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Raddatz et al.

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[54] **ADHESION RECEPTOR ANTAGONISTS**

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[*] Notice: The portion of the term of this patent subsequent to Jul. 21, 2014, has been disclaimed.

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[30] **Foreign Application Priority Data**

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[52] **U.S. Cl.** **514/326**; 514/210; 514/212; 514/255; 514/278; 514/376; 540/200; 540/362; 540/603; 544/369; 546/18; 546/229; 548/229; 548/962

[58] **Field of Search** 540/603, 200, 540/362; 546/209, 18; 548/229, 962; 544/369; 514/210, 212, 255, 278, 326, 376

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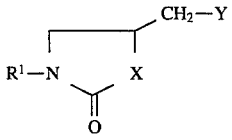
[57] **ABSTRACT**

Compounds of the formula



I

in which R^1, X and Y have the meanings defined herein, and their salts, inhibit the binding of fibrinogen to the fibrinogen receptor and can be used for treating thrombosis, stroke, cardiac infarction, inflammations, arteriosclerosis, osteoporosis and tumors.

22 Claims, No Drawings

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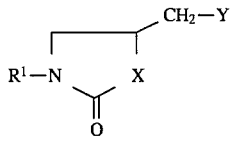
ADHESION RECEPTOR ANTAGONISTS

The invention relates to novel compounds of the formula I:



I

in which

X is O, S, NH or NA,

Y is an aziridino, azetidino, pyrrolidino, piperidino, 1-oxa-8-azaspiro[4.5]dec-8-yl, hexahydroazepino or 4-R^4-piperazino radical which is unsubstituted or substituted once by R^2 and optionally additionally substituted by an OZ, SZ or $N(Z)_2$ group and/or by carbonyl oxygen,

Z is in each case H, A, phenyl-C_kH_{2k} or Ac,

R^1 is a phenyl radical which is substituted once by CN, $H_2N—CH_2—$, $(A)_2N—CH_2—$, $H_2N—C(=NH)—$, $H_2N—C(=NH)—NH—$, $H_2N—C(=NH)—NH—CH_2—$, HO—NH—C(=NH)— or HO—NH—C(=NH)—NH—,

R^2 is $—C_mH_{2m}—COOR^3$ or $—C_nH_{2n}—O—C_pH_{2p}—COOR^3$,

R^3 is H, A or benzyl,

R^4 is H, A, benzyl or $—C_mH_{2m}—COOR^3$,

A is in each case alkyl having 1–6 C atoms,

Ac is acyl having 1–11 C atoms,

k and m are in each case 0, 1, 2 or 3,

n is 0, 2 or 2, and

p is 1, 2 or 3,

and salts thereof.

An object of the invention is to provide novel compounds with valuable properties, especially those which can be used for the preparation of drugs.

Similar compounds are known from EP-A1-0 381 003.

Upon further study of the specification and appended claims, further objects and advantages of this invention will become apparent to those skilled in the art.

These objects have been achieved by the compounds according to the invention. It has been found that the compounds of formula I and their solvates and salts possess valuable pharmacological properties coupled with a good tolerance. In particular, they inhibit the binding of fibrinogen, fibrinonectin and the von Willebrand factor to the fibrinogen receptor of blood platelets (glycoprotein IIb/IIIa), as well as the binding of these proteins, and further adhesive proteins, such as vitronectin, collagen and laminin, to the corresponding receptors on the surface of various cell types. The compounds consequently influence cell-cell and cell-matrix interactions. They prevent the development of blood-platelet thrombi in particular, and can therefore be used for the treatment of thrombosis, stroke, cardiac infarction, inflammations and arteriosclerosis. In addition, the compounds have an effect on tumor cells, by preventing them from forming metastases. Consequently, they can also be employed as anti-tumor agents.

There is evidence that tumor cells spreading from a solid tumor into the vasculature are carried by microthrombi and thus are protected from being detected by cells of the immune system. The second step of attachment to the vessel wall seems to be facilitated by microthrombi as well. Since

to the fibrinogen receptor (glycoprotein IIb/IIIa) on activated platelets, fibrinogen-binding inhibitors are expected to be effective as antimetastatics.

Also, since fibrinogen-binding inhibitors are ligands with fibrinogen receptor on platelets, they can be used as diagnostic tools for detection and localization of thrombi in the vascular in vivo. Thus, for example, in accordance with known procedures, the fibrinogen-binding inhibitors can be labeled with a signal generating or detectable moiety whereby, once the labeled fibrinogen-binding inhibitor is bound to a fibrinogen receptor on platelets, it is possible to detect and locate thrombi.

