF PATENTS
OUR REF: 101097
S&F CODE: 55541

REPRINT OF RECEIPT
SOO9005 24/07/89

5845/2

AUSTRALIA CONVENTION STANDARD & PETTY PATENT DECLARATION

COMMONWEALTH OF AUSTRALIA

THE PATENTS ACT 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

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

~~RAN 40811/80~~

Title of Invention

Ethylenediamine monoamide derivatives

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

I Roland Borer

of 10 Stockackerstrasse, CH-4153 Reinach, Switzerland

do solemnly and sincerely declare as follows:-

Full name(s) of Applicant(s)

1. I am authorised by

F.HOFFMANN-LA ROCHE AG

of 124-184 Grenzacherstrasse, CH-4002 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 28, 1988

Basic Applicant(s) by [X] F.Hoffmann-La Roche & Co. Aktiengesellschaft

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

3.

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

1) Walter Gassner
31 Zehntenfreistrasse, CH-4103 Bottmingen, Switzerland

2) René Imhof
3 Bleumatthöhe, CH-5264 Gipf-Oberfrick, Switzerland

3) Emilio Kyburz
127 Unterer Rebbergweg, CH-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)

(X) the inventor(s) have assigned the invention to F.Hoffmann-La Roche & Co. Aktiengesellschaft who have re-assigned all their rights for Australia to the Applicant.

( ) 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 23rd day of June 1989

To:

The Commissioner of Patents,
COMMONWEALTH OF AUSTRALIA

Roland Borer

Signature of Declarant(s)

(12) PATENT ABRIDGMENT (11) Document No. AU-B-38927/89
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 627203

(54) Title
ETHYLENEDIAMINE MONOAMIDE DERIVATIVES

International Patent Classification(s)
(51)[4] C07D 277/56 A61K 031/42 C07D 231/14 C07D 261/18
C07D 263/34 C07D 263/48 C07D 405/04 C07D 409/04
C07D 413/04 C07D 417/04 A61K 031/415 A61K 031/425

(21) Application No. : 38927/89 (22) Application Date : 24.07.89

(30) Priority Data

(31) Number (32) Date (33) Country
2871/88 28.07.88 CH SWITZERLAND

(43) Publication Date : 01.02.90

(44) Publication Date of Accepted Application : 20.08.92

(71) Applicant(s)
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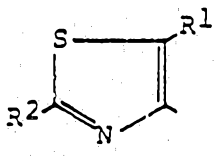
(56) Prior Art Documents
AU 24147/88 C07D 277/56 417/12
AU 606089 80830/87 C07D 277/36 263/46 231/16
GB 2163746

(57) Claim

1. Ethylenediamine monoamide derivatives of the general formula

$$R\text{-}CO\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}NH_2 \qquad I$$

wherein R signifies one of the groups



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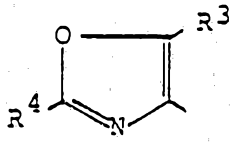

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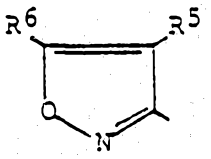

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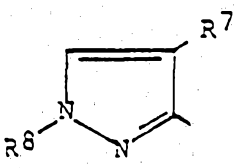


(d)

.../2

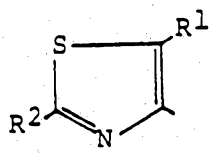
in which R^1 signifies phenyl, which is optionally monosubstituted by halogen, lower-alkyl, lower-alkoxy, trifluoromethyl, cyano or aryl-lower-alkoxy, dihalophenyl, furyl or thienyl, which is optionally monosubstituted by halogen, R^2 signifies hydrogen, halogen or amino, R^3, R^5 and R^7 each signify phenyl, which is optionally mono- or di-substituted by halogen, thienyl or furyl, which is optionally monosubstituted by halogen, R^4 and R^6 each signify hydrogen or amino and R^8 signifies hydrogen or lower-alkyl,

as well as pharmaceutically usable acid addition salts thereof.

9. Compounds of the general formula

R-CO-Y

wherein R signifies one of the groups



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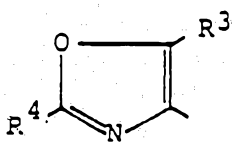

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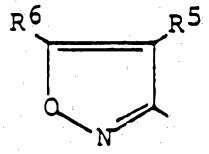

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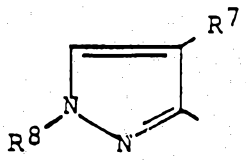


(d)

and Y signifies hydroxy or the group $-NH-CH_2-CH_2-R^{14}$, in which R^1 signifies phenyl, which is optionally monosubstituted by halogen, lower-alkyl, lower-alkoxy, trifluoromethyl, cyano or aryl-lower-alkoxy, dihalophenyl, furyl or thienyl, which is optionally monosubstituted by halogen, R^2 signifies hydrogen,

.../3

halogen or amino, R^3, R^5 and R^7 each signify phenyl, which is optionally mono- or di-substituted by halogen, thienyl or furyl, which is optionally mono-substituted by halogen, R^4 and R^6 each signify hydrogen or amino, R^8 signifies hydrogen or lower--alkyl and R^{14} signifies a leaving group or a residue which is convertible into an amino group.

19. A method of treating or preventing depressive states and cognitive disorders in a mammal requiring such treatment or prevention, comprising administering to said mammal an effective amount of the compound as defined in claim 14 or 16 or the composition as defined in any one of claims 11, 17 or 18.

627203

S & F Ref: 101097

FORM 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE:

Class Int Class

Complete Specification Lodged:
Accepted:
Published:

Priority:

Related Art:

Name and Address of Applicant: F Hoffmann-La Roche AG
124 Grenzacherstrasse
CH-4002 Basle
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:

Ethylenediamine Monoamide Derivatives

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

Abstract

The ethylenediamine monoamides of the formula

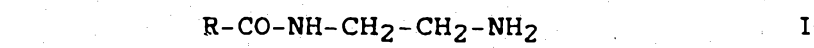
$$R\text{-}CO\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}NH_2 \qquad I$$

wherein R signifies an aromatic, 5-membered heterocyclic residue as defined in claim 1,

as well as their pharmaceutically usable acid addition salts have interesting monoamine oxidase inhibiting properties with low toxicity and can accordingly be used for the treatment of depressive states and cognitive disorders. They can be manufactured according to known methods.

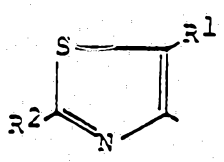
RAN 4081/80

The present invention is concerned with ethylenediamine monoamide derivatives. In particular, it is concerned with ethylenediamine monoamides of the general formula



I

wherein R signifies one of the groups



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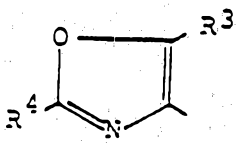

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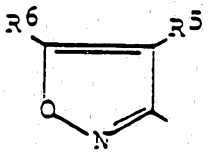

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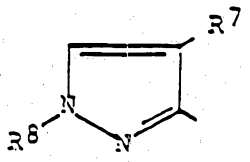


(d)

in which R^1 signifies phenyl, which is optionally monosubstituted by halogen, lower-alkyl, lower-alkoxy, trifluoromethyl, cyano or aryl-lower-alkoxy, dihalophenyl, furyl or thienyl, which is optionally monosubstituted by halogen, R^2 signifies hydrogen, halogen or amino, R^3, R^5 and R^7 each signify phenyl, which is optionally mono- or di-substituted by halogen, thienyl or furyl, which is optionally monosubstituted by halogen, R^4 and R^6 each signify

hydrogen or amino and R^8 signifies hydrogen or lower-alkyl, as well as pharmaceutically usable acid addition salts thereof.

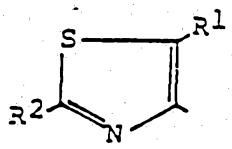
In the scope of the present invention it has surprisingly been found that the compounds of formula I have interesting and therapeutically valuable pharmacodynamic properties with low toxicity. In animal experiments it could be shown that the compounds of formula I above as well as their pharmaceutically usable acid addition salts possess monoamine oxidase (MAO) inhibiting properties.

Objects of the present invention are the compounds of general formula I as well as their pharmaceutically usable acid addition salts per se and as pharmaceutically active substances, medicaments containing a compound of general formula I or a pharmaceutically usable acid addition salt thereof, the manufacture of such medicaments and the use of compounds of general formula I as well as their pharmaceutically usable acid addition salts in the control or prevention of illnesses or in the improvement of health, especially in the control or prevention of depressive states and cognitive disorders, especially of those which are caused by age. Finally, a process for the manufacture of the compounds of formula I above and of their pharmaceutically usable acid addition salts as well as the intermediates used in this process are objects of the present invention.

According to a first embodiment of this invention, there is provided ethylenediamine monoamide derivatives of the general formula

$$R\text{-}CO\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}NH_2 \qquad I$$

wherein R signifies one of the groups



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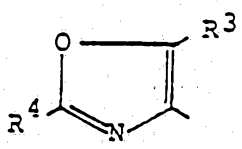

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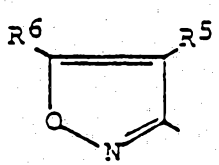

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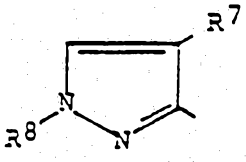


(d)

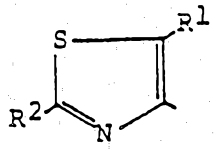
in which R^1 signifies phenyl, which is optionally monosubstituted by halogen, lower-alkyl, lower-alkoxy, trifluoromethyl, cyano or aryl-lower-alkoxy, dihalophenyl, furyl or thienyl, which is optionally monosubstituted by halogen, R^2 signifies hydrogen, halogen or amino, R^3, R^5 and R^7 each signify phenyl, which is optionally mono- or di-substituted by halogen, thienyl or furyl, which is optionally monosubstituted by halogen, R^4 and R^6 each signify hydrogen or amino and R^8 signifies hydrogen or lower-alkyl,

as well as pharmaceutically usable acid addition salts thereof.

According to a second embodiment of this invention, there is provided compounds of the general formula

R-CO-Y

wherein R signifies one of the groups



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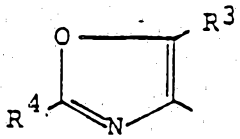

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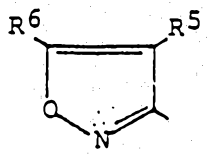

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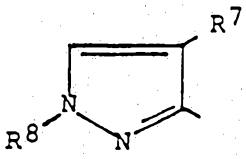


(d)

and Y signifies hydroxy or the group $-NH-CH_2-CH_2-R^{14}$, in which R^1 signifies phenyl, which is optionally monosubstituted by halogen, lower-alkyl, lower-alkoxy, trifluoromethyl, cyano or aryl-lower-alkoxy, dihalophenyl, furyl or thienyl, which is optionally monosubstituted by halogen, R^2 signifies hydrogen, halogen or amino, R^3, R^5 and R^7 each signify phenyl, which is optionally mono- or di-substituted by halogen, thienyl or furyl, which is optionally monosubstituted by halogen, R^4 and R^6 each signify hydrogen or amino, R^8 signifies hydrogen or lower-alkyl and R^{14} signifies a leaving group or a residue which is convertible into an

amino group.

According to a third embodiment of this invention, there is provided a process for the manufacture of compounds in accordance with the first embodiment as well as of pharmaceutically usable acid addition salts thereof, which process comprises

a) reacting a compound of the general formula

$$R\text{-}CO\text{-}OH \qquad II$$

wherein R has the significance given in the first embodiment, in the form of the free acid or in the form of a reactive functional derivative thereof with ethylenediamine, or

b) reacting a compound of the general formula

$$R\text{-}CO\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}R^9 \qquad III$$

wherein R has the significance given in the first embodiment and R^9 signifies a leaving group,

with ammonia, or

c) converting the residue R^{10} in a compound of the general formula

$$R\text{-}CO\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}R^{10} \qquad IV$$

wherein R has the significance given in the first embodiment and R^{10} signifies a residue which is convertible into an amino group,

into the amino group, and, if desired, converting a compound obtained into a pharmaceutically usable acid addition salt.

According to a fourth embodiment of this invention, there is provided an antidepressant composition for the treatment or prevention of cognitive disorders, comprising a compound in accordance with the first embodiment and a therapeutically inert excipient, diluent, carrier and/or adjuvant.

According to a fifth embodiment of this invention, there is provided compounds in accordance with the first embodiment, whenever prepared according to the process of the third embodiment or by an obvious chemical equivalent thereof.

According to a sixth embodiment of this invention, there is provided a method of treating or preventing depressive states and cognitive disorders which comprises administering to a patient requiring

such treatment an effective amount of a compound in accordance with the first embodiment.

The term "lower-alkyl" used in this description relates to straight-chain and branched hydrocarbon residues with 1-3 carbon atoms, i.e. methyl, ethyl, n-propyl and isopropyl. The term "lower-alkoxy" relates to lower alkyl ether groups in which the term "lower-alkyl"

has the above significance. The term "aryl-lower-alkoxy" relates to lower alkyl ether groups in which one hydrogen atom is replaced by a phenyl residue which is optionally substituted by halogen, lower-alkyl, lower-alkoxy, nitro, cyano or hydroxy. The term "halogen" embraces the four halogens fluorine, chlorine, bromine and iodine. The term "leaving group" signifies in the scope of the present invention known groups such as halogen, preferably chlorine or bromine, arylsulphonyloxy such as, for example, tosyloxy, alkylsulphonyloxy such as, for example, mesyloxy, and the like.

The term "pharmaceutically usable acid addition salts" embraces salts with inorganic and organic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like. Such salts can be manufactured readily by any person skilled in the art having regard to the state of the art and taking into consideration the nature of the compound to be converted into a salt.

Preferred compounds of formula I are those in which R signifies group (a) or (b).

There are thus preferred those compounds in which R^1 signifies phenyl, which is optionally monosubstituted by halogen, lower-alkyl, lower-alkoxy, trifluoromethyl or cyano, dihalophenyl, furyl or thienyl, which is optionally monosubstituted by halogen, and R^2 signifies hydrogen or amino and those compounds in which R^3 signifies phenyl, which is mono- or di-substituted by halogen, thienyl or furyl, which is optionally monosubstituted by halogen, and R^4 signifies hydrogen.

Especially preferred are those compounds in which R^1 signifies phenyl, which is monosubstituted by halogen, or dihalophenyl and R^2 signifies hydrogen and those compounds in which R^3 signifies phenyl, which is mono- or di-substituted by halogen, and R^4 signifies hydrogen.

From the above it follows that of the compounds of formula I there are especially preferred those in which R signifies group (a) or (b), R^1 signifies phenyl, which is monosubstituted by halogen, or dihalophenyl and R^2 signifies hydrogen or R^3 signifies phenyl, which is mono- or di-substituted by halogen, and R^4 signifies hydrogen.

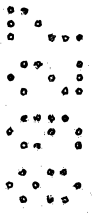
Particularly preferred compounds of formula I are:

N-(2-Aminoethyl)-5-phenyl-4-thiazolecarboxamide
N-(2-aminoethyl)-5-(2-fluorophenyl)-4-thiazolecarboxamide
N-(2-aminoethyl)-5-(3-fluorophenyl)-4-thiazolecarboxamide
N-(2-aminoethyl)-5-(4-fluorophenyl)-4-thiazolecarboxamide
N-(2-aminoethyl)-5-(4-chlorophenyl)-4-oxazolecarboxamide
N-(2-aminoethyl)-5-(2-furyl)-4-oxazolecarboxamide
N-(2-aminoethyl)-5-(3,5-dichlorophenyl)-4-thiazolecarboxamide
N-(2-aminoethyl)-5-(2,4-difluorophenyl)-4-thiazolecarboxamide
N-(2-aminoethyl)-5-(3,5-difluorophenyl)-4-thiazolecarboxamide
N-(2-aminoethyl)-5-(4-fluorophenyl)-4-oxazolecarboxamide
N-(2-aminoethyl)-5-(4-bromophenyl)-4-oxazolecarboxamide

N-(2-aminoethyl)-4-(3-fluorophenyl)-3-isoxazolecarboxamide and
N-(2-aminoethyl)-4-(3-fluorophenyl)-1-methyl-3--pyrazolecarboxamide.

