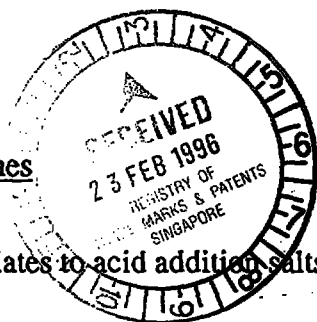
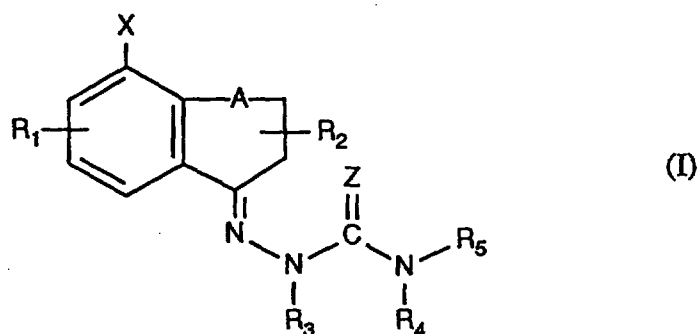


4-18815/A

Salts of hydrazones

The invention relates to acid addition salts of bases of formula I



wherein A is a direct bond or $-(CH_2)_n-$, wherein n is 1, 2 or 3; X is a radical $-C(=Y)-NR_6R_7$; Y is NR_8 , O or S; Z is NR_9 , O or S; each of R_1 and R_2 , independently of the other, is hydrogen or one or more substituents other than hydrogen; each of the radicals R_3 , R_4 , R_6 , R_8 and R_9 , independently of the others, is hydrogen or lower alkyl; and each of R_5 and R_7 , independently of the other, is hydrogen, lower alkyl, hydroxy, etherified or esterified hydroxy or unsubstituted or mono- or di-substituted amino;

with an acid [PA] that is a mono- or poly-protic acid selected from carbonic acid, alkanolic acids that are unsubstituted or mono- or poly-substituted, with the exception of formic acid, unsubstituted acetic acid, lysine and arginine; alkenoic acids that are unsubstituted or substituted, with the exception of unsubstituted fumaric acid; cycloalkylcarboxylic acids, arylcarboxylic acids, aryl-lower alkylcarboxylic acids, wherein lower alkyl is unsubstituted or substituted, aryl-lower alkenylcarboxylic acids, heterocyclylcarboxylic acids, alkylsulfonic acids that are unsubstituted or substituted, with the exception of unsubstituted methylsulfonic acid; arylsulfonic acids, alkylsulfuric acids, N-substituted sulfamic acids, organic acids without carboxy, sulfo, sulfate or phospho groups, and also selected from pyrophosphoric acid and hydriodic acid, and tautomers thereof,

also to processes for the preparation of those acid addition salts, to pharmaceutical compositions comprising those acid addition salts, and to the use of those acid addition salts in the therapeutic treatment of the human or animal body or in the preparation of pharmaceutical compositions.

Tautomers may occur, for example, when Z is NR_9 and R_3 and/or R_4 and/or R_5 are hydrogen:

the corresponding guanyl radical, shown in formula I as $-\text{N}(\text{R}_3)-\text{C}(=\text{Z})-\text{NR}_4\text{R}_5$, may then, for example, also be in the tautomeric form $-\text{N}=\text{C}(-\text{ZH})-\text{NR}_4\text{R}_5$, $-\text{N}(\text{R}_3)-\text{C}(-\text{ZH})=\text{NR}_5$ or $-\text{N}(\text{R}_3)-\text{C}(-\text{ZH})=\text{NR}_4$.

If, for example, Y is NR_8 and if R_6 and/or R_7 is hydrogen, then the corresponding amidine structure, defined in formula I as $\text{X} = -\text{C}(=\text{Y})-\text{NR}_6\text{R}_7$, may also occur in the tautomeric form $-\text{C}(-\text{YH})=\text{NR}_7$ or $-\text{C}(-\text{YH})=\text{NR}_6$. The person skilled in the art is familiar with the presence of those and similar tautomers. All those tautomers are included in the general formula I.

If A is a group $-(\text{CH}_2)_n-$ and R_2 is other than hydrogen, the substituent(s) corresponding to the radical R_2 may also be linked to the carbon atoms of the group $-(\text{CH}_2)_n-$.