Fibrinogen-binding inhibitors are also very effective as research tools for studying the metabolism of platelets in the different activation states or intracellular signalling mechanisms of the fibrinogen receptor. For example, as described above, fibrinogen-binding inhibitor can be labeled with a signal generating or detectable moiety. The fibrinogen-binding inhibitor-signal generating/detectable moiety conjugate can then be employed in vitro as a research tool. By binding the conjugate to fibrinogen receptors, it is possible to monitor and study the metabolism of platelets, as well as the activation states and signalling mechanisms of the fibrinogen receptors.

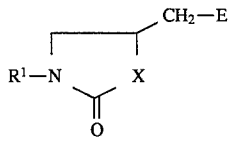
The compounds are also suitable as anti-microbial active substances which are able to prevent infections, for example, those initiated by bacteria, fungi or yeasts. The substances can therefore preferably be given as accompanying anti-microbial active substances, when organisms are subjected to interventions in which exogenous, for example, biomaterials, implants, catheters, or pacemakers, are employed. They act as antiseptics. Antimicrobial activity of the compounds can be demonstrated by the procedure described by P. Valentin-Weigand et al., Infection and Immunity, 2851–2855 (1988).

The properties of the compounds can be demonstrated by methods which are described in EP-A1-0 462 960. The inhibition of the binding of fibrinogen to the fibrinogen receptor can be demonstrated by the method given in EP-A1-0 381 033. The inhibitory effect on blood platelet aggregation can be demonstrated in vitro by the method of Born (Nature, 4832, 927–929, 1962).

The invention relates additionally to a process for preparing a compound of the given formula I, and its salts, characterized in that

(a) a compound of the formula I is liberated from one of its functional derivatives by treating with a solvolyzing or hydrogenolyzing agent, or in that

(b) a compound of the formula II



II

in which

E is Cl, Br, I, or a reactive esterified OH group, and

R^1 and X have the abovementioned meanings,

is reacted with an amino compound of the formula III

III

in which

Y has the abovementioned meaning,

or in that

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R^1—NH—CH_2—CH(XH)—CH_2—Y IV

in which

R^1, X and Y have the abovementioned meanings, or one of its reactive derivatives,

is reacted with a reactive derivative of carbonic acid, or in that

(d) in order to prepare a guanidino compound of the formula I (R^1=phenyl radical substituted once by H_2N—C(=NH)—NH—), an amino compound corresponding to the formula I, which, however, contains an aminophenyl group in place of the radical R^1, is treated with an amidinating agent,

and/or in that, in a compound of the formula I, one or both radicals R^1 and/or Y is/are transformed into (an) other radical(s) R^1 and/or Y, and/or a compound of the formula I is converted into one of its salts by treatment with an acid or a base.

The compounds of the formula I possess at least one chiral center and can therefore occur in several enantiomeric forms. All these forms (e.g., D and L forms), and their mixtures (e.g., the DL forms), are included in the formula I.

Both in the above and in the following, the radicals or parameters X, Y, Z, R^1 to R^4, A, Ac, k, m, n, p and E have the meanings given in the formulae I or II, unless otherwise expressly indicated. In the case where several groups A and/or Z are present in the molecule I, II and/or III, they can be identical or different from one another.

In the above formulae, the group A has 1–6, preferably 1,2, 3 or 4, C atoms. Specifically, A preferably is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, and, additionally, also pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl or 1-, 2-, 3- or 4-methylpentyl.

X is preferably O, or else S, NH or NA, e.g., N—CH_3.

Y is preferably 3-(R^3OOC)-azetidino, 3-(R^3OOC—CH_2—O—)-azetidino, 2-(R^3OOC—)-pyrrolidino, 3-(R^3OOC—)-pyrrolidino, 2-(R^3OOC—)-piperidino, 3-(R^3OOC—)-piperidino, 4-(R^3OOC—)-piperidino, 2-(R^3OOC—CH_2—)-piperidino, 3-(R^3OOC—CH_2—)-piperidino, 4-(R^3OOC—CH_2—)-piperidino, 4-(R^3OOC—CH_2CH_2—)-piperidino, 4-hydroxy-4-(R^3OOC)-piperidino, 4-hydroxy-4-(R^3OOC—CH_2—)-piperidino, 4-amino-4-(R^3OOC)-piperidino, 4-amino-4-(R^3OOC—CH_2—)piperidino, 3-oxo-4-(R^3OOC—CH_2—)-piperidino, 2-(R^3OOC—CH_2—O—)-piperidino, 3-(R^3OOC—CH_2—O—)-piperidino, 4-(R^3OOC—CH_2—O—)-piperidino, 1-oxa-2-oxo-8-azaspiro[4.5]dec-8-yl, 2-, 3- or 4-(R^3OOC)-hexahydroazepino, 4-(R^3OOC—CH_2—)-piperazino, 4-(R^3OOC—CH_2CH_2—)-piperazino, 2-(R^3OOC)-piperazino, 3-(R^3OOC)-piperazino, or 4-benzyl-3-(R^3OOC)-piperazino.