The compounds of formula I and their pharmaceutically usable acid addition salts can be manufactured in accordance with the invention by

a) reacting a compound of the general formula



R-CO-OH II

wherein R has the above significance,
in the form of the free acid or in the form of a reactive functional derivative thereof with ethylenediamine, or

b) reacting a compound of the general formula

$R-CO-NH-CH_2-CH_2-R^9$ III

wherein R has the above significance and R^9 signifies a leaving group,
with ammonia, or

c) converting the residue R^{10} in a compound of the general formula

$R-CO-NH-CH_2-CH_2-R^{10}$ IV

wherein R has the above significance and R^{10} signifies a residue which is convertible into an amino group,

into the amino group, and, if desired, converting a compound obtained into a pharmaceutically usable acid addition salt.

As reactive functional derivatives of the acids of formula II there come into consideration, for example, halides, e.g. chlorides, symmetrical or mixed anhydrides, esters, e.g. methyl esters, p-nitrophenyl esters or N-hydroxysuccinimide esters, azides and amides, e.g. imidazolides or succinimides.

The reaction of an acid of formula II or a reactive functional derivative thereof with ethylenediamine according to variant a) of the above process can be carried out according to usual methods. Thus, e.g. a free acid of formula II can be reacted with ethylenediamine in the presence of a condensation agent in an inert solvent. If a carbodiimide such as 1,1'-carbonyldiimidazole or dicyclohexylcarbodiimide is used as the condensation agent, then the reaction is conveniently carried out in an alkanecarboxylic acid ester such as ethyl acetate, an ether such as tetrahydrofuran or dioxan, a chlorinated hydrocarbon such as methylene chloride or chloroform, an aromatic hydrocarbon such as benzene, toluene or xylene, acetonitrile or dimethylformamide at a temperature between about 0°C and about 100°C, preferably at about 60°C. If phosphorus trichloride is used as the condensation agent, then the reaction is conveniently carried out in a solvent such as pyridine at a temperature between about 0°C and the reflux temperature of the reaction mixture. In another embodiment of variant a), ethylenediamine is reacted with one of the above-mentioned reactive functional derivatives of an acid of formula II. Thus, e.g. a halide, e.g. the

chloride, of an acid of formula II can be reacted at about 0°C with ethylenediamine in the presence of a solvent such as e.g. methylene chloride or ether.

The compounds of formula III are, for example, N-(2--haloethyl)carboxamides such as N-(2-chloroethyl)carboxamides, N-(2-methylsulphonylethyl)carboxamides or N-(2-p--toluenesulphonylethyl)carboxamides and the like.

In accordance with variant b) a compound of formula III can be reacted with ammonia in a manner known per se at a temperature between about -40°C and 50°C, if desired in the presence of a solvent such as dimethylformamide, dimethylacetamide, dimethyl sulphoxide and the like. The reaction is conveniently carried out in the presence of a solvent at about room temperature.

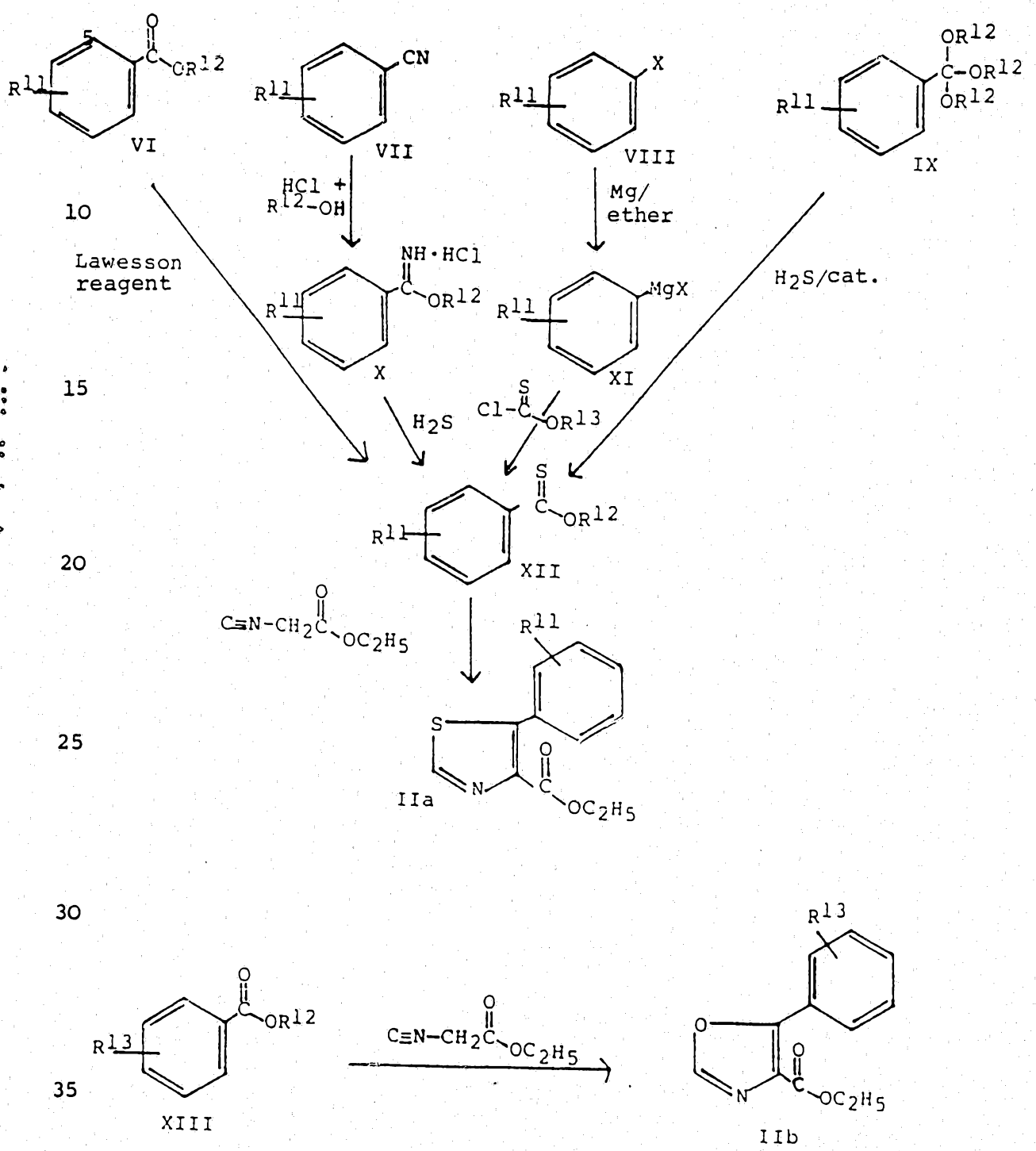
The conversion of the residue R^{10} into amino in accordance with variant c) is also effected in a manner known per se depending on the nature of the residue R^{10}. If this is an amide, then the conversion is conveniently effected by acidic or basic hydrolysis. For the acidic hydrolysis there is advantageously used a solution of a mineral acid such as hydrochloric acid, aqueous hydrogen bromide, sulphuric acid, phosphoric acid and the like in an inert solvent such as an alcohol, e.g. methanol or ethanol, an ether, e.g. tetrahydrofuran or dioxan, and the like. For the basic hydrolysis there can be used aqueous solutions of alkali metal hydroxides such as potassium hydroxide solution or sodium hydroxide solution. Inert organic solvents such as those referred to above for the acidic hydrolysis can be added as solubilizers. The reaction temperature can be varied for the acidic and basic hydrolysis in a range from about room temperature to the reflux temperature, with the reaction being preferably carried out at the boiling temperature of the reaction

mixture or slightly thereunder. If R^{10} is phthalimido, then, in addition to the acidic and basic hydrolysis, an aminolysis with an aqueous solution of a lower alkylamine such as methylamine or ethylamine can also be carried out. A lower alkanol such as ethanol can be used as the organic solvent. The reaction is preferably carried out at room temperature. A third method for the conversion of phthalimido into amino comprises reacting compounds of formula IV with hydrazine in an inert solvent such as ethanol, a mixture of ethanol and chloroform, tetrahydrofuran or aqueous ethanol. The reaction temperature can be varied in a range from about room temperature up to about 100°C, with the reaction being preferably carried out at the boiling temperature of the chosen solvent. The resulting product can be extracted with dilute mineral acid and can subsequently be obtained by making the acidic solution basic. The t-butoxycarbonylamino residue is conveniently converted into the amino group with trifluoroacetic acid or formic acid in the presence or absence of an inert solvent such as methylene chloride at about room temperature, while the conversion of the trichloroethoxycarbonylamino group is effected with zinc or cadmium under acidic conditions. The acidic conditions are conveniently achieved by carrying out the reaction in acetic acid in the presence or absence of an additional inert solvent such as an alcohol, e.g. methanol. The benzyloxycarbonylamino residue can be converted into the amino group in a known manner by acidic hydrolysis as described above or hydrogenolytically. An azido group can be reduced to the amino group according to known methods, for example with elementary hydrogen in the presence of a catalyst such as palladium/carbon, Raney-nickel, platinum oxide and the like. A hexamethylenetetraammonium group can be converted into the amino group by acidic hydrolysis according to likewise known methods.

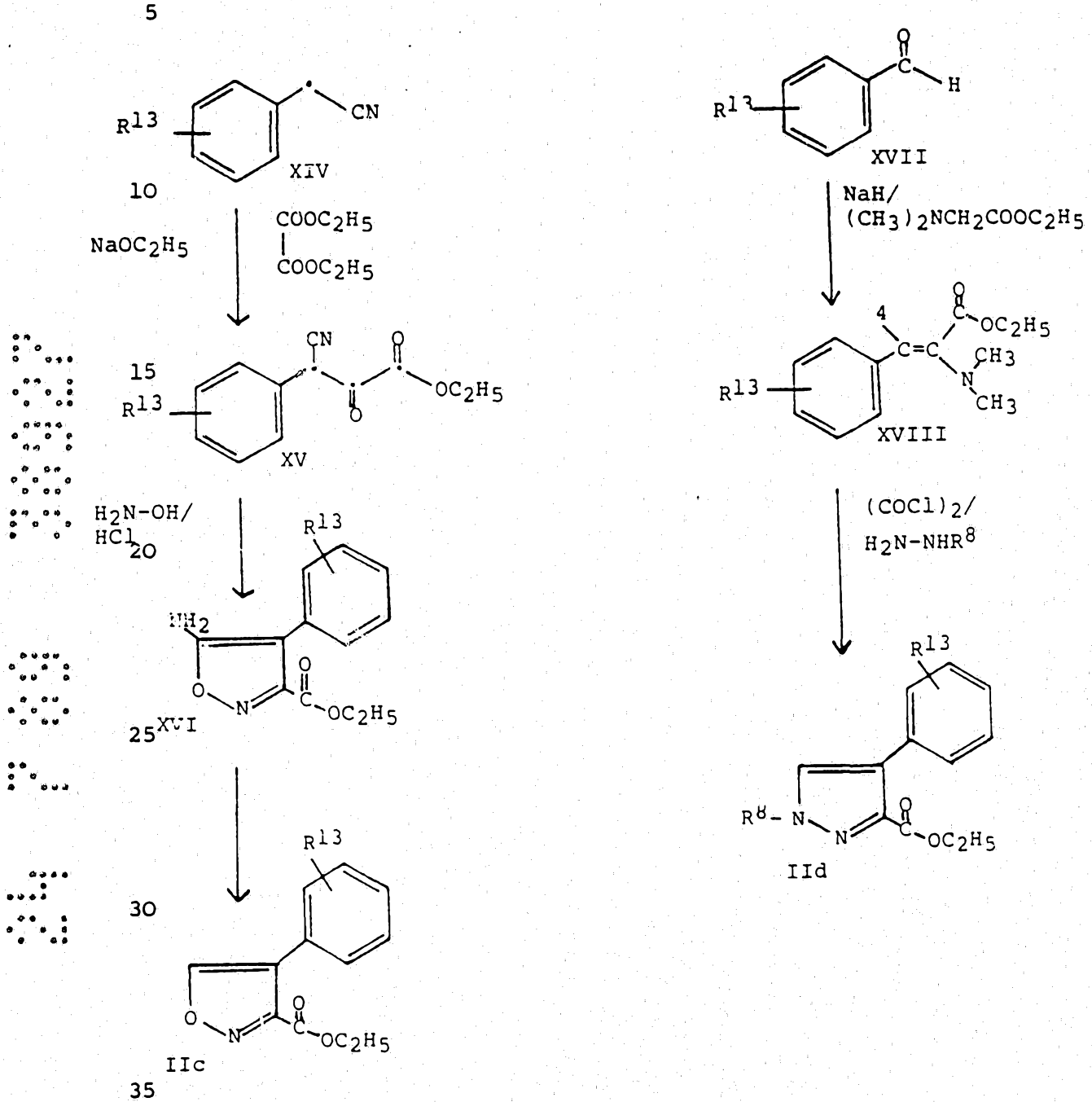
The compounds of formula II and their reactive functional derivatives, which are used as starting materials in variant a), are novel, but belong to known classes of substances and can be obtained in analogy to the preparation of known compounds. They are also an object of the present invention.

Processes for the preparation of in each case one type of compound of formula II in which R signifies group (a), (b), (c) or (d) are sketched in the following Schemes I and II in which R^8 signifies hydrogen or lower-alkyl and R^{11} signifies hydrogen, halogen, lower-alkyl, lower-alkoxy, trifluoromethyl, cyano or aryl-lower-alkoxy, R^{12} signifies lower-alkyl, R^{13} signifies hydrogen or halogen and X signifies halogen. With respect to the specific reaction conditions, reference is made to the experimental part.

Scheme I


VI
VII
VIII
IX
HCl + R12-OH
Mg/ ether
Lawesson reagent
H2S/cat.
X
XI
H2S
XII
IIa
XIII
IIb

Scheme II


R13
CN
XIV
NaOC2H5
COOC2H5
COOC2H5
CN
OC2H5
XV
H2N-OH/
HCl
NH2
XVI
IIc
XVII
NaH/
(CH3)2NCH2COOC2H5
4
OC2H5
CH3
N
CH3
XVIII
(COCl)2/
H2N-NHR8
R8
IId

The compounds of formula III, which are used as starting materials in variant b), are also novel, but again belong to known classes of substances and can be prepared in a manner known per se. They also form an object of the present invention. For example, a compound of formula II or a reactive functional derivative thereof can be reacted with ethanolamine under the reaction conditions given for variant a) and the N-(2-hydroxyethyl)carboxamide obtained can be converted into the desired compound of formula III in a manner known per se, e.g. by reaction with a halogenating agent such as phosphorus trichloride, phosphorus tribromide, phosphorus pentachloride, phosphorus oxychloride and the like, an arylsulphonyl halide such as tosyl chloride or an alkylsulphonyl halide such as mesyl chloride.

The compounds of formula IV, which are used as starting materials in variant c), are novel and are also an object of the present invention. They can be prepared in a manner known per se, for example by reacting a compound of formula II or a reactive functional derivative thereof with a compound of the general formula

$$H_2N\text{-}CH_2\text{-}CH_2\text{-}R^{10} \qquad V$$

wherein R^{10} has the above significance, under the reaction conditions given for variant a). The compounds of formula V are known or can be obtained in analogy to the preparation of the known compounds.

According to an alternative process the compounds of formula IV in which R^{10} signifies phthalimido, azido or hexamethylenetetraammonium can also be obtained by reacting a compound of formula III with potassium

phthalimide, an alkali metal azide or hexamethylene-tetramine. The reaction is effected in a manner known per se under the reaction conditions given for variant b).

As mentioned above, the compounds of formula I and their pharmaceutically usable acid addition salts have monoamine oxidase (MAO) inhibiting activity. On the basis of this activity the compounds of formula I and their pharmaceutically usable acid addition salts can be used for the treatment of depressive states and cognitive disorders, especially of those which are caused by age. Examples of such disorders are hypomnesis caused by age, primary and secondary degenerative dementia, e.g. dementia of the Alzheimer type or multi-infarct caused dementia, and cerebrovascular disorders and consequences of brain damages.

The MAO inhibiting activity of the compounds in accordance with the invention can be determined using standard methods. Thus, the preparations to be tested were subjected to the in vitro test described hereinafter, which followed the method published by R. J. Wurtmann and J. A. Axelrod [Biochem. Pharmac. 12, 1439-1441 (1963)].

Isolated rats brains are homogenized in the ratio 1:4 (weight/volume) in 0.1 molar potassium phosphate buffer (pH 7.4), whereupon the homogenates are diluted in the ratio 1:4 (volume/volume) with the same buffer and stored at -20°. A mixture of the following composition is used for the incubation:

- 100 µl of 1M phosphate buffer (pH 7.4);
- 100 µl solubilizate of the substance to be tested in water or dimethyl sulphoxide;
- 20 µl of rat brain homogenate; and as the substrate

- 80 µl of ^{14}C-serotonin (5-HT) or ^{14}C-phenylethylamine (PEA), in each case 100,000 decays per minute, corresponding to a final concentration of 2.10^{-4} Mol/l and, respectively, 2.10^{-5} Mol/l.

Prior to the addition of the substrate a pre-incubation at 37°C was effected for 30 minutes. The incubation (in the presence of the substrate) was also effected at 37°C and lasted 10 minutes.

The reaction is stopped by the addition of 200 µl of 2N hydrochloric acid.

The deaminated product, depending on the use of 5-HT or of PEA as the substrate, is extracted by shaking for 10 minutes with 5 ml of diethyl ether or with 5 ml of n-heptane, whereupon the mixture is centrifuged, the aqueous phase is frozen in a dry-ice bath and the organic phase is poured into a counting glass.

The activity of the MAO in comparison to control homogenates (without substance to be tested) is determined on the basis of the ß-counter value and the IC 50 is defined as that concentration of a substance to be tested which decreases the activity of the MAO in the substrate 5-HT or PEA to 50%.

The thus-determined activity of some compounds in accordance with the invention will be evident from the IC_{50} values listed in the following Table:

Compound "N-(2-Aminoethyl)-...carboxamide"	IC 50, µMol/l 5-HT	PEA
... 5-phenyl-4-thiazol ...	0.02	20
... 5-(2-fluorophenyl)-4-thiazol...	0.04	>10
... 5-(3-fluorophenyl)-4-thiazol...	0.02	>10
... 5-(4-fluorophenyl)-4-thiazol...	0.06	100
... 5-(4-chlorophenyl)-4-oxazol...	<0.01	>100
... 5-(2-furyl)-4-oxazol...	0.022	2.0
... 5-(3,5-dichlorophenyl)-4-thiazol...	0.007	0.3
... 5-(2,4-difluorophenyl)-4-thiazol...	0.12	3.6

The compounds of formula I as well as their pharmaceutically usable acid addition 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.

For the manufacture of tablets, coated tablets, dragees and hard gelatine capsules the compounds of formula I and their pharmaceutically usable acid addition salts can be processed with pharmaceutically inert, inorganic or organic excipients. Lactose, maize starch or derivatives thereof, talc, stearic acid or its salts etc. can be used as such excipients for e.g. tablets, dragees and hard gelatine capsules.

Suitable excipients for soft gelatine capsules are e.g. vegetable oils, waxes, fats, semi-solid and liquid polyols etc.

Suitable excipients for the manufacture of solutions and syrups are e.g. water, polyols, saccharose, invert sugar, glucose etc.

Suitable excipients for injection solutions are e.g. water, alcohols, polyols, glycerine, vegetable oils etc.

Suitable excipients for suppositories are e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols etc.

The pharmaceutical preparations can also contain 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 compounds of general formula I as well as their pharmaceutically usable acid addition salts can be used in the control or prevention of depressive states and cognitive disorders, especially those which are caused by age. 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 50 to 500 mg, preferably of about 100 to 300 mg, of a compound of general formula I should be appropriate, although the upper limit just mentioned can also be exceeded when this is shown to be indicated.

The following Examples are intended to illustrate the present invention, but they are not intended to be limiting in any manner. All temperatures are given in degrees Celsius.

Example 1

(A) 4.3 g (12.37 mmol) of t-butyl [2-(5-phenyl-4--thiazolecarboxmido)ethyl]carbamate are dissolved in 10 ml of methylene chloride, treated with 5.0 ml of trifluoroacetic acid and stirred at 20° for 16 hours and at 60° for 1 hour. Subsequently, the mixture is concentrated under reduced pressure. The residue is dissolved in 10 ml of ethanol, treated with 3 ml of 17.5% (w/v) ethanolic hydrochloric acid and evaporated. The residue is recrystallized from methanol, whereby 3.3 g (94%) of N-(2-aminoethyl)-5--phenyl-4-thiazolecarboxamide hydrochloride are obtained as white crystals, melting point 243-245°.

The t-butyl [2-(5-phenyl-4-thiazolecarboxamido)ethyl]-carbamate used as the starting material was prepared as follows:

(B) 70 ml (0.487 mmol) of ethyl benzoate are heated to reflux for 12 hours with 100 g (0.247 mol) of Lawesson reagent in 350 ml of xylene. After cooling to 20° the reaction mixture is diluted with 500 ml of hexane and filtered. The filtrate is flash-chromatographed on 1 kg of silica gel. Elution is carried out with hexane. The fractions which are pure according to the thin-layer chromatrogram (eluent: toluene) are combined and evaporated under reduced pressure. There are obtained 72 g (89%) of O-ethyl thiobenzoate as a dark yellow evil--smelling oil which is used without further purification.

(C) Analogously to the method described in Synthesis 10, (1976), 681-682, the O-ethyl thiobenzoate is converted with ethyl isocyanoacetate in the presence of 1-5% powdered potassium hydroxide in ethanol in 70% yield into ethyl 5-phenyl-4-thiazolecarboxylate which melts at 79-80° after recrystallization from ethyl acetate/hexane.

(D) The ethyl 5-phenylthiazole-4-carboxylate is hydrolyzed according to known methods with 2N aqueous sodium hydroxide solution at 70° for 30 minutes, whereby, after acidification, there is obtained in 72% yield 5-phenyl-4-thiazolecarboxylic acid which melts at 189-190°C after recrystallization from methanol/diethyl ether.

(E) 4.03 g (24.85 mmol) of 1,1'-carbonyldiimidazole are added to a solution of 5.0 g (24.36 mmol) of 5-phenyl--4-thiazolecarboxylic acid in 100 ml of abs. tetrahydrofuran and the reaction mixture is stirred at 25° for 2 hours, whereby a CO_2-evolution occurs. Thereafter, 4.1 g (25.59 mmol) of t-butyl (2-aminoethyl)carbamate are added thereto. The reaction mixture is left to stir at 50° for 2 hours and is thereafter evaporated under reduced pressure. The oily residue is dissolved in methylene chloride and chromatographed on 50 g of silica gel. Elution is carried out firstly with methylene chloride, then with an 8:2 and 7:3 mixture of methylene chloride and ethyl acetate and finally with ethyl acetate. The fractions which are pure according to the thin-layer chromatogram (methylene chloride/ethyl acetate 7:3) are combined and recrystallized from ethyl acetate/hexane, whereby there are obtained 7.7 g (91%) of t-butyl [2-(5--phenyl-4-thiazolecarboxamido)ethyl]carbamate as white crystals, melting point 139-140°.

(E1) 4.8 g (20.58 mmol) of ethyl 5-phenyl-4-thiazolecarboxylate and 4.0 g (25.0 mmol) of t-butyl (2-aminoethyl)carbamate are heated under reduced pressure for 21 hours at a bath temperature of 100°, whereby the ethanol formed is distilled off continuously. Subsequently, the mixture is cooled, dissolved in 50 ml of methylene chloride and chromatographed on 150 g of silica gel. Elution is carried out firstly with methylene

chloride, then with a 9:1, 8:2 and finally 7:3 mixture of methylene chloride and ethyl acetate. The fractions which are pure according to the thin-layer chromatogram are combined and recrystallized from ethyl acetate/hexane. In this manner there are obtained 4.3 g (60.1%) of t-butyl [2-(5-phenyl-4-thiazolecarboxamido)ethyl]carbamate as white crystals, melting point 139-140°.

(E2) 2.0 g (9.75 mmol) of 5-phenyl-4-thiazole-carboxylic acid are placed in 20 ml of chloroform with 0.8 g (10.4 mmol) of methyl chloroformate and cooled to 0°. 1.5 ml (10.8 mmol) of triethylamine are added dropwise thereto at 0-5°. After stirring at 0-5° for 30 minutes the reaction mixture is added dropwise within 1.5 hours to an ice-cooled solution of 1.6 g (10 mmol) of t-butyl (2-aminoethyl)carbamate in 20 ml of chloroform. The reaction mixture is stirred at 0-5° for a further 30 minutes, subsequently diluted with 150 ml of methylene chloride and washed with in each case 100 ml of water, saturated sodium bicarbonate solution as well as sodium chloride solution. The aqueous phases are back-extracted with 100 ml of methylene chloride. The combined organic phases are dried over magnesium sulphate and evaporated. The crystalline residue is recrystallized from ethyl acetate/hexane, whereby there are obtained, after drying, 2.4 g (70.9%) of t-butyl [2-(5-phenyl-4-thiazolecarbox-amido)ethyl]carbamate as white crystals, melting point 139-140°.

Example 2

The following compounds were manufactured in an analogous manner to that described in Example 1(A):

- From t-butyl [2-[5-(2-fluorophenyl)-4-thiazole-carboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(2-

-fluorophenyl)-4-thiazolecarboxamide hydrochloride in 95% yield, melting point 239-240° (from methanol/diethyl ether);

- from t-butyl [2-[5-(3-fluorophenyl)-4-thiazole-carboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(3--fluorophenyl)-4-thiazolecarboxamide hydrochloride in 90% yield, melting point 244-246° (from methanol/diethyl ether);

- from t-butyl [2-[5-(4-fluorophenyl)-4-thiazole-carboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(4--fluorophenyl)-4-thiazolecarboxamide hydrochloride in 90% yield, melting point 258-259° (from methanol/diethyl ether);

- from t-butyl [2-[5-(2-chlorophenyl)-4-thiazole-carboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(2--chlorophenyl)-4-thiazolecarboxamide hydrochloride in 85% yield, melting point 264-266° (from methanol/diethyl ether);

- from t-butyl [2-[5-(3-chlorophenyl)-4-thiazole-carboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(3--chlorophenyl)-4-thiazolecarboxamide hydrochloride in 92% yield, melting point 257-258° (from methanol/diethyl ether);

- from t-butyl [2-[5-(4-chlorophenyl)-4-thiazole-carboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(4--chlorophenyl)-4-thiazolecarboxamide hydrochloride in 86% yield, melting point 272-274° (from methanol/diethyl ether);

- from t-butyl [2-[5-(3-bromophenyl)-4-thiazole-carboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(3-

-bromophenyl)-4-thiazolecarboxamide hydrochloride in 92% yield, melting point 260-261° (from methanol/diethyl ether);

- from t-butyl [2-[5-(3,5-dichlorophenyl)-4-thiazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(3,5-dichlorophenyl)-4-thiazolecarboxamide hydrochloride in 67% yield, melting point 294-295° (from methanol);

- from t-butyl [2-[5-(2-methylphenyl)-4-thiazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(2-methylphenyl)-4-thiazolecarboxamide hydrochloride in 80% yield, melting point 278-279° (from methanol/diethyl ether);

- from t-butyl [2-[5-(3-methylphenyl)-4-thiazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(3-methylphenyl)-4-thiazolecarboxamide hydrochloride in 89% yield, melting point 261-262° (from methanol/diethyl ether);

- from t-butyl [2-[5-(4-methylphenyl)-4-thiazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(4-methylphenyl)-4-thiazolecarboxamide hydrochloride in 91% yield, melting point 259-261° (from methanol/diethyl ether);

- from t-butyl [2-[5-(2-methoxyphenyl)-4-thiazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(2-methoxyphenyl)-4-thiazolecarboxamide hydrochloride in 84% yield, melting point 230-231° (from methanol/diethyl ether);

- from t-butyl [2-[5-(3-methoxyphenyl)-4-thiazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(3-methoxyphenyl)-4-thiazolecarboxamide hydrochloride in 82%

yield, melting point 242-243° (from methanol/diethyl ether);

- from t-butyl [2-[5-(4-methoxyphenyl)-4-thiazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(4-methoxyphenyl)-4-thiazolecarboxamide hydrochloride in 82% yield, melting point 263-265° (from methanol/diethyl ether);

- from t-butyl [2-[5-(α,α,α-trifluoro-3-methylphenyl)-4-thiazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(α,α,α-trifluoro-3-methylphenyl)-4-thiazolecarboxamide hydrochloride in 86% yield, melting point 226-227° (from methanol);

- from t-butyl [2-[5-(α,α,α-trifluoro-4-methylphenyl)-4-thiazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(α,α,α-trifluoro-4-methylphenyl)-4-thiazolecarboxamide hydrochloride in 86% yield, melting point 281-284° (from methanol/diethyl ether);

- from t-butyl [2-[5-(3-cyanophenyl)-4-thiazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(3-cyanophenyl)-4-thiazolecarboxamide hydrochloride in 75% yield, melting point 244-246° (from methanol/diethyl ether);

- from t-butyl [2-[5-(4-cyanophenyl)-4-thiazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(4-cyanophenyl)-4-thiazolecarboxamide hydrochloride in 73% yield, melting point 250-252° (from methanol);

- from t-butyl [2-[5-(2,4-dichlorophenyl)-4-thiazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(2,4-dichlorophenyl)-4-thiazolecarboxamide hydrochloride in 86% yield, melting point 278-280° (from methanol/diethyl ether);

- from t-butyl [2-[5-(3,4-dichlorophenyl)-4-thiazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(3,4-dichlorophenyl)-4-thiazolecarboxamide hydrochloride in 90% yield, melting point 244-247° (from methanol/diethyl ether);

- from t-butyl [2-[5-(2,4-difluorophenyl)-4-thiazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(2,4-difluorophenyl)-4-thiazolecarboxamide hydrochloride in 94% yield, melting point 269-271° (from methanol);

- from t-butyl [2-[5-(2-thienyl)-4-thiazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(2-thienyl)-4-thiazolecarboxamide hydrochloride in 93% yield, melting point 251-254° (from methanol/diethyl ether);

- from t-butyl [2-[5-(3-thienyl)-4-thiazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(3-thienyl)-4-thiazolecarboxamide hydrochloride in 89% yield, melting point 265-266° (from methanol/diethyl ether);

- from t-butyl [2-[5-(5-bromo-2-thienyl)-4-thiazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(5-bromo-2-thienyl)-4-thiazolecarboxamide hydrochloride in 77% yield, melting point 267-269° (from methanol/diethyl ether);

- from t-butyl [2-[5-(2-furyl)-4-thiazolecarboxamido]-ethyl]carbamate the N-(2-aminoethyl)-5-(2-furyl)-4-thiazolecarboxamide hydrochloride in 80% yield, melting point 254° (from methanol/diethyl ether);

- from t-butyl [2-[5-(2,3-dichlorophenyl)-4-thiazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(2,3-dichlorophenyl)-4-thiazolecarboxamide hydrochloride in 96% yield, melting point 263-265° (from methanol/diethyl ether);

- from t-butyl [2-[5-(2,5-dichlorophenyl)-4-thiazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(2,5-dichlorophenyl)-4-thiazolecarboxamide hydrochloride in 80% yield, melting point 252-253° (from methanol); and

- from t-butyl [2-[5-(3,4-difluorophenyl)-4-thiazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(3,4-difluorophenyl)-4-thiazolecarboxamide hydrochloride in 94% yield, melting point 242-244° (from methanol/diethyl ether).