Z is preferably H, more preferably A such as methyl or ethyl, phenyl, benzyl, acetyl or benzoyl.

R^1 is preferably a phenyl radical, which is substituted, as indicated, in the 4 position, or else in the 2 or 3 position, those which are specifically preferred being 2-, 3- or (in particular) 4-cyanophenyl, 2-, 3- or (in particular) 4-aminomethylphenyl, 2-, 3- or (in particular) 4-dimethylaminomethylphenyl, 2-, 3- or (in particular) 4-amidinophenyl, 2-, 3- or 4-guanidinophenyl or 2-, 3- or 4-guanidinomethylphenyl, 2-, 3- or (in particular) 4-hydroxyamidinophenyl.

R^2 is preferably —$COOR^3$, —CH_2COOR^3 or —O—CH_2COOR^3.

R^4 is preferably H, methyl, ethyl, benzyl or —CH_2COOR^3.

Ac is preferably alkanoyl having 1–6 carbon atoms, such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl or caproyl, and also benzoyl, tolyl, 1- or 2-naphthoyl or phenylacetyl.

The parameters k and m are preferably 0 or 1. The parameter n is preferably 0. The parameter p is preferably 1.

Those compounds of the formula I are preferred in which at least one of the indicated radicals, groups and/or parameters has one of the indicated preferred meanings. Some groups of preferred compounds are those of the formulae Ia to Id which correspond to the formula I where, however,

in Ia X is O;

in Ib X is O, and

R^1 is cyanophenyl;

in Ic X is O, and

R^1 is aminomethylphenyl;

in Id X is O, and

R^1 is amidinophenyl.

Furthermore, compounds are preferred which are of the formulae Ie, as well as Iae, Ibe, Ice and Ide, which correspond to the formulae I, Ia, Ib, Ic and Id where, however in addition,

Y is 3-R^2-azetidino, 2-R^2-pyrrolidino, 2-R^2-piperidino, 3-R^2-piperidino, 4-R^2-piperidino, 4-R^2-piperazino or 3-R^2-4-R^4-piperazino,

R^2 is —$COOR^3$, —CH_2COOR^3 or —OCH_2COOR^3, and

R^4 is —CH_2COOR^3.

Smaller, selected, groups of compounds are those of the formulae If and Ig. They correspond to the formula I where, however, in If

X is O,

Y is 3-(R^3OOC—CH_2—O—)-azetidino, 2-(R^3OOC—)-pyrrolidino, 2-, 3- or 4-(R^3OOC—)-piperidino, 4-(R^3OOC—CH_2—)-piperidino, 3- or 4-(R^3OOC—CH_2—O—)-piperidino, 4-(R^3OOC—CH_2)-piperazino or 3-(R^3OOC—)-4-R^4-piperazino,

R^1 is 4-cyanophenyl, 4-aminomethylphenyl, 4-amidinophenyl, or 4-guanidinomethylphenyl,

R^3 is H, C_1–C_4-alkyl or benzyl and

R^4 is H or benzyl, and

in Ig X is O,

Y is 4-(R^3OOC—)-piperidino or 4-(R^3OOC—CH_2O—)-piperidino,

R^1 is 4-cyanophenyl, 4-aminomethylphenyl or 4-amidinophenyl, and

R^3 is H, C_1–C_4-alkyl or benzyl.

The compounds of the formula I, and also the starting compounds for their preparation, are otherwise prepared by methods which are known per se, as described in the literature (e.g., in the standard works, such as Houben-Weyl, Methoden der organischen Chemie (Methods of Organic Chemistry), Georg-Thieme Verlag, Stuttgart; additionally EP-A1-0381033 and EP-A1-0462960), specifically under reaction conditions which are known, and suitable, for the reactions. In this context, use can also be made of variants which are known per se but which are not mentioned here in detail.