The above-mentioned carbamates used as the starting materials were prepared as follows:

The following carbamates were prepared in an analogous manner to that described in Example 1(E1):

- From ethyl 5-(2-fluorophenyl)-4-thiazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(2-fluorophenyl)-4-thiazolecarboxamido]ethyl]carbamate in 59% yield, melting point 143° (from ethyl acetate/hexane);

- from ethyl 5-(3-fluorophenyl)-4-thiazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(3-fluorophenyl)-4-thiazolecarboxamido]ethyl]carbamate in 60% yield, melting point 142-143° (from ethyl acetate/hexane);

- from ethyl 5-(4-fluorophenyl)-4-thiazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(4-flurophenyl)-4-thiazolecarboxamido]ethyl]carbamate in 46% yield, melting point 110-111° (from ethyl acetate/hexane);

- from ethyl 5-(2-chlorophenyl)-4-thiazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(2-chlorophenyl)-4-thiazolecarboxamido]ethyl]carbamate in

68% yield, melting point 166-167° (from ethyl acetate/hexane);

- from ethyl 5-(3-chlorophenyl)-4-thiazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(3--chlorophenyl)-4-thiazolecarboxamido]ethyl]carbamate in 72% yield, melting point 122-123° (from ethyl acetate/hexane);

- from ethyl 5-(4-chlorophenyl)-4-thiazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(4--chlorophenyl)-4-thiazolecarboxamido]ethyl]carbamate in 63% yield, melting point 147-148° (from ethyl acetate/hexane);

- from ethyl 5-(3-bromophenyl)-4-thiazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(3--bromophenyl)-4-thiazolecarboxamido]ethyl]carbamate in 79% yield, melting point 124-125° (from ethyl acetate/hexane);

- from ethyl 5-(3,5-dichlorophenyl)-4-thiazole-carboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(3,5-dichlorophenyl)-4-thiazolecarboxamido]-ethyl]carbamate in 42% yield, melting point 130-132° (from ethyl acetate/hexane);

- from ethyl 5-(2-methylphenyl)-4-thiazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(2--methylphenyl)-4-thiazolecarboxamido]ethyl]carbamate in 44% yield, melting point 163-164° (from ethyl acetate/hexane);

- from ethyl 5-(3-methylphenyl)-4-thiazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(3--methylphenyl)-4-thiazolecarboxamido]ethyl]carbamate in 35% yield, melting point 112-113° (from ethyl acetate/hexane);

- from ethyl 5-(4-methylphenyl)-4-thiazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(4--methylphenyl)-4-thiazolecarboxamido]ethyl]carbamate in 60% yield, melting point 133-134° (from ethyl acetate/hexane);

- from ethyl 5-(2-methoxyphenyl)-4-thiazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(2--methoxyphenyl)-4-thiazolecarboxamido]ethyl]carbamate in 17.5% yield, melting point 142-143° (from ethyl acetate/hexane);

- from ethyl 5-(3-methoxyphenyl)-4-thiazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(3--methoxyphenyl)-4-thiazolecarboxamido]ethyl]carbamate in 66% yield, melting point 98-100° (from ethyl acetate/hexane);

- from ethyl 5-(4-methoxyphenyl)-4-thiazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(4--methoxyphenyl)-4-thiazolecarboxamido]ethyl]carbamate in 61% yield, melting point 102° (from ethyl acetate/hexane);

- from ethyl 5-(α,α,α-trifluoro-3-methylphenyl)--4-thiazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(α,α,α-trifluoro-3-methylphenyl)--4-thiazolecarboxamido]ethyl]carbamate in 24% yield, melting point 119-120° (from ethyl acetate/hexane);

- from ethyl 5-(α,α,α-trifluoro-4-methylphenyl)--4-thiazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(α,α,α-trifluoro-4-methylphenyl)--4-thiazolecarboxamido]ethyl]carbamate in 82% yield, melting point 152-153° (from ethyl acetate/hexane);

- from ethyl 5-(3-cyanophenyl)-4-thiazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(3--cyanophenyl)-4-thiazolecarboxamido]ethyl]carbamate in 68% yield, melting point 127-128° (from ethyl acetate/ hexane);

- from ethyl 5-(4-cyanophenyl)-4-thiazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(4--cyanophenyl)-4-thiazolecarboxamido]ethyl]carbamate in 60% yield, melting point 149-149.5° (from ethyl acetate/ hexane);

- from ethyl 5-(2-thienyl)-4-thiazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(2--thienyl)-4-thiazolecarboxamido]ethyl]carbamate in 60% yield, melting point 100-101° (from ethyl acetate/hexane);

- from ethyl 5-(3-thienyl)-4-thiazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(3--thienyl)-4-thiazolecarboxamido]ethyl]carbamate in 43% yield, melting point 83° (from ether);

- from ethyl 5-(5-bromo-2-thienyl)-4-thiazole-carboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(5-bromo-2-thienyl)-4-thiazolecarboxamido]-ethyl]carbamate in 56% yield, melting point 144-145° (from ethyl acetate/hexane); and

- from ethyl 5-(2-furyl)-4-thiazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(2--furyl)-4-thiazolecarboxamido]ethyl]carbamate in 56% yield, melting point 93-94° (from ethyl acetate/hexane).

The following carbamates were prepared in an analogous manner to that described in Example 1(E):

- From 5-(2,4-dichlorophenyl)-4-thiazolecarboxylic acid and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(2,4-dichlorophenyl)-4-thiazolecarboxamido]ethyl]-carbamate in 92.2% yield, melting point 142° (from ethyl acetate/hexane);

- from 5-(3,4-dichlorophenyl)-4-thiazolecarboxylic acid and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(3,4-dichlorophenyl)-4-thiazolecarboxamido]ethyl]-carbamate in 82.1% yield, melting point 128° (from ethyl acetate/hexane);

- from 5-(2,4-difluorophenyl)-4-thiazolecarboxylic acid and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(2,4-difluorophenyl)-4-thiazolecarboxamido]ethyl]-carbamate in 73% yield, melting point 109-110° (from ethyl acetate/hexane);

- from 5-(2,3-dichlorophenyl)-4-thiazolecarboxylic acid and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(2,3-dichlorophenyl)-4-thiazolecarboxamido]ethyl]-carbamate in 91% yield, melting point 144-145° (from ethyl acetate/hexane);

- from 5-(2,5-dichlorophenyl)-4-thiazolecarboxylic acid and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(2,5-dichlorophenyl)-4-thiazolecarboxamido]ethyl]-carbamate in 90% yield, melting point 129-130° (from ethyl acetate/hexane); and

- from 5-(3,4-difluorophenyl)-4-thiazolecarboxylic acid and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(3,4-difluorophenyl)-4-thiazolecarboxamido]ethyl]-carbamate in 93% yield, melting point 115-116° (from ethyl acetate/hexane).

The ethyl 4-thiazolecarboxylates used as starting materials are listed hereinafter. They were prepared in an analogous manner to that described in Example 1(C) by reacting the corresponding thioester with ethyl isocyanoacetate in the presence of potassium hydroxide.

- From O-methyl 2-fluorothiobenzoate the ethyl 5-(2-fluorophenyl)-4-thiazolecarboxylate in 67.3% yield as a yellow oil;

- from O-methyl 3-fluorothiobenzoate the ethyl 5-(3-fluorophenyl)-4-thiazolecarboxylate in 63.7% yield as a pale yellow oil;

- from O-methyl 4-fluorothiobenzoate the ethyl 5-(4-fluorophenyl)-4-thiazolecarboxylate in 51% yield, melting point 65-66° (from ethyl acetate/hexane);

- from O-ethyl 2-chlorothiobenzoate the ethyl 5-(2-chlorophenyl)-4-thiazolecarboxylate in 30% yield as a yellow oil;

- from O-ethyl 3-chlorothiobenzoate the ethyl 5-(3-chlorophenyl)-4-thiazolecarboxylate in 41% yield, melting point 73-75° (from ether/petroleum ether);

- from O-ethyl 4-chlorothiobenzoate the ethyl 5-(4-chlorophenyl)-4-thiazolecarboxylate in 57% yield, melting point 99-100° (from ethyl acetate/hexane);

- from O-methyl 3-bromothiobenzoate the ethyl 5-(3-bromophenyl)-4-thiazolecarboxylate in 42% yield, melting point 66-67° (from ethyl acetate/hexane);

- from O-methyl 3,5-dichlorothiobenzoate the ethyl 5-(3,5-dichlorophenyl)-4-thiazolecarboxylate in 54% yield as an oil;

- from O-methyl 2-methylthiobenzoate the ethyl 5-(2--methylphenyl)-4-thiazolecarboxylate in 23% yield, melting point 72-73° (from ethyl acetate/hexane);

- from O-methyl 3-methylthiobenzoate the ethyl 5-(3--methylphenyl)-4-thiazolecarboxylate in 37% yield as a red-brown oil;

- from O-methyl 4-methylthiobenzoate the ethyl 5-(4--methylphenyl)-4-thiazolecarboxylate in 52% yield, melting point 78-79° (from ethyl acetate/hexane);

- from O-methyl 2-methoxythiobenzoate the ethyl 5-(2--methoxyphenyl)-4-thiazolecarboxylate in 8.6% yield as a yellow oil;

- from O-methyl 3-methoxythiobenzoate the ethyl 5-(3--methoxyphenyl)-4-thiazolecarboxylate in 25.6% yield as an oil;

- from O-methyl 4-methoxythiobenzoate the ethyl 5-(4--methoxyphenyl)-4-thiazolecarboxylate in 48% yield, melting point 69-70° (from ethyl acetate/hexane);

- from O-methyl 3-(α,α,α-trifluoromethyl)thiobenzoate the ethyl 5-(α,α,α-trifluoro-3-methylphenyl)-4-thiazolecarboxylate in 51% yield as an oil;

- from O-methyl 4-(α,α,α-trifluoromethyl)thiobenzoate the ethyl 5-(α,α,α-trifluoro-4-methylphenyl)-4-thiazolecarboxylate in 60% yield, melting point 124-125° (from ethyl acetate/hexane);

- from O-methyl 3-cyanothiobenzoate the ethyl 5-(3--cyanophenyl)-4-thiazolecarboxylate in 63% yield, melting point 149° (from ethyl acetate/hexane);

- from O-methyl 4-cyanothiobenzoate the ethyl 5-(4--cyanophenyl)-4-thiazolecarboxylate in 37.6% yield, melting point 111-112° (from ethyl acetate/hexane);

- from O-methyl 2,4-dichlorothiobenzoate the ethyl 5-(2,4-dichlorophenyl)-4-thiazolecarboxylate in 66.6% yield, melting point 79-80° (from ethyl acetate/hexane);

- from O-methyl 3,4-dichlorothiobenzoate the ethyl 5-(3,4-dichlorophenyl)-4-thiazolecarboxylate in 80.6% yield, melting point 113° (from ethyl acetate/hexane);

- from O-methyl 2,4-difluorothiobenzoate the ethyl 5-(2,4-difluorophenyl)-4-thiazolecarboxylate in 83% yield, melting point 73-74° (from ethyl acetate/hexane);

- from O-methyl 2-thiophenethiocarboxylate the ethyl 5-(2-thienyl)-4-thiazolecarboxylate in 63% yield, melting point 37-38° (from ethyl acetate/hexane);

- from O-methyl 3-thiophenethiocarboxylate the ethyl 5-(3-thienyl)-4-thiazolecarboxylate in 49% yield, melting point 65-67° (from ethyl acetate/hexane);

- from O-methyl 5-bromo-2-thiophenethiocarboxylate the ethyl 5-(5-bromo-2-thienyl)-4-thiazolecarboxylate in 48% yield, melting point 80-86° (from ethyl acetate/hexane);

- from O-methyl 2-furanthiocarboxylate the ethyl 5-(2--furyl)-4-thiazolecarboxylate in 70% yield, melting point 51-52° (from ethyl acetate/hexane);

- from O-methyl 2,3-dichlorothiobenzoate the ethyl 5-(2,3-dichlorophenyl)-4-thiazolecarboxylate in 83% yield, melting point 131° (from ethanol);

- from O-methyl 2,5-dichlorothiobenzoate the ethyl 5-(2,5-dichlorophenyl)-4-thiazolecarboxylate in 56% yield, melting point 89-90° (from ethyl acetate/hexane); and

- from O-methyl 3,4-difluorothiobenzoate the ethyl 5-(3,4-difluorophenyl)-4-thiazolecarboxylate in 78% yield, melting point 75° (from ethyl acetate/hexane).

The 4-thiazolecarboxylic acids used as starting materials were prepared from the corresponding methyl 4-thiazolecarboxylates by hydrolysis in an analogous manner to that described in Example 1(D):

5-(2,4-Dichlorophenyl)-4-thiazolecarboxylic acid in 78% yield, melting point 185-186° (from ethyl acetate/hexane);

5-(3,4-dichlorophenyl)-4-thiazolecarboxylic acid in 95% yield, melting point 202-203° (from water);

5-(2,4-difluorophenyl)-4-thiazolecarboxylic acid in 95% yield, melting point 182-183° (from water);

5-(2,3-dichlorophenyl)-4-thiazolecarboxylic acid in 97% yield, melting point 199-201° (from water);

5-(2,5-dichlorophenyl)-4-thiazolecarboxylic acid in 95% yield, melting point 172-173° (from water); and

5-(3,4-difluorophenyl)-4-thiazolecarboxylic acid in 55% yield, melting point 195-196° (from water).

Finally, the thioesters used above as starting materials were obtained from the corresponding carboxylic acid esters by reaction with Lawesson reagent in an analogous manner to that described in Example 1(B):

O-Methyl 2-fluorothiobenzoate in 51% yield as a yellow oil;

O-methyl 3-fluorothiobenzoate in 53% yield as a yellow oil;

O-methyl 4-fluorothiobenzoate in 91% yield as a yellow oil;

O-ethyl 2-chlorothiobenzoate in 62% yield as a yellow oil;

O-ethyl 3-chlorothiobenzoate in 80% yield as a yellow oil;

O-ethyl 4-chlorothiobenzoate in 70% yield as an orange oil;

O-ethyl 3-bromothiobenzoate in 43% yield as a yellow oil;

O-methyl 3,5-dichlorothiobenzoate in 41% yield as a yellow oil;

O-methyl 2-methylthiobenzoate in 74% yield as a yellow oil;

O-methyl 3-methylthiobenzoate in 76% yield as a dark yellow oil;

O-methyl 4-methylthiobenzoate in 75% yield as a yellow oil;

O-methyl 2-methoxythiobenzoate in 50% yield as an orange oil;

O-methyl 3-methoxythiobenzoate in 72.5% yield as an orange oil;

O-methyl 4-methoxythiobenzoate in 52% yield as an orange oil;

O-methyl 3-(α,α,α-trifluoromethyl)thiobenzoate in 59% yield as a yellow oil;

O-methyl 4-(α,α,α-trifluoromethyl)thiobenzoate in 45% yield as a yellow oil;

O-methyl 3-cyanothiobenzoate in 43% yield as a yellow oil;

O-methyl 4-cyanothiobenzoate in 88% yield, melting point 53-54°;

O-methyl 2,4-dichlorothiobenzoate in 20% yield as a yellow oil;

O-methyl 3,4-dichlorothiobenzoate in 50% yield as a yellow oil:

O-methyl 2,4-difluorothiobenzoate in 69.4% yield as a yellow oil;

O-methyl 2-thiophenethiocarboxylate in 93% yield as a yellow oil;

O-methyl 3-thiophenethiocarboxylate in 81% yield as a yellow oil;

O-methyl 5-bromo-2-thiophenethiocarboxylate in 79% yield as a yellow oil;

O-methyl 2-furanthiocarboxylate in 72.4% yield as an orange oil;

O-methyl 2,3-dichlorothiobenzoate in 36% yield as a yellow oil;

O-methyl 2,5-dichlorothiobenzoate in 26% yield as a yellow oil; and

O-methyl 3,4-difluorothiobenzoate in 67% yield as a yellow oil.

Example 3

In an analogous manner to that described in Example 1(A), from 19.4 g (42.8 mmol) of t-butyl [2-[5-[3-(benzyloxy)phenyl]-4-thiazolecarboxamido]ethyl]carbamate there were obtained 14.7 g (91%) of N-(2-aminoethyl)-5-[3-(benzyloxy)phenyl]-4-thiazolecarboxamide hydrochloride as beige crystals, melting point 230-231° (from methanol).

The t-butyl [2-[5-[3-(benzyloxy)phenyl]-4-thiazolecarboxamido]ethyl]carbamate used as the starting material was prepared as follows:

In an analogous manner to that described in Example 1(B), 40 g (0.165 mol) of methyl 3-(benzyloxy)-benzoate are heated at reflux for 8 hours with 33.4 g (0.0826 mol) of Lawesson reagent in xylene and thereafter chromatographed on silica gel, whereby there are obtained 21.7 g (51%) of O-methyl 3-(benzyloxy)thiobenzoate as a red-brown oil which gradually crystallizes upon standing.