If desired, the starting compounds can also be formed in situ, such that they are not isolated from the reaction mixture but, instead, immediately further reacted to give the compounds of the formula I.

The compounds of the formula I can be obtained by liberating them from their functional derivatives by solvoly-

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Preferred starting compounds for the solvolysis or hydrogenolysis are those which, while otherwise corresponding to the formula I, contain corresponding protected amino and/or hydroxyl groups in place of one or more free amino and/or hydroxyl groups, preferably those which carry an amino protective group in place of an H atom which is linked to an N atom, in particular those which carry an R'—N— group, where R' is an amino protective group, in place of an HN group, and/or those which carry a hydroxyl protective group in place of the H atom of a hydroxyl group, e.g., those which correspond to the formula I but carry a —COOR" group, where R" is a hydroxyl protective group, in place of a —COOH group.

Several—identical or different—protected amino and/or hydroxyl groups may also be present in the molecule of the starting compouund. If the protective groups which are present differ from each other, they can in many cases be eliminated selectively.

The expression "amino protective group" is well known and relates to groups which are suitable for protecting (for blocking) an amino group from chemical reactions but which are readily removable once the desired chemical reaction at another site in the molecule has been carried out. Typical groups of this nature are, in particular, unsubstituted or substituted acyl, aryl (e.g., 2,4-dinitrophenyl (DNP)), aralkoxymethyl (e.g., benzyloxymethyl (BOM)) or aralkyl (e.g., benzyl, 4-nitrobenzyl or triphenylmethyl) groups. Since the amino protective groups are removed following the desired reaction (or sequence of reactions), their nature and size is otherwise not critical; however, those are preferred which have 1–20, in particular 1–8, C atoms. In connection with the present process, the expression "acyl group" is to be interpreted in the widest sense. It embraces acyl groups derived from aliphatic, araliphatic, aromatic or heterocyclic carboxylic acids or sulfonic acids, such as, in particular, alkoxycarbonyl, aryloxycarbonyl and, above all, aralkoxycarbonyl groups. Examples of acyl groups of this nature are alkanoyl, such as acetyl, propionyl or butyryl; aralkanoyl, such as phenylacetyl; aroyl, such as benzoyl or tolyl; aryloxyalkanoyl, such as phenoxyacetyl; alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl (BOC) or 2-iodoethoxycarbonyl; aralkyloxycarbonyl, such as benzyloxycarbonyl (CBZ), 4-methoxybenzyloxycarbonyl or 9-fluorenylmethoxycarbonyl (FMOC). Those amino protective groups which are preferred are BOC, DNP and BOM, and, additionally, CBZ, benzyl and acetyl.

The expression "hydroxyl protective group" is likewise well known and relates to groups which are suitable for protecting a hydroxyl group from chemical reactions but which are readily removable once the desired chemical reaction has been carried out at another site in the molecule. Typical groups of this nature are the abovementioned unsubstituted or substituted aryl, aralkyl or acyl groups, and additionally, alkyl groups. The nature and size of the hydroxyl protective groups is not critical, since they are removed once more following the desired chemical reaction or sequence of reactions; groups having 1–20, in particular 1–10, C atoms are preferred. Examples of hydroxyl protective groups are, inter alia, tert-butyl, benzyl, p-nitrobenzoyl, p-toluenesulfonyl and acetyl, with benzyl and acetyl being particularly preferred.

The functional derivatives of the compounds of the formula I to be used as starting compounds can be prepared by customary methods, such as are described, for example, in reaction of compounds which correspond to the formulae II and III, with, however, at least one of these compounds containing a protective group in place of a H atom.

The liberation of the compounds of the formula I from their functional derivatives is achieved—in dependence on the protective group used—e.g., using strong acids, expediently using trifluoroacetic acid or perchloric acid, or else using other strong inorganic acids, such as hydrochloric acid or sulfuric acid, strong organic carboxylic acids, such as trichloroacetic acid, or sulfonic acids, such as benzenesulfonic acid or p-toluenesulfonic acid. It is possible, but not always necessary, for an additional inert solvent to be present.