In an analogous manner to that described in Example 1(C), 21.7 g of O-methyl 3-(benzyloxy)thiobenzoate (44.13 mmol) are reacted with ethyl isocyanoacetate,

whereby there are obtained 26.5 g (92.9%) of ethyl 5-[3--(benzyloxy)phenyl]-4-thiazolecarboxylate as an orange oil.

From 26.5 g (78.1 mmol) of ethyl 5-[3-(benzyloxy)-phenyl]-4-thiazolecarboxylate there are obtained, by reaction with t-butyl (2-aminoethyl)carbamate, 19.4 g (54.8%) of t-butyl [2-[5-[3-(benzyloxy)phenyl]-4-thiazole-carboxamido]ethyl]carbamate as an oil which is used without further purification.

Example 4

In an analogous manner to that described in Example 1(A), from 8.4 g (17.2 mmol) of t-butyl [2-[5-[3--[(3-chlorobenzyl)oxy]phenyl]-4-thiazolecarboxamido]ethyl]-carbamate there were obtained 6.4 g of N-(2-aminoethyl)-5--[3-[(3-chlorobenzyl`oxy]phenyl]-4-thiazolecarboxamide hydrochloride as whit ,stals, melting point 212-213° (from methanol/ether, yield: 87.6%).

The t-butyl [2-[5-[3-[(3-chlorobenzyl)oxy]phenyl]-4--thiazolecarboxamido]ethyl]carbamate used as th starting material was prepared as follows:

In an analogous manner to that described in Example 1(B), 36.5 g (131.9 mmol) of methyl 3-[(3-chloro-benzyl)oxy]benzoate were heated at reflux for 16 hours with 26.7 g (66 mmol) of Lawesson reagent in xylene and thereafter chromatographed on silica gel. Elution with hexane/toluene (2%, 5% and 10%) yielded 28.2 g (73%) of O-methyl 3-[(3-chlorobenzyl)oxy]thiobenzoate as an orange, crystallizing oil.

In an analogous manner to that described in Example 1(C), 28.2 g (96.3 mmol) of O-methyl 3-[(3-chloro-benzyl)oxy]thiobenzoate were reacted with ethyl isocyano-

acetate and subsequently chromatographed on silica gel. Elution with 9:1, 8:2 and 1:1 mixtures of methylene chloride and ethyl acetate as well as ethyl acetate alone yielded 28 g (77.8%) of ethyl 5-[3-[(3-chlorobenzyl)oxy]-phenyl]-4-thiazolecarboxylate as an orange oil.

From 10.0 g (26.75 mmol) of ethyl 5-[3-[(3-chloro-benzyl)oxy]phenyl]-4-thiazolecarboxylate there were obtained by reaction with t-butyl (2-aminoethyl)carbamate 10.5 g of crystals which were recrystallized from ethyl acetate/hexane. In this manner there were obtained 8.4 g (64.4%) of t-butyl [2-[5-[3-[(3-chlorobenzyl)oxy]phenyl]--4-thiazolecarboxamido]ethyl]carbamate as white crystals, melting point 116-117°.

Example 5

In an analogous manner to that described in Example 1(A), from 9 g (6.06 mmol) of t-butyl [2-(5-(3-[(3-cyanobenzyl)oxy]phenyl]-4-thiazolecarboxamido)-ethyl]carbamate there were obtained 2.1 g (83.5%) of N-(2-aminoethyl)-5-(3-[(3-cyanobenzyl)oxy]phenyl)-4-thiazole carboxamide hydrochloride as white crystals, melting point 211-215° (from methanol/ether).

The t-butyl [2-(5-(3-[(3-cyanobenzyl)oxy]phenyl]-4--thiazolecarboxamido)ethyl]carbamate used as the starting material was prepared as follows:

In an analogous manner to that described in Example 1(B), 8.9 g (33.3 mmol) of methyl 3-[(3-cyano-benzyl)oxy]benzoate were heated to reflux for 17 hours with 13.5 g (33.4 mmol) of Lawesson reagent in xylene and thereafter chromato- graphed on silica gel. Elution with an 8:2 and 7:3 mixture of hexane and methylene chlori- yielded 7.6 g (65.8%) of O-methyl 3-[(3-cyanobenzyl)ox.]-thiobenzoate as a yellow oil which gradually crystallized upon standing.

7.6 g (26.82 mmol) of O-methyl 3-[(3-cyanobenzyl)oxy]-thiobenzoate are dissolved in 50 ml of ethanol together with 3.6 g (32.1 mmol) of ethyl isocyanoacetate and added dropwise at room temperature to a solution of 0.4 g of potassium hydroxide in 30 ml of ethanol. After completion of the addition the reaction mixture is heated to reflux while stirring for a further 20 hours and then evaporated. The residue is partitioned between ether and water, the aqueous phase is extracted a further twice with ether and the combined organic phases are washed with water and saturated sodium chloride solution, dried over magnesium sulphate, filtered and evaporated. The residue is chromatographed on 150 g of silica gel with methylene chloride and methylene chloride which contains 5% and, respectively, 10% of ethyl acetate as the eluting agent. The pure fractions are combined and evaporated, whereby there are obtained 4.5 g of an oil which is crystallized from ethyl acetate/hexane. In this manner there are obtained 3.5 g (36%) of ethyl 5-[3-[(3-cyanobenzyl)oxy]-phenyl]-4-thiazolecarboxylate as beige crystals, melting point 85°.

From 3.5 g (9.6 mmol) of ethyl 5-[3-[(3-cyanobenzyl)-oxy]phenyl]-4-thiazolecarboxylate there were obtained by reaction with t-butyl (2-aminoethyl)carbamate in an analogous manner to that described in Example 1(E1) and subsequent chromatography on silica gel with a 9:1 and 8:2 mixture of methylene chloride and ethyl acetate as the eluting agent 3.4 g of an oil which crystallized from ethyl acetate/hexane. In this manner there were obtained 3.0 g (65.3%) of t-butyl [2-(5-(3-[(3-cyanobenzyl)oxy]-phenyl]-4-thiazolecarboxamido)ethyl]carbamate as white crystals, melting point 115°.

Example 6

2.0 g (5.5 mmol) of t-butyl [2-(2-amino-5-phenyl-4--thiazolecarboxamido)ethyl]carbamate are dissolved in

15 ml of methylene chloride and heated to reflux for 3 hours with 2.1 ml (27.6 mmol) of trifluoroacetic acid. Thereafter, the reaction mixture is evaporated under reduced pressure and the residue is dissolved in methanol, treated with ~ 2M methanolic hydrochloric acid and evaporated. Recrystallization of the residue from methanol/ether with the addition of a small amount of hexane yields 1.65 g (90%) of 2-amino-N-(2-aminoethyl)-5--phenyl-4-thiazolecarboxamide dihydrochloride as white crystals, melting point 203-205°.

The following two compounds were manufactured in an analogous manner to that described above:

- From 0.9 g (2.27 mmol) of t-butyl [2-(2-amino-5-(4--chlorophenyl)-4-thiazolecarboxamido)ethyl]carbamate 0.8 g (95%) of 2-amino-N-(2-aminoethyl)-5-(4-chlorophenyl)-4--thiazolecarboxamide dihydrochloride as white crystals, melting point 228-230°; and

- from 2.1 g (5.52 mmol) of t-butyl [2-(2-amino-5-(3--fluorophenyl)-4-thiazolecarboxamido)ethyl]carbamate 0.7 g (36%) of 2-amino-N-(2-aminoethyl)-5-(3-fluorophenyl)-4--thiazolecarboxamide hydrochloride as white crystals, melting point 296-297°.

The t-butyl [2-(2-amino-5-phenyl-4-thiazolecarboxamido)ethyl]carbamate used as the starting material was prepared as follows:

5.0 g (21.3 mmol) of methyl 2-amino-5-phenyl-4--thiazolecarboxylate (which was prepared as described in J. Chem. Soc. Perk. Trans. I (1982) 159-164) and 6.84 g (42.7 mmol) of t-butyl (2-aminoethyl)carbamate are heated under reduced pressure for 2 hours at a bath temperature of 140°, whereby the methanol formed is distilled off

continuously. After cooling the residue is dissolved in 50 ml of methylene chloride and chromatographed on 200 g of silica gel with a 9:1 mixture of methylene chloride and methanol as the eluting agent. The fractions which are pure according to the thin-layer chromatogram are combined and evaporated under reduced pressure, whereby there are obtained 4.5 g of a red, crystallizing oil. Crystallization from methanol and an ether/hexane mixture yields 3.48 g (45%) of t-butyl [2-(2-amino-5-phenyl-4-thiazolecarboxamido)ethyl]carbamate as beige crystals which are used without further purification.

The following two carbamates were prepared in an analogous manner to that described above:

- From 4.0 g (14.89 mmol) of methyl 2-amino-5-(4-chlorophenyl)-4-thiazolecarboxylate 1.2 g (20%) of t-butyl [2-(2-amino-5-(4-chlorophenyl)-4-thiazolecarboxamido)ethyl]carbamate as almost white crystals, melting point 156-157°; and

- from 5.0 g (19.82 mmol) of methyl 2-amino-5-(3-fluorophenyl)-4-thiazolecarboxylate 2.1 g (27.5%) of t-butyl [2-(2-amino-5-(3-fluorophenyl)-4-thiazolecarboxamido)ethyl]carbamate as white crystals, melting point 178-179°

The two methyl esters used as starting materials were prepared according to the method described in J. Chem. Soc. Perk. Trans. I (1982) 159-164:

- Methyl 2-amino-5-(4-chlorophenyl)-4-thiazolecarboxylate in 95% yield, melting point 242-244° (from water); and

- methyl 2-amino-5-(3-fluorophenyl)-4-thiazolecarboxylate in 86.9% yield, melting point 224-226°.

Example 7

In an analogous manner to that described in Example 6, from 1.55 g (4.1 mmol) of t-butyl [2-(2-chloro-5-phenyl-4--thiazolecarboxamido)ethyl]carbamate there were obtained 1.23 g (94%) of N-(2-aminoethyl)-2-chloro-5-phenyl-4--thiazolecarboxamide hydrochloride as white crystals, melting point 186-187°.

The t-butyl [2-(2-chloro-5-phenyl-4-thiazolecarboxamido)ethyl]carbamate used as the starting material was prepared as follows:

14.04 g (60 mmol) of methyl 2-amino-5-phenyl-4--thiazolecarboxylate are reacted as described in J. Chem. Soc. Perk. Trans. I (1982), pp 159-164; there are obtained about 15 g of a yellow oil. Chromatography on silica gel with methylene chloride as the eluting agent and crystallization of the crude product obtained from ether/hexane yields 10.6 g (70%) of methyl 2-chloro-5-phenyl-4--thiazolecarboxylate as crystals, melting point 68-69°.

5.4 g (21.3 mmol) of methyl 2-chloro-5-phenyl-4--thiazolecarboxylate and 3.6 g (22.3 mmol) of t-butyl (2-aminoethyl)carbamate are stirred under reduced pressure for 22 hours at a bath temperature of 110°, whereby the methanol formed is distilled off continuously. The reaction mixture is cooled, dissolved in methylene chloride and chromatographed on 150 g of silica gel with methylene chloride and a 4:1 mixture of methylene chloride and ethyl acetate as the eluting agent. The fractions which are pure according to the thin-layer chromatogram are combined and evaporated. Crystallization of the residue from ethyl acetate/hexane yields 1.83 g (27.5%) of t-butyl [2-(2-chloro-5-phenyl-4-thiazolecarboxamido)-ethyl]carbamate as white crystals, melting point 114-116°.

Example 8

In an analogous manner to that described in Example 6, from 1.2 g (3.0 mmol) of t-butyl [2-(2-chloro-5-(3-fluorophenyl)-4-thiazolecarboxamido)ethyl]carbamate there was obtained 0.75 g (76%) of N-(2-aminoethyl)-2-chloro-5-(3-fluorophenyl)-4-thiazolecarboxamide hydrochloride as white crystals, melting point 206-207°.

The t-butyl [2-(2-chloro-5-(3-fluorophenyl)-4-thiazolecarboxamido)ethyl]carbamate used as the starting material was prepared as follows:

In an analogous manner to that described in Example 7, from 5.0 g (19.82 mmol) of methyl 2-amino-5-(3-fluorophenyl)-4-thiazolecarboxylate there were obtained 2.0 g (37.1%) of methyl 2-chloro-5-(3-fluorophenyl)-4-thiazolecarboxylate as white crystals, melting point 99-100° (from ethyl acetate/hexane).

In an analogous manner to that described in Example 7, from 2.6 g (9.57 mmol) of methyl 2-chloro-5-(3-fluorophenyl)-4-thiazolecarboxylate there were obtained 1.2 g (32%) of t-butyl [2-(2-chloro-5-(3-fluorophenyl)-4-thiazolecarboxamido)ethyl]carbamate as white crystals which were used directly.

Example 9

0.5 g (1.2 mmol) of t-butyl [2-(2-bromo-5-phenyl-4-thiazolecarboxamido)ethyl]carbamate, 2 ml of trifluoroacetic acid and 10 ml of methylene chloride are heated to reflux for 2 hours and then evaporated. The residue is dissolved in methanol and treated with 1 ml of hydrobromic acid in glacial acetic acid (~ 30%). Renewed evaporation and recrystallization of the residue from methanol/ether

yields 0.45 g (94.2%) of N-(2-aminoethyl)-2-bromo-5-phenyl-4-thiazolecarboxamide hydrobromide as beige crystals, melting point 214-215° (dec.).

The t-butyl [2-(2-bromo-5-phenyl-4-thiazolecarboxamido)ethyl]carbamate used as the starting material was prepared as follows:

From 7.02 g (30 mmol) of methyl 2-amino-5-phenyl-4-thiazolecarboxylate, 15.48 g (62 mmol) of copper sulphate, 13.73 g (133 mmol) of sodium bromide, 5.1 g (73.9 mmol) of sodium nitrite and 300 g of conc. sulphuric acid in 225 ml of water there were obtained in an analogous manner to that described in Example 7 7.0 g (78%) of methyl 2-bromo-5-phenyl-4-thiazolecarboxylate as crystals which melt at 86-87° after recrystallization from ether/hexane.

2.0 g (6.7 mmol) of methyl 2-bromo-5-phenyl-4-thiazolecarboxylate and 1.61 g (10.1 mmol) of t-butyl (2-aminoethyl)carbamate are stirred under reduced pressure for 2.5 hours at 110° bath temperature, whereby the methanol formed is distilled off continuously. After chromatography on 100 g of silica gel with methylene chloride and a 4:1 mixture of methylene chloride and ethyl acetate there is obtained 0.58 g (26%) of t-butyl [2-(2-bromo-5-phenyl-4-thiazolecarboxamido)ethyl]carbamate as a pale yellow, crystallizing oil which is used directly.

Example 10

3.6 g (19.1 mmol) of 5-phenyl-4-oxazolecarboxylic acid are added portionwise to a suspension of 3.1 g (19.1 mmol) of 1,1'-carbonyldiimidazole in 20 ml of dry tetrahydrofuran, whereby a brown solution forms with the evolution of gas. After a reaction period of 15 minutes at 20°

3.05 g (19.0 mmol) of t-butyl (2-aminoethyl)carbamate in 10 ml of dry tetrahydrofuran are added dropwise (slight warming) and the reaction mixture is stirred for a further 30 minutes. Thereafter, the reaction mixture is evaporated under reduced pressure and the residue is partitioned between methylene chloride and 0.1N hydrochloric acid. After washing neutral with saturated sodium chloride solution the organic phase is dried over magnesium sulphate and evaporated, whereby there are obtained 5.8 g (92%) of t-butyl [2-(5-phenyl-4-oxazolecarboxamido)ethyl]-carbamate which are stirred at 20° for 20 minutes in 20 ml of trifluoroacetic acid. Thereafter, the reaction mixture is evaporated under reduced pressure. The residue is dissolved in 5 ml of methanol and treated with 10 ml of 5.5N hydrogen chloride in methanol. Filtration of the separated crystals yields 2.4 g (51%) of N-(2-aminoethyl)--5-phenyl-4-oxazolecarboxamide hydrochloride as white crystals, melting point 257° (dec.).