Suitable inert solvents are, preferably, organic, for example carboxylic, acids, such as acetic acid, ethers, such as tetrahydrofuran or dioxane, amides, such as dimethylformamide (DMF), halogenated hydrocarbons, such as dichloromethane, sulfoxides such as dimethyl sulfoxide (DMSO), and, in addition, alcohols, such as methanol, ethanol or isopropanol, as well as water. Additionally mixtures of the abovementioned solvents are suitable. Trifluoroacetic acid is preferably used in excess without addition of any further solvent; perchloric acid is used in the form of a mixture consisting of acetic acid and 70% perchloric acid in the ratio 9:1. The reaction temperatures for the cleavage are expediently about 0°–50°; preferably 15°–30° (room temperature).

The BOC group can, for example, preferably be eliminated using 40% trifluoroacetic acid in dichloromethane, or using about 3 to 5N HCl in dioxane, at preferably about 15°–60°, and the FMOC group using an approximately 5–20% solution of dimethylamine, diethylamine or piperidine in DMF at preferably about 15°–50°. Elimination of the DNP group is also achieved, for example, using an approximately 3–10% solution of 2-mercaptoethanol in DMF/water at preferably about 15°–30°.

Protective groups (e.g., BOM, CBZ or benzyl) which are removable by hydrogenolysis can be eliminated, for example, by treating with hydrogen in the presence of a catalyst (e.g., a precious metal catalyst such as palladium, expediently on a carrier such as carbon). In this context, suitable solvents are those given above, in particular, for example, alcohols, such as methanol or ethanol or amides, such as DMF. The hydrogenolysis is carried out, as a rule, at temperatures of preferably about 0°–100° and pressures of preferably about 1–200 bar, especially at 20°–30° and 1–10 bar. Hydrogenolysis of the CBZ group is achieved satisfactorily, for example, on 5–10% Pd-C in methanol at preferably about 20°–30°.

Compounds of the formula I can preferably also be obtained by reacting a compound of the formula II with a base of the formula III. The known methods of N-alkylation are then expediently utilized.

The leaving group E is preferably Cl, Br, I, C_1–C_6-alkylsulfonyloxy, such as methanesulfonyloxy or ethanesulfonyloxy, or C_6–C_{10}-arylsulfonyloxy, such as benzenesulfonyloxy, p-toluenesulfonyloxy or 1- or 2-naphthalenesulfonyloxy.

The reaction is preferably effected in the presence of an additional base, e.g., of an alkali metal or alkaline earth metal hydroxide or carbonate, such as sodium, potassium or calcium hydroxide, or sodium, potassium or calcium carbonate, in an inert solvent, e.g., a halogenated hydrocarbon, such as dichloromethane, an ether, such as THF or dioxane, an amide, such as DMF or dimethylacetamide, or a nitrile, such as acetonitrile, at temperatures of preferably about −10°–200°, especially 0°–120°. If the leaving group E of I is different, the addition of an iodide, such as potassium

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The starting compounds of the formula II are novel, as a rule. They can be prepared, for example, by reacting a substituted aniline of the formula R^1—NH_2 with a compound of the formula R^5CH_2—CHR^6—CH_2OH (where R^5 is E, R^6 is XR^7, R^7 is a protective group, or R^5 and R^6 together are also O) to give a compound of the formula R^1—NH—CH_2—CHR^8—CH_2OH (where R^8 is XR^7 or OH), where appropriate eliminating the protective group R^7 to give compounds of the formula R^1—NH—CH_2—CH(XH)—CH_2OH, reacting with a derivative of carbonic acid, such as diethyl carbonate, to give 3-R^1-5-hydroxymethyl-2-oxazolidinones, and converting the hydroxymethyl group into a CH_2E group, e.g., using $SOCl_2$, $SOBr_2$, methanesulfonyl chloride or p-toluenesulfonyl chloride. The compounds of the formula H—Y (III) are known, as a rule, or can be prepared in analogy with known compounds.

In addition, compounds of the formula I can be obtained by reacting a compound of the formula IV (or a reactive derivative thereof) with a reactive derivative of carbonic acid.

Suitable carbonic acid derivatives are, in particular, dialkyl carbonates, such as diethyl carbonate, and, additionally, alkyl esters of chloroformic acid, such as ethyl chloroformate. Preferably, the carbonic acid derivative, which is expediently employed in excess, also serves as a solvent or suspending agent. One of the given solvents can be present as well, provided it is inert in this reaction. Furthermore, the addition of a base is advisable, in particular of an alkali metal alcoholate, such as potassium tert-butylate. Reaction temperatures of preferably about 0°–150°, especially 70°–120°, are expediently employed.

The starting compounds of the formula IV are novel, as a rule. They can be obtained, for example, by functionalizing the abovementioned compounds of the formula R^1—NH—CH_2—CH(XH)—CH_2OH to give compounds of the formula R^1—NH—CH_2—CH(XH)—CH_2—E and reacting with compounds of the formula H—Y (III).

In order to prepare compounds of the formula I, in which R^1 is a guanidinophenyl group, a corresponding aminophenyl compound can be treated with an amidinating agent. 1-Amidino-3,5-dimethylpyrazol which is, in particular, employed in the form of its nitrate, is preferred as an amidinating agent. The reaction is expediently carried out in the presence of a base, such as triethylamine or ethyl diisopropylamine, in an inert solvent or solvent mixture, e.g., water/dioxane, at temperatures of preferably about 0°–120°, especially 60°–120°.

It is furthermore possible, in a compound of the formula I, to convert one or both of the radicals R^1 and/or Y into (an) other radical(s) R^1 and/or Y.

In particular, cyano groups can be reduced to aminomethyl groups, or converted into amidino groups or hydroxyamidino groups, carboxyl groups esterified, ester groups cleaved, benzyl groups removed hydrogenolytically, and aminomethyl groups converted into guanidinomethyl groups.

Reduction of cyano groups to aminomethyl groups is expediently effected by catalytic hydrogenation, e.g., on Raney nickel at temperatures of preferably about 0°–100°, especially 10°–30°, and pressures of preferably about 1–200 bar, especially at atmospheric pressure, in an inert solvent, e.g., a lower alcohol, such as methanol or ethanol, expediently in the presence of ammonia. If the reaction is carried out, for example, at about 20° and 1 bar, benzyl ester groups or N-benzyl groups present in the starting material are then preserved. If it is desired to cleave these groups hydrogen, is then expediently used, it being possible to add an acid, such as acetic acid, and water as well, to the solution.

In order to prepare an amidine of the formula I (R^1=amidinophenyl), ammonia can be added onto a nitrile of the formula I (R^1=cyanophenyl). The addition is preferably effected in several steps, by, in a manner known per se, a) transforming the nitrile with H_2S into a thioamide, which is converted with an alkylating agent, e.g., CH_3I, into the corresponding S-alkyl imidothio ester, which latter reacts with NH_3 to give the amidine, b) transforming the nitrile with an alcohol, e.g., ethanol, in the presence of HCl into the corresponding imido ester, and treating the latter with ammonia, or c) reacting the nitrile with lithium bis(trimethylsilyl)amide and subsequently hydrolyzing the product.

The corresponding N-hydroxyamidines of the formula I (R^1=phenyl substituted by HO—NH—C(=NH)) can be obtained from the nitriles in an analogous manner if the work is carried out according to a) or b) but using hydroxylamine in place of ammonia.

For the esterification, an acid of the formula I (R^3=H) can be treated with an excess of alcohol of the formula R^3—OH (R^3=A or benzyl), expediently in the presence of a strong acid, such as hydrochloric acid or sulfuric acid, at temperatures of preferably about 0°–100°, especially 20°–50°.

Conversely, an ester of the formula I (R^3=A or benzyl) can be converted into the corresponding acid of the formula I (R^3=H), expediently by solvolysis in accordance with one of the abovementioned methods, e.g. with NaOH or KOH in water/dioxane at temperatures of preferably about 0°–40°, especially 10°–30°.

A base of the formula I can be converted with an acid into the associated acid addition salt. Those acids, in particular, are suitable for this reaction which yield physiologically harmless salts. Thus, inorganic acids, e.g., sulfuric acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as orthophosphoric acid, and sulfamic acid, and, in addition, organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, e.g., formic acid, acetic acid, trifluoroacetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methanesulfonic acid or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenemonosulfonic and naphthalenedisulfonic acids, and laurylsulfuric acid, can be used. Salts with acids which are not physiologically harmless, e.g., picrates, may be used for isolating and/or purifying the compounds of the formula I.

The free bases of the formula I can, if desired, be liberated from their salts by treating with strong bases, such as sodium or potassium hydroxide, or sodium or potassium carbonate.

It is also possible to convert carboxylic acids of the formula I (R^3=H) into their metal or ammonium salts, e.g., their sodium, potassium or calcium salts, by reaction with corresponding bases.

The compounds of the formula I contain one or more chiral centers and can therefore be present in racemic or in optically active form. Racemates which are obtained can be resolved mechanically or chemically into the enantiomers in accordance with methods which are known per se. Preferably, diastereomers are formed from the racemic mixture by reaction with an optically active resolving agent. Suitable

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