The 5-phenyl-4-oxazolecarboxylic acid used as the starting material was prepared as follows:

Analogously to the method described in Tetrahedron Letters, 23, 235-236 (1982), from ethyl isocyanoacetate, benzoic acid, phosphoric acid diphenyl ester azide and potassium carbonate in dimethylformamide/water there was prepared ethyl 5-phenyl-4-oxazolecarboxylate which was then converted into the desired acid likewise according to known methods by hydrolysis with 2N sodium hydroxide solution at 50° during 15 minutes.

Example 11

The following compounds were manufactured in an analogous manner to that described in Example 10:

- From t-butyl [2-[5-(2-chlorophenyl)-4-oxazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(2-chlorophenyl)-4-oxazolecarboxamide hydrochloride in 66.4% yield, melting point 247-248° (from methanol/diethyl ether);

- from t-butyl [2-[5-(3-chlorophenyl)-4-oxazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(3-chlorophenyl)-4-oxazolecarboxamide hydrochloride in 86.5% yield, melting point 229-231° (from methanol/diethyl ether);

- from t-butyl [2-[5-(4-chlorophenyl)-4-oxazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(4-chlorophenyl)-4-oxazolecarboxamide hydrochloride in 73.4% yield, melting point 274-275° (from methanol/diethyl ether);

- from t-butyl [2-[5-(2-fluorophenyl)-4-oxazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(2-fluorophenyl)-4-oxazolecarboxamide hydrochloride in 65.4% yield, melting point 271-272° (from methanol/diethyl ether);

- from t-butyl [2-[5-(3-fluorophenyl)-4-oxazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(3-fluorophenyl)-4-oxazolecarboxamide hydrochloride in 95% yield, melting point 258-260° (from methanol/diethyl ether);

- from t-butyl [2-[5-(4-fluorophenyl)-4-oxazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(4-fluorophenyl)-4-oxazolecarboxamide hydrochloride in 84% yield, melting point 287° (from methanol/diethyl ether);

- from t-butyl [2-[5-(4-bromophenyl)-4-oxazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(4-bromophenyl)-4-oxazolecarboxamide hydrochloride in 89% yield, melting point 254-256° (from methanol/diethyl ether);

- from t-butyl [2-[5-(3,4-dichlorophenyl)-4-oxazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(3,4-dichlorophenyl)-4-oxazolecarboxamide hydrochloride in 98% yield, melting point 275-276° (from methanol);

- from t-butyl [2-[5-(2-furyl)-4-oxazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(2-furyl)-4-oxazolecarboxamide hydrochloride in 95% yield, melting point 238-239° (from methanol/diethyl ether);

- from t-butyl [2-[5-(2-thienyl)-4-oxazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(2-thienyl)-4-oxazolecarboxamide hydrochloride in 71% yield, melting point 263-264° (from methanol/diethyl ether);

- from t-butyl [2-[5-(5-bromo-2-furyl)-4-oxazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(5-bromo-2-furyl)-4-oxazolecarboxamide hydrochloride in 91% yield, melting point 231-233° (from methanol/diethyl ether);

- from t-butyl [2-[5-(2,4-difluorophenyl)-4-oxazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(2,4-difluorophenyl)-4-oxazolecarboxamide hydrochloride in 91% yield, melting point >290° (from methanol); and

- from t-butyl [2-[5-(2,6-difluorophenyl)-4-oxazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-5-(2,6-difluorophenyl)-4-oxazolecarboxamide hydrochloride in 80% yield, melting point 266-267° (from methanol).

The carbamates used as starting materials were prepared in an analogous manner to that described in Example 1(E1):

- From ethyl 5-(2-chlorophenyl)-4-oxazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(2--chlorophenyl)-4-oxazolecarboxamido]ethyl]carbamate in 38% yield (was processed without further purification);

- from ethyl 5-(3-chlorophenyl)-4-oxazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(3--chlorophenyl)-4-oxazolecarboxamido]ethyl]carbamate in 38% yield, melting point 140-141° (from ethyl acetate/hexane);

- from ethyl 5-(4-chlorophenyl)-4-oxazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(4--chlorophenyl)-4-oxazolecarboxamido]ethyl]carbamate in 49% yield, melting point 164° (from ethyl acetate/hexane);

- from ethyl 5-(2-fluorophenyl)-4-oxazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(2--fluorophenyl)-4-oxazolecarboxamido]ethyl]carbamate in 58% yield, melting point 130-133° (from ethyl acetate/hexane);

- from ethyl 5-(3-fluorophenyl)-4-oxazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(3--fluorophenyl)-4-oxazolecarboxamido]ethyl]carbamate in 69% yield, melting point 135-136° (from ethyl acetate/hexane);

- from ethyl 5-(4-fluorophenyl)-4-oxazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(4--fluorophenyl)-4-oxazolecarboxamido]ethyl]carbamate in 24% yield, melting point 146-148° (from ethyl acetate/hexane);

- from ethyl 5-(4-bromophenyl)-4-oxazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(4--bromophenyl)-4-oxazolecarboxamido]ethyl]carbamate in 32% yield, melting point 170-171° (from ethyl acetate/hexane);

- from ethyl 5-(3,4-dichlorophenyl)-4-oxazole-carboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(3,4-dichlorophenyl)-4-oxazolecarboxamido]-ethyl]carbamate in 72% yield, melting point 126-128° (from ethyl acetate/hexane);

- from ethyl 5-(2-furyl)-4-oxazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(2--furyl)-4-oxazolecarboxamido]ethyl]carbamate in 32% yield, melting point 86-87° (from ethyl acetate/hexane); and

- from ethyl 5-(2-thienyl)-4-oxazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(2--thienyl)-4-oxazolecarboxamido]ethyl]carbamate in 12% yield, melting point 109-110° (from ethyl acetate/hexane).

The following carbamates were prepared in an analogous manner to that described in Example 1(E):

- From 5-(5-bromo-2-furyl)-4-oxazolecarboxylic acid and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5-(5--bromo-2-furyl)-4-oxazolecarboxamido]ethyl]carbamate in 97% yield, melting point 120-121° (from ethyl acetate/hexane);

- from 5-(2,4-difluorophenyl)-4-oxazolecarboxylic acid and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5--(2,4-difluorophenyl)-4-oxazolecarboxamido]ethyl]carbamate in 92% yield, melting point 133° (from ethyl acetate/hexane); and

- from 5-(2,6-difluorophenyl)-4-oxazolecarboxylic acid and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[5--(2,6-difluorophenyl)-4-oxazolecarboxamido]ethyl]carbamate in 61% yield, melting point 166-167° (from ethyl acetate/hexane).

The ethyl carboxylates used as starting materials were prepared analogously to the method described in Tetrahedron Letters, 23, 235-236 (1982) from ethyl isocyanoacetate, the corresponding substituted benzoic acids or furancarboxylic acids or thiophenecarboxylic acids, phosphoric acid diphenyl ester azide and potassium carbonate:

- From 2-chlorobenzoic acid and ethyl isocyanoacetate the ethyl 5-(2-chlorophenyl)-4-oxazolecarboxylate in 58% yield as a yellow oil (was processed without further purification);

- from 3-chlorobenzoic acid and ethyl isocyanoacetate the ethyl 5-(3-chlorophenyl)-4-oxazolecarboxylate in 57% yield, melting point 57-58° (from ethyl acetate/hexane);

- from 4-chlorobenzoic acid and ethyl isocyanoacetate the ethyl 5-(4-chlorophenyl)-4-oxazolecarboxylate in 76% yield, melting point 103-105° (from ethyl acetate/hexane);

- from 2-fluorobenzoic acid and ethyl isocyanoacetate the ethyl 5-(2-fluorophenyl)-4-oxazolecarboxylate in 41% yield, melting point 62-63° (from ethyl acetate/hexane);

- from 3-fluorobenzoic acid and ethyl isocyanoacetate the ethyl 5-(3-fluorophenyl)-4-oxazolecarboxylate in 84% yield, melting point 48-49° (from ethyl acetate/hexane);

- from 4-fluorobenzoic acid and ethyl isocyanoacetate the ethyl 5-(4-fluorophenyl)-4-oxazolecarboxylate in 51% yield, melting point 53-54° (from ethyl acetate/hexane);

- from 4-bromobenzoic acid and ethyl isocyanoacetate the ethyl 5-(4-bromophenyl)-4-oxazolecarboxylate in 62% yield, melting point 118-119° (from ethyl acetate/hexane);

- from 3,4-dichlorobenzoic acid and ethyl isocyanoacetate the ethyl 5-(3,4-dichlorophenyl)-4-oxazolecarboxylate in 42% yield, melting point 102-103° (from ethyl acetate/ hexane);

- from 2-furancarboxylic acid and ethyl isocyanoacetate the ethyl 5-(2-furyl)-4-oxazolecarboxylate in 52% yield, melting point 97-98° (from ethyl acetate/hexane);

- from 2-thiophenecarboxylic acid and ethyl isocyanoacetate the ethyl 5-(2-thienyl)-4-oxazolecarboxylate in 26% yield, melting point 41-42° (from ethyl acetate/ hexane);

- from 5-bromo-2-furancarboxylic acid and ethyl isocyanoacetate the ethyl 5-(5-bromo-2-furyl)-4-oxazolecarboxylate in 32% yield, melting point 93° (from ethyl acetate/hexane);

- from 2,4-difluorobenzoic acid and ethyl isocyanoacetate the ethyl 5-(2,4-difluorophenyl)-4-oxazolecarboxylate in 13% yield, melting point 76-77° (from ethyl acetate/hexane); and

- from 2,6-difluorobenzoic acid and ethyl isocyanoacetate the ethyl 5-(2,6-difluorophenyl)-4-oxazolecarboxylate in 13% yield as a yellow oil which crystallizes upon standing.

The following carboxylic acids were prepared in an analogous manner to that described in Example 1(D):

- From ethyl 5-(5-bromo-2-furyl)-4-oxazolecarboxylate the 5-(5-bromo-2-furyl)-4-oxazolecarboxylic acid in 66% yield, melting point 226-228° (from ethyl acetate/hexane);

- from ethyl 5-(2,4-difluorophenyl)-4-oxazole-

carboxylate the 5-(2,4-difluorophenyl)-4-oxazolecarboxylic acid in 72% yield, melting point 180-182° (from water); and

- from ethyl 5-(2,6-difluorophenyl)-4-oxazolecarboxylate the 5-(2,6-difluorophenyl)-4-oxazolecarboxylic acid in 64% yield (was used without further purification).

Example 12

1.46 g (4.2 mmol) of t-butyl [2-(2-amino-5-phenyl-4-oxazolecarboxamido)ethyl]carbamate are dissolved in 50 ml of methylene chloride and treated with 5 ml of trifluoroacetic acid. The reaction mixture is heated to reflux while stirring for 2.5 hours and thereafter evaporated under reduced pressure. The residue is dissolved in methanol, treated with 5 ml of 2M methanolic hydrochloric acid and evaporated. Recrystallization of the residue from methanol/diethyl ether yields 1.3 g (94%) of 2-amino-N-(2-aminoethyl)-5-phenyl-4-oxazolecarboxamide dihydrochloride as white crystals, melting point 260°.

The t-butyl [2-(2-amino-5-phenyl-4-oxazolecarboxamido)ethyl]carbamate used as the starting material was prepared as follows:

A solution of 3 g (0.13 gram atom) of sodium in 50 ml of methanol are added dropwise at 0-5° within 20 minutes to a solution, cooled to 0°, of 16.1 g (152 mmol) of benzaldehyde and 20.0 g (140 mmol) of methyl dichloroacetate in 50 ml of ether. Thereafter, the reaction mixture is stirred at 0-5° for a further 1.5 hours, then diluted with 100 ml of ethyl acetate and extracted with saturated sodium chloride solution. The organic phase is dried over magnesium sulphate and evaporated. The residue is dissolved in 50 ml of methanol and heated to reflux for 14 hours with 6.72 g (112 mmol) of urea. The reaction mixture is evaporated under reduced pressure, partitioned

between methylene chloride and water, adjusted to pH 9 with conc. sodium hydroxide solution and extracted. The alkaline, aqueous phases are further extracted with methylene chloride. The organic phases are combined and washed twice with saturated sodium chloride solution, dried and evaporated. The residue is purified by medium pressure chromatography on 1 kg of silica gel. Elution with methylene chloride as well as methylene chloride/methanol 9:1 yields 8.4 g of an oil which crystallizes from a mixture of methylene chloride, ether and hexane. In this manner there are obtained 4.7 g (35%) of methyl 2-amino-5-phenyl-4-oxazolecarboxylate as light yellowish crystals which are processed without further purification.

2.0 g (9.2 mmol) of methyl 2-amino-5-phenyl-4-oxazolecarboxylate are stirred with 4.4 g (27,5 mmol) of t-butyl (2-aminoethyl)carbamate under reduced pressure for 6 hours at 120°. The reaction mixture is then chromatographed on 200 g of silica gel using ethyl acetate with the addition of 5% methanol as the eluting agent. The fractions which are pure according to the thin-layer chromatogram are crystallized from methylene chloride/ether/hexane and yield 1.46 g (62%) of t-butyl [2-(2-amino-5-phenyl-4--oxazolecarboxamido)ethyl]carbamate as white crystals which are processed without further purification.

Example 13

1.5 g (4.33 mmol) of t-butyl [2-(5-amino-4-phenyl-3--isoxazolecarboxamido)ethyl]carbamate in 5 ml of methylene chloride are stirred at room temperature for 16 hours with 1.7 ml of trifluoroacetic acid. Thereafter, the reaction mixture is evaporated under reduced pressure; the residue is dissolved in ethanol, whereupon the solution is treated with 2 ml of ethanolic hydrochloric acid (17.5% w/v) and again evaporated. Recrystallization of the residue from methanol/ether yields 0.9 g (73.5%) of 5-amino-N-(2-amino-

ethyl)-4-phenyl-3-isoxazolecarboxamide hydrochloride as white crystals, melting point 187-189°.

The t-butyl [2-(5-amino-4-phenyl-3-isoxazolecarboxamido)ethyl]carbamate used as the starting material was prepared as follows:

Reaction of benzyl cyanide, sodium ethylate and diethyl oxalate according to the method described in Org. Synth. Coll. Vol. II (1943) 287 and Chem. Ber. 107 (1974) 2794-2795 in alcohol, acidification with conc. (37%) hydrochloric acid to pH 2 and subsequent recrystallization of the separated precipitate from ethanol yields ethyl phenylcyanopyruvate in 90% yield as yellow crystals, melting point 127-128°.

5.0 g (23 mmol) of ethyl phenylcyanopyruvate are reacted according to the method described in Chem. Ber. 107 (1974) 2794-2795 and Ber. Deutsch. Chem. Ges. 33 (1900) 2592-2595, whereby there is obtained in 69.7% yield ethyl 5-amino-4-phenyl-3-isoxazolecarboxylate as beige crystals which melt at 119-121° after recrystallization from ethyl acetate/hexane.

2.9 g (12.5 mmol) of ethyl 5-amino-4-phenyl-3-isoxazolecarboxylate are heated to 110° for 2 hours under reduced pressure with 5.0 g (31.2 mmol) of t-butyl (2-aminoethyl)carbamate, whereby the ethanol formed is distilled off continuously. The cooled reaction mixture is dissolved in methylene chloride and chromatographed on 100 g of silica gel. Elution with methylene chloride which contains 5%, 10% and, respectively, 20% of ethyl acetate, combining of the pure fractions and evaporation yields 1.9 g of crystals. Recrystallization from ethyl acetate/hexane yields 1.5 g (34.7%) of t-butyl [2-(5-amino-4-phenyl-3-isoxazolecarboxamido)ethyl]carbamate as white crystals, melting point 144°.

Example 14

5.0 g (15.1 mmol) of t-butyl [2-(4-phenyl-3-isoxazolecarboxamido)ethyl]carbamate are stirred at room temperature for 16 hours with trifluoroacetic acid analogously to Example 13. After concentration there is obtained a residue which is converted into the hydrochloride. Recrystallization of the crude product from methanol/ether yields 3.8 g (94.1%) of N-(2-aminoethyl)-4-phenyl-3-isoxazolecarboxamide hydrochloride as white crystals, melting point 211-212°.

The t-butyl [2-(4-phenyl-3-isoxazolecarboxamido)-ethyl]carbamate used as the starting material was prepared as follows:

In an analogous manner to that described in J. Org. Chem. 50 (13) 1985, 2372-2375, 7.6 g (32.72 mmol) of ethyl 5-amino-4-phenyl-3-isoxazolecarboxylate in 160 ml of glacial acetic acid, 50 ml of water and 80 ml of tetrahydrofuran are treated portionwise at 15-20° while stirring within 1 hour with a total of 22.6 g of sodium nitrite. The reaction mixture is thereafter poured into 1 litre of water and extracted 3 times with 400 ml of methylene chloride each time. The organic phases are combined and washed firstly twice with 1 l of saturated sodium bicarbonate solution each time and then once with 1 l of water, dried, filtered and concentrated in a vacuum, whereby after chromatography on silica gel and elution with methylene chloride there are obtained 3.9 g (55%) of ethyl 4-phenyl-3-isoxazolecarboxylate as a yellow oil which is used without further purification.

3.9 g (17.95 mmol) of ethyl 4-phenyl-3-isoxazolecarboxylate and 5.8 g (36.2 mmol) of t-butyl (2-aminoethyl)carbamate are heated together to 110° for 2 hours

under reduced pressure. Chromatography on silica gel and elution with methylene chloride which contains 5% and, respectively, 10% of ethyl acetate yields an oil which crystallizes from ethyl acetate/hexane. In this manner there are obtained 5.0 g (84%) of t-butyl [2-(4-phenyl-3--isoxazolecarboxamido)ethyl]carbamate as white crystals, melting point 170-171°.

Example 15

The following compounds were manufactured in an analogous manner to that described in Examples 13 and 14:

- From t-butyl [2-[4-(2-chlorophenyl)-3-isoxazole-carboxamido]ethyl]carbamate the N-(2-aminoethyl)-4-(2--chlorophenyl)-3-isoxazolecarboxamide hydrochloride in 32.8% yield, melting point 255-256° (from methanol/diethyl ether);

- from t-butyl [2-[4-(3-chlorophenyl)-3-isoxazole-carboxamido]ethyl]carbamate the N-(2-aminoethyl)-4-(3--chlorophenyl)-3-isoxazolecarboxamide hydrochloride in 93% yield, melting point 181-183° (from methanol/diethyl ether);

- from t-butyl [2-[4-(4-chlorophenyl)-3-isoxazole-carboxamido]ethyl]carbamate the N-(2-aminoethyl)-4-(4--chlorophenyl)-3-isoxazolecarboxamide hydrochloride in 72% yield, melting point 254-256° (from methanol/diethyl ether);

- from t-butyl [2-[4-(3-fluorophenyl)-3-isoxazole-carboxamido]ethyl]carbamate the N-(2-aminoethyl)-4-(3--fluorophenyl)-3-isoxazolecarboxamide hydrochloride in 91.7% yield, melting point 183-186° (from methanol/diethyl ether); and

- from t-butyl [2-[4-(4-fluorophenyl)-3-isoxazolecarboxamido]ethyl]carbamate the N-(2-aminoethyl)-4-(4-fluorophenyl)-3-isoxazolecarboxamide hydrochloride (5:6) • 0.3 mol H_2O in 30% yield, melting point 237-239° (from ethanol).

The carbamates used as starting materials were prepared as follows:

- From ethyl 4-(2-chlorophenyl)-3-isoxazolecarboxylate and t-butyl 2-(aminoethyl)carbamate the t-butyl [2-[4-(2-chlorophenyl)-3-isoxazolecarboxamido]ethyl]carbamate in 87% yield, melting point 132-133° (from ethyl acetate/hexane);

- from ethyl 4-(3-chlorophenyl)-3-isoxazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[4-(3-chlorophenyl)-3-isoxazolecarboxamido]ethyl]carbamate in 78.6% yield, melting point 147-148° (from ethyl acetate/hexane);

- from ethyl 4-(4-chlorophenyl)-3-isoxazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[4-(4-chlorophenyl)-3-isoxazolecarboxamido]ethyl]carbamate in 87% yield, melting point 135-137° (from ethyl acetate/hexane);

- from ethyl 4-(3-fluorophenyl)-3-isoxazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[4-(3-fluorophenyl)-3-isoxazolecarboxamido]ethyl]carbamate in 75% yield, melting point 162-163° (from ethanol/diethyl ether); and

- from ethyl 4-(4-fluorophenyl)-3-isoxazolecarboxylate and t-butyl (2-aminoethyl)carbamate the t-butyl [2-[4-(4-fluorophenyl)-3-isoxazolecarboxamido]ethyl]carbamate in

95.9% yield, melting point 140-141° (from ethyl acetate/hexane).

The substituted ethyl 3-isoxazolecarboxylates used as starting materials were obtained from the corresponding substituted 5-amino-3-isoxazolecarboxylic acid esters which, in turn, were obtained from the corresponding ß-cyano-α-oxo-dihydrocinnamic acid esters:

Ethyl 4-(2-chlorophenyl)-3-isoxazolecarboxylate in 52% yield as a red oil;

ethyl 4-(3-chlorophenyl)-3-isoxazolecarboxylate in 73% yield as a red oil;

ethyl 4-(4-chlorophenyl)-3-isoxazolecarboxylate in 51% yield as an orange oil;

ethyl 4-(3-fluorophenyl)-3-isoxazolecarboxylate in 65% yield as a yellow oil;

ethyl 4-(4-fluorophenyl)-3-isoxazolecarboxylate in 42% yield, melting point 57-58° (from ethyl acetate/hexane);

ethyl 5-amino-4-(2-chlorophenyl)-3-isoxazole-carboxylate in 76% yield, melting point 141-142° (from ethyl acetate/hexane);

ethyl 5-amino-4-(3-chlorophenyl)-3-isoxazole-carboxylate in 22% yield, melting point 151-152° (from ethyl acetate/hexane);

ethyl 5-amino-4-(4-chlorophenyl)-3-isoxazole-carboxylate in 52% yield, melting point 132-133° (from ethyl acetate/hexane);

ethyl 5-amino-4-(3-fluorophenyl)-3-isoxazole-carboxylate in 75% yield, melting point 119° (from ethyl acetate/hexane); and

ethyl 5-amino-4-(4-fluorophenyl)-3-isoxazole-carboxylate in 75% yield, melting point 137-138° (from ethyl acetate/hexane).

The dihydrocinnamic acid esters used as starting materials were prepared from the corresponding benzyl cyanides, sodium ethylate and diethyl oxalate according to the procedure described in Org. Synth. Coll. Vol. II (1943) 287 and Chem. Ber. 107 (1974) 2794-2795:

Ethyl 2-chloro-ß-cyano-α-oxo-dihydrocinnamate in 67% yield, melting point 133-135° (from ethanol/water);

ethyl 3-chloro-ß-cyano-α-oxo-dihydrocinnamate in 90% yield, melting point 76-77° (from ethanol/water);

ethyl 4-chloro-ß-cyano-α-oxo-dihydrocinnamate in 89.5% yield, melting point 137-139° (from water);

ethyl 2-fluoro-ß-cyano-α-oxo-dihydrocinnamate in 85% yield, melting point 94-95° (from ethanol/water); and

ethyl 4-fluoro-ß-cyano-α-oxo-dihydrocinnamate in 90% yield, melting point 142-144° (from ethanol/water).

Example 16

5.0 g (15.1 mmol) of t-butyl [2-(4-phenyl-3-pyrazole-carboxamido)ethyl]carbamate are stirred at room temperature for 16 hours with 6 ml (78.4 mmol) of trifluoroacetic acid and 10 ml of methylene chloride and thereafter evaporated under reduced pressure. The residue

is treated with 7 ml of ethanolic hydrochloric acid (17.5% w/v) and evaporated. Recrystallization of the residue from methanol yields 3.1 g (76.8%) of N-(2-amino-ethyl)-4-phenyl-3-pyrazolecarboxamide hydrochloride as white crystals, melting point 285-286°.

The t-butyl [2-(4-phenyl-3-pyrazolecarboxamido)ethyl]-carbamate used as the starting material was prepared as follows:

(A) Benzaldehyde, N,N-dimethylglycine ethyl ester and sodium hydride are reacted in ether with the addition of a catalytic amount of ethanol according to the method described in Lieb. Ann. Chem. 703 (1967) 37-43 to give ethyl α-dimethylaminocinnamate. This is then reacted according to the method described in Tetrahedron Letters, 46, (1978) 4573-4574 with oxalyl chloride and hydrazine in 60% yield to give ethyl 4-phenyl-3-pyrazolecarboxylate, melting point 164-165° after recrystallization from ethanol/diethyl ether.

The following 3-pyrazolecarboxylic acid esters were prepared in an analogous manner to that described above; for the preparation of the 1-methyl substituted compounds N-methylhydrazine was used in place of hydrazine, whereby in each case the resulting mixtures of the 1- and 2-methyl derivatives were separated by chromatography on silica gel with methylene chloride:

Ethyl 4-(3-fluorophenyl)-3-pyrazolecarboxylate in 46% yield, melting point 161-162° (from ethanol/diethyl ether);

ethyl 4-(4-fluorophenyl)-3-pyrazolecarboxylate in 33.7% yield, melting point 177-179° (from ethanol/diethyl esther);

ethyl 1-methyl-4-phenyl-3-pyrazolecarboxylate in 27% yield, melting point 92° (from ethyl acetate/hexane);

ethyl 4-(3-fluorophenyl)-1-methyl-3-pyrazolecarboxylate in 20% yield, melting point 93-94° (from ethyl acetate/hexane); and

ethyl 4-(4-fluorophenyl)-1-methyl-3-pyrazolecarboxylate in 28% yield, melting point 58-59° (from diethyl ether/petroleum ether).

(B) 5.0 g (23.12 mmol) of ethyl 4-phenyl-3-pyrazolecarboxylate are heated to 120° under reduced pressure for 2 hours with 7.4 g (46.19 mmol) of t-butyl (2-aminoethyl)-carbamate, whereby the ethanol formed is distilled off continuously. The reaction mixture is then taken up in methylene chloride and chromatographed on 150 g of silica gel with a 9:1, 8:2 and 7:3 mixture of methylene chloride and ethyl acetate as the eluting agent. The fractions which are pure according to the thin-layer chromatogram are combined and evaporated, and the residue is crystallized from ethyl acetate/hexane, whereby there are obtained 5.1 g (66.8%) of t-butyl [2-(4-phenylpyrazole-3--carboxamido)ethyl]carbamate as white crystals, melting point 71°/162-163° (still containing 0.05 mol of hexane).

Example 17

4.4 g (12.63 mmol) of t-butyl [2-(4-(3-fluorophenyl)--3-pyrazolecarboxamido)ethyl]carbamate are stirred at room temperature for 16 hours with trifluoroacetic acid in an analogous manner to that in Example 16. Thereafter, the reaction mixture is evaporated and the residue is converted into the hydrochloride which is recrystallized from methanol/diethyl ether. After drying there are obtained 2.7 g (75%) of N-(2-aminoethyl)-4-(3-fluoro-

phenyl)-3-pyrazolecarboxamide hydrochloride as white crystals, melting point 284-285°.

The t-butyl [2-(4-(3-fluorophenyl)-3-pyrazolecarboxamido)ethyl]carbamate used as the starting material was prepared as follows:

4.6 g (19.64 mmol) of ethyl 4-(3-fluorophenyl)-3-pyrazolecarboxylate were reacted with t-butyl (2-aminoethyl)carbamate in an analogous manner to that described in Example 16. Chromatography of the crude product and recrystallization from ethyl acetate/hexane yields 4.4 g (64.6%) of t-butyl [2-(4-(3-fluorophenyl)-3-pyrazolecarboxamido)ethyl]carbamate as white crystals, melting point 175-176°.

Example 18

In an analogous manner to that described in Examples 16 and 17, from 6.4 g (18.37 mmol) of t-butyl [2-(4-(4-fluorophenyl)-3-pyrazolecarboxamido)ethyl]carbamate there are obtained after cleavage of the t-butoxycarbonyl group with trifluoroacetic acid and working-up 6.2 g of the desired hydrochloride as the crude product. Recrystallization from methanol/ether yields 4.2 g (80%) of N-(2-aminoethyl)-4-(4-fluorophenyl)-3-pyrazolecarboxamide hydrochloride as white crystals, melting point 271-273°.

The t-butyl [2-(4-(4-fluorophenyl)-3-pyrazolecarboxamido)ethyl]carbamate used as the starting material was prepared as follows:

In an analogous manner to that described in Examples 16 and 17, from 6.1 g (26 mmol) of ethyl 4-(4-fluorophenyl)-3-pyrazolecarboxylate there were obtained 6.4 g (67.2%) of t-butyl [2-(4-(4-fluorophenyl)-3-pyrazolecarboxamido)ethyl]carbamate as white crystals

which melt at 162-163° after recrystallization from ethyl acetate/hexane.

Example 19

In an analogous manner to that described in Examples 16 and 17, from 4.6 g (13.4 mmol) of t-butyl [2-(1-methyl-4-phenyl-3-pyrazolecarboxamido)ethyl]carbamate there were obtained, after cleavage of the t-butoxycarbonyl group with trifluoroacetic acid and working-up, 4.8 g of the crude hydrochloride. Recrystallization from ethanol/ diethyl ether yields 3.4 g (90%) of N-(2-aminoethyl)-1-methyl-4-phenyl-3-pyrazolecarboxamide hydrochloride as white crystals, melting point 182°.

The t-butyl [2-(1-methyl-4-phenyl-3-pyrazolecarboxamido)ethyl]carbamate used as the starting material was prepared as follows:

In an analogous manner to that described in Examples 16 and 17, from 6.6 g (28.7 mmol) of ethyl 1-methyl-4-phenyl-3-pyrazolecarboxylate there were obtained 4.6 g (71.5%) of t-butyl [2-(1-methyl-4-phenyl--3-pyrazolecarboxamido)ethyl]carbamate as white crystals, melting point 145° (from ethyl acetate/hexane).

Example 20

3.4 g (9.38 mmol) of t-butyl [2-[4-(3-fluorophenyl)-1--methyl-3-pyrazolecarboxamido]ethyl]carbamate are stirred at room temperature with trifluoroacetic acid for 16 hours in an analogous manner to that described in Example 16. The reaction mixture is thereafter evaporated and the residue is converted into the hydrochloride. Recrystallization from ethanol/diethyl ether yields 2.6 g (92.8%) of N-(2-aminoethyl)-4-(3-fluorophenyl)-1-methyl-3-

-pyrazolecarboxamide hydrochloride as white crystals, melting point 160-161°.

The t-butyl [2-[4-(3-fluorophenyl)-1-methyl-3--pyrazolecarboxamido]ethyl]carbamate used as the starting material was prepared as follows:

3.4 g (13.7 mmol) of ethyl 4-(3-fluorophenyl)-1--methyl-3-pyrazolecarboxylate and 5.5 g (34.32 mmol) of t-butyl (2-aminoethyl)carbamate are stirred under reduced pressure for 18 hours at 130° and subsequently chromatographed on 100 g of silica gel. Elution with a 9:1, 8:2 and 7:3 mixture of methylene chloride and ethyl acetate yields 3.9 g of crystals which are recrystallized from ethyl acetate/hexane. In this manner there are obtained 3.4 g (68.5%) of t-butyl [2-[4-(3-fluorophenyl)-1-methyl--3-pyrazolecarboxamido]ethyl]carbamate as white crystals, melting point 124°.

Example 21

9.8 g (27.0 mmol) of t-butyl [2-[4-(4-fluorophenyl)-1--methyl-3-pyrazolecarboxamido]ethyl]carbamate are stirred with trifluoroacetic acid at room temperature for 16 hours in an analogous manner to that described in Example 16. Thereafter, the reaction mixture is evaporated and the residue is converted into the hydrochloride. Recrystallization from ethanol/diethyl ether yields 7.5 g (92.8%) of N-(2-aminoethyl)-4-(4-fluorophenyl)-1-methyl-3--pyrazolecarboxamide hydrochloride as white crystals, melting point 195-196°.

The t-butyl [2-[4-(4-fluorophenyl)-1-methyl-3--pyrazolecarboxamido]ethyl]carbamate used as the starting material was prepared as follows:

8.6 g (34.6 mmol) of ethyl 4-(4-fluorophenyl)-1--methyl-3-pyrazolecarboxylate are heated to 70° for 60 minutes with 90 ml of 2N sodium hydroxide solution and 50 ml of water. Conversion into the acid form and recrystallization of the crude product from ethyl acetate/hexane yields 6.9 g (90.4%) of 4-(4-fluorophenyl)--1-methyl-3-pyrazolecarboxylic acid as white crystals, melting point 146-147°.

6.9 g (31.34 mmol) of 4-(4-fluorophenyl)-1-methyl-3--pyrazolecarboxylic acid are heated to reflux for 2 hours with 400 ml of tetrahydrofuran and 5.2 g (32 mmol) of 1,1'-carbonyldiimidazole. Thereafter, 5.3 g (33 mmol) of t-butyl (2-aminoethyl)carbamate are added. The reaction mixture is heated to reflux for a further 2 hours and thereafter evaporated. The residue is partitioned between ethyl acetate and water, the organic phase is washed several times with water, dried over magnesium sulphate and evaporated. Recrystallization of the crystalline residue from ethyl acetate/hexane yields 9.8 g (86.3%) of t-butyl [2-[4-(4-fluorophenyl)-1-methyl-3-pyrazolecarboxamido]ethyl]carbamate as white crystals, melting point 144°.

Example 22

In an analogous manner to that described in Example 1, from 7.2 g (18.78 mmol) of t-butyl [2-[5-(3,5-difluorophenyl)-4-thiazolecarboxamido]ethyl]carbamate there were obtained 5.7 g (95%) of N-(2-aminoethyl)-5-(3,5-difluorophenyl)-4-thiazolecarboxamide hydrochloride as white crystals, melting point 266-267° (from methanol).

The t-butyl [2-[5-(3,5-difluorophenyl)-4-thiazolecarboxamido]ethyl]carbamate used as the starting material was prepared as follows:

25.0 g (179.7 mmol) of 3,5-difluorobenzonitrile are dissolved in 250 ml of ethanol and cooled to -10°. Thereafter, hydrochloric acid gas is conducted in during 20 minutes, whereby the internal temperature rises to 30°. The mixture is thereafter stirred at room temperature for 1 hour and nitrogen is conducted through the reaction mixture for 30 minutes in order to remove excess hydrochloric acid. The mixture is cooled to 0° and 200 ml of ether are added thereto. The turbid solution is left to stand at about 0° for 5 days and thereafter the crystals are filtered off. After drying at 50° in a vacuum there are obtained 27.8 g (70%) of 3,5-difluorobenzimino ethyl ether hydrochloride as white crystals of melting point 133-134°.

300 ml of pyridine are cooled to 0-5°. 5-10 g of hydrogen sulphide are conducted in, then 27.5 g (124 mmol) of 3,5-difluorobenzimino ethyl ether hydrochloride are added thereto and the reaction mixture is left to stand closed at room temperature for about 48 hours. The excess hydrogen sulphide is removed by flushing with nitrogen and the reaction mixture is then concentrated in a vacuum. The residue is treated with 500 ml of hexane while stirring, whereupon the mixture is cooled to 5°. After 30 minutes insoluble constituents are filtered off under suction. The yellow, clear solution is concentrated in a vacuum. There are obtained as the residue 23.8 g (95%) of o-ethyl 3,5-difluorothicbenzoate as an orange evil-smelling oil.

As described in Example 1(C), from o-ethyl 3,5-difluorothiobenzoate there is obtained in 82% yield ethyl 5-(3,5-difluorophenyl)-4-thiazolecarboxylate which melts at 112-113° after recrystallization from ethyl acetate/hexane.

The ethyl 5-(3,5-difluorophenyl)-4-thiazolecarboxylate is saponified in an analogous manner to that described in Example 1(D), whereby after acidification there is obtained 5-(3,5-difluorophenyl)-4-thiazolecarboxylic acid in 97% yield, melting point 200° (from water).

In an analogous manner to that described in Example 1(E), from 5-(3,5-difluorophenyl)-4-thiazolecarboxylic acid there is obtained in 88% yield t-butyl [2-[5-(3,5-difluorophenyl)-4-thiazolecarboxamido]ethyl]-carbamate as white crystals of melting point 141-142°.

Example 23

(A) 6.3 g (13.1 mmol) of t-butyl [2-[5-(3-iodophenyl)-4-thiazolecarboxamido]ethyl]carbamate are dissolved in 70 ml of methylene chloride, treated with 5.1 ml of trifluoroacetic acid and stirred under reflux for 2 hours. Subsequently, the mixture is concentrated under reduced pressure. The residue is dissolved in 50 ml of methanol and treated with 5.2 ml of 2.7N ethanolic hydrochloric acid, whereby 4.8 g (88%) of N-(2-aminoethyl)-5-(3-iodophenyl)-4-thiazolecarboxamide hydrochloride are obtained as white crystals, melting point 272-273°.

The t-butyl [2-[5-(3-iodophenyl)-4-thiazolecarboxamido]ethyl]carbamate used as the starting material was prepared as follows:

(B) 52.5 g (0.2 mol) of methyl 3-iodobenzoate are heated to reflux for 18 hours with 81 g (0.2 mol) of Lawesson reagent in 330 ml of xylene. By working-up in an analogous manner to that described in Example 1(B) there are obtained 47 g (84.4%) of O-methyl 3-iodothiobenzoate as a yellow evil-smelling oil which is used without further purification.

(C) Analogously to the method described in Synthesis 10, (1976), 681-682, 47 g (169 mmol) of O-methyl 3-iodothiobenzoate are reacted with ethyl isocyanoacetate in the presence of 1-5% powdered potassium hydroxide in ethanol. Recrystallization from ether yields 45.8 g (75.4%) of ethyl 5-(3-iodophenyl)-4-thiazolecarboxylate as ochre crystals, melting point 77-78°.

(D) 20 g (55.68 mmol) of ethyl 5-(3-iodophenyl)-4--thiazolecarboxylate are hydrolyzed in an analogous manner to that described in Example 1(D), whereby 17.6 g (95.5%) of 5-(3-iodophenyl)-4-thiazolecarboxylic acid are obtained as yellow crystals, melting point 186°.

(E) Reaction of 5.0 g (15.1 mmol) of 5-(3-iodophenyl)-4-thiazolecarboxylic acid with 2.6 g (16.2 mmol) of t-butyl (2-aminoethyl)carbamate in an analogous manner to that described in Example 1(E) yields 6.3 g (88.1%) of t-butyl [2-[5-(3-iodophenyl)-4-thiazolecarboxamido]ethyl]-carbamate as white crystals, melting point 111-112°.

Example A

Coated tablets of the following composition can be manufactured in a manner known per se according to methods which are familiar to any person skilled in the art:

Nucleus

N-(2-Aminoethyl)-5-phenyl-4-thiazole-carboxamide hydrochloride	100.00 mg
Powd. lactose	148.00 mg
Maize starch	120.00 mg
Polyvinylpyrrolidone	20.00 mg
Sodium carboxymethylstarch	10.00 mg
Magnesium stearate	2.00 mg
Nucleus weight	400.00 mg

Coating layer

Hydroxypropylmethylcellulose	5.00 mg
Talc	3.76 mg
Titanium dioxide	1.00 mg
Yellow iron oxide	0.20 mg
Sienna iron oxide	0.04 mg
Total weight of a coated tablet	410.00 mg

Example B

Coated tablets of the following composition can be manufactured in a manner known per se according to methods which are familiar to any person skilled in the art:

N-(2-Aminoethyl)-5-phenyl-4-thiazole-carboxamide hydrochloride	150.00 mg
Powd. lactose	148.00 mg
Maize starch	60.00 mg
Polyvinylpyrrolidone	25.00 mg
Sodium carboxymethylstarch	15.00 mg
Magnesium stearate	2.50 mg
Nucleus weight	400.00 mg

Coating layer

Hydroxypropylmethylcellulose	4.50 mg
Ethylcellulose	1.50 mg
Polyethyleneglycol 6000	0.60 mg
Talc	2.40 mg
Titanium dioxide	2.90 mg
Yellow iron oxide	0.10 mg
Total weight of a coated tablet	412.00 mg

Example C

Coated tablets can be manufactured from the following, likewise preferred compounds in analogy to Examples A and B:

N-(2-Aminoethyl)-5-(2-fluorophenyl)-4-thiazolecarboxamide hydrochloride;

N-(2-aminoethyl)-5-(3-fluorophenyl)-4-thiazolecarboxamide hydrochloride;

N-(2-aminoethyl)-5-(4-fluorophenyl)-4-thiazolecarboxamide hydrochloride;

N-(2-aminoethyl)-5-(4-chlorophenyl)-4-oxazolecarboxamide hydrochloride;

N-(2-aminoethyl)-5-(2-furyl)-4-oxazolecarboxamide hydrochloride;

N-(2-aminoethyl)-5-(3,5-dichlorophenyl)-4-thiazolecarboxamide hydrochloride;

N-(2-aminoethyl)-5-(2,4-difluorophenyl)-4-thiazolecarboxamide hydrochloride; and

N-(2-aminoethyl)-5-(3,5-difluorophenyl)-4-thiazolecarboxamide hydrochloride.

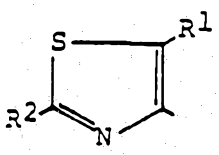
The claims defining the invention are as follows:

~~Claims~~

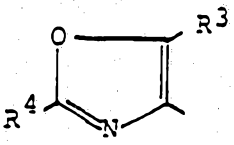
1. Ethylenediamine monoamide derivatives of the general formula

I

wherein R signifies one of the groups



(a)



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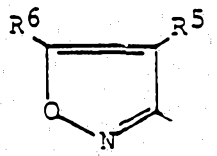
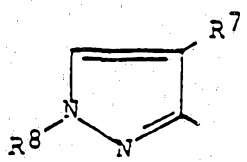


(c)

and



(d)

in which R^1 signifies phenyl, which is optionally monosubstituted by halogen, lower-alkyl, lower-alkoxy, trifluoromethyl, cyano or aryl-lower-alkoxy, dihalophenyl, furyl or thienyl, which is optionally monosubstituted by halogen, R^2 signifies hydrogen, halogen or amino, R^3, R^5 and R^7 each signify phenyl, which is optionally mono- or di-substituted by halogen, thienyl or furyl, which is optionally monosubstituted by halogen, R^4 and R^6 each signify hydrogen or amino and R^8 signifies hydrogen or lower-alkyl,

as well as pharmaceutically usable acid addition salts thereof.

2. Compounds in accordance with claim 1, wherein R signifies group (a) or (b).

3. Compounds in accordance with claim 2, wherein R^1 signifies phenyl, which is optionally monosubstituted by halogen, lower-alkyl, lower-alkoxy, trifluoromethyl or cyano, dihalophenyl, furyl or thienyl, which is optionally monosubstituted by halogen, and R^2 signifies hydrogen or amino or R^3 signifies phenyl, which is mono- or di-substituted by halogen, thienyl or furyl, which is optionally monosubstituted by halogen, and R^4 signifies hydrogen.

4. Compounds in accordance with claim 3, wherein R^1 signifies phenyl, which is monosubstituted by halogen, or dihalophenyl and R^2 signifies hydrogen or R^3 signifies phenyl, which is mono- or di-substituted by halogen, and R^4 signifies hydrogen.

5. N-(2-Aminoethyl)-5-phenyl-4-thiazolecarboxamide.

6. N-(2-Aminoethyl)-5-(3-fluorophenyl)-4-thiazolecarboxamide.

7. N-(2-Aminoethyl)-5-(3,5-difluorophenyl)-4--thiazolecarboxamide.

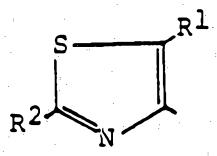
8. N-(2-Aminoethyl)-5-(2-fluorophenyl)-4-thiazolecarboxamide, N-(2-aminoethyl)-5-(4-fluorophenyl)-4--thiazolecarboxamide, N-(2-aminoethyl)-5-(4-chlorophenyl)--4-oxazolecarboxamide, N-(2-aminoethyl)-5-(2-furyl)-4--oxazolecarboxamide, N-(2-aminoethyl)-5-(3,5-dichlorophenyl)-4-thiazolecarboxamide, N-(2-aminoethyl)-5-(2,4--difluorophenyl)-4-thiazolecarboxamide, N-(2-aminoethyl)--5-(4-fluorophenyl)-4-oxazolecarboxamide, N-(2-aminoethyl)-5-(4-bromophenyl)-4-oxazolecarboxamide, N-(2-amino-

ethyl)-4-(3-fluorophenyl)-3-isoxazolecarboxamide and N-(2--aminoethyl)-4-(3-fluorophenyl)-1-methyl-3-pyrazolecarboxamide.

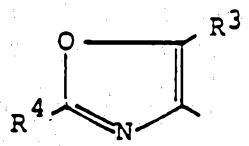
9. Compounds of the general formula

R-CO-Y

wherein R signifies one of the groups



(a)



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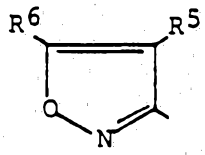
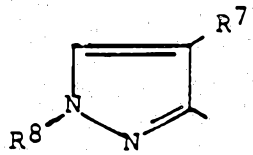


(c)

and



(d)

and Y signifies hydroxy or the group $-NH-CH_2-CH_2-R^{14}$, in which R^1 signifies phenyl, which is optionally monosubstituted by halogen, lower-alkyl, lower-alkoxy, trifluoromethyl, cyano or aryl-lower-alkoxy, dihalophenyl, furyl or thienyl, which is optionally monosubstituted by halogen, R^2 signifies hydrogen, halogen or amino, R^3, R^5 and R^7 each signify phenyl, which is optionally mono- or di-substituted by halogen, thienyl or furyl, which is optionally monosubstituted by halogen, R^4 and R^6 each signify hydrogen or amino, R^8 signifies hydrogen or lower--alkyl and R^{14} signifies a leaving group or a residue which is convertible into an amino group.

10. A process for the manufacture of compounds in accordance with any one of claims 1-8 as well as of pharmaceutically usable acid addition salts thereof, which process comprises

a) reacting a compound of the general formula

R-CO-OH II

wherein R has the significance given in claim 1, in the form of the free acid or in the form of a reactive functional derivative thereof with ethylenediamine, or

b) reacting a compound of the general formula

$$R\text{-}CO\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}R^9 \qquad III$$

wherein R has the significance given in claim 1 and R^9 signifies a leaving group,
with ammonia, or

c) converting the residue R^{10} in a compound of the general formula

$$R\text{-}CO\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}R^{10} \qquad IV$$

wherein R has the significance given in claim 1 and R^{10} signifies a residue which is convertible into an amino group,
into the amino group, and, if desired, converting a compound obtained into a pharmaceutically usable acid addition salt.

11. An antidepressant composition for the treatment or prevention of cognitive disorders, comprising a compound in accordance with any one of claims 1-8 and a therapeutically inert excipient, diluent, carrier and/or adjuvant.

12. Compounds in accordance with any one of claims 1-8, whenever prepared according to the process as claimed in claim 10 or by an obvious chemical equivalent thereof.

13. A method of treating or preventing depressive states and cognitive disorders which comprises administering to a patient requiring such treatment an effective amount of a compound in accordance with any one of claims 1-8.

14. An ethylenediamine monoamide derivative of formula I substantially as herein described with reference to any one of Examples 1 to 23.

15. A process for the manufacture of an ethylenediamine monoamide derivative of formula I which process is substantially as herein described with reference to any one of Examples 1 to 23.

16. An ethylenediamine monoamide derivative of formula I whenever prepared by a process substantially as herein described with reference to any one of Examples 1 to 23.

17. An antidepressant composition for the treatment or prevention of cognitive disorders comprising a compound as defined in claim 14 or 16 together with a pharmaceutically acceptable carrier, diluent, excipient and/or adjuvant.

18. An antidepressant composition for the treatment or prevention of cognitive disorders substantially as herein described with reference to any one of Examples A to C.

19. A method of treating or preventing depressive states and cognitive disorders in a mammal requiring such treatment or prevention, comprising administering to said mammal an effective amount of the compound as defined in claim 14 or 16 or the composition as defined in any one of claims 11, 17 or 18.

DATED this FIRST day of MAY 1992
F Hoffmann-La Roche AG

Patent Attorneys for the Applicant
SPRUSON & FERGUSON

LMM/1338v