R_2 is, for example, hydrogen or from 1 to 4 substituents other than hydrogen, especially hydrogen or 1 or 2 substituents other than hydrogen, and more especially hydrogen or one substituent other than hydrogen.

R_1 is, for example, hydrogen or from 1 to 3 substituents other than hydrogen, and especially hydrogen or 1 or 2 substituents other than hydrogen.

Within the framework of the present Application, the general terms used hereinbefore and hereinafter have preferably the following meanings:

The following definitions relate to the radicals mentioned in the bases of formula I.

Lower alkyl is, for example, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl or n-heptyl, preferably ethyl or methyl, especially methyl.

A substituent other than hydrogen is, for example, lower alkyl, trifluoromethyl, cycloalkyl, aryl-lower alkyl, hydroxy, lower alkoxy, aryl-lower alkoxy, aryloxy; acyloxy, for example lower alkanoyloxy; halogen, amino, N-lower alkylamino, N,N-di-lower alkylamino; acyl-amino, for example lower alkanoylamino; nitro, lower alkanoyl, arylcarbonyl, carboxy, lower alkoxy carbonyl, carbamoyl ($-\text{CONH}_2$), N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N-arylcarbamoyl, cyano, mercapto, lower alkylthio, lower alkylsulfonyl, sulfamoyl ($-\text{SO}_2\text{NH}_2$), N-lower alkylsulfamoyl or N,N-di-lower alkylsulfamoyl.

Aryl is, for example, phenyl or naphthyl, such as 1- or 2-naphthyl. The phenyl and naphthyl radicals may be unsubstituted or substituted, especially as indicated below for phenyl. Aryl is preferably phenyl that is unsubstituted or substituted by one or more, especially one or two, substituents selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, nitro, amino, halogen, trifluoromethyl, carboxy, lower alkoxy carbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, cyano, lower alkanoyl, arylcarbonyl, lower alkylsulfonyl, sulfamoyl, N-lower alkylsulfamoyl and N,N-di-lower alkylsulfamoyl. Aryl is especially phenyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen or by trifluoromethyl, more especially phenyl.

Arylcarbonyl is, for example, benzoyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen or by trifluoromethyl, especially benzoyl.

Aryl-lower alkyl is, for example, phenyl-lower alkyl, especially benzyl.

Halogen is especially chlorine and bromine, but may also be fluorine or iodine.

Lower alkanoyl is, for example, formyl, acetyl, propionyl or pivaloyl.

Cycloalkyl is preferably C_3 - C_8 - and especially C_5 - C_6 -cycloalkyl, which is to denote that it contains from 3 to 8 and 5 or 6 ring carbon atoms, respectively. It may, however, also be substituted, for example by lower alkyl.

Etherified hydroxy is, for example, lower alkoxy. Esterified hydroxy is, for example, lower alkanoyloxy. Mono-substituted amino is, for example, lower alkylamino. Di-substituted amino is, for example, di-lower alkylamino, lower alkyleneamino, for example

C₄-C₇- and, especially, C₄-C₅-alkyleneamino, for example piperidino, or oxa-, thia- or aza-lower alkyleneamino, for example morpholino, thiomorpholino, piperazino or 4-lower alkylpiperazino.

The following definitions relate to the acids [PA] ([PA] stands for "Protic Acid"):

Alkanoic acids are especially C₁-C₂₀alkanoic acids with the exception of formic acid and unsubstituted acetic acid, preferably C₂-C₇alkanoic acids, such as propionic acid, butyric acid, isobutyric acid, pentanoic acid, hexanoic acid or heptanoic acid, or also octanoic acid, decanoic acid or dodecanoic acid, especially propionic acid or octanoic acid, all of those alkanoic acids being unsubstituted or substituted one or more times, especially from one to six times, preferably by hydroxy, either once, such as in glycolic acid, lactic acid or 2-hydroxybutyric acid, or several times, for example up to five times, such as in gluconic acid or glucose monocarboxylic acid ("glucoheptonic acid"), by carboxy, for example in C₂-C₂₀alkanoic di-acids, especially C₂-C₇alkanoic di-acids, such as in succinic acid, or also adipic acid, pimelic acid, suberic acid or azelaic acid, by hydroxy and carboxy, such as in malic acid, tartaric acid, citric acid, glucaric acid or galactaric acid, by amino or amino and carboxy and/or by one or two radicals selected independently from mercapto, methylmercapto, hydroxy, phenyl, 4-hydroxyphenyl, naphthyl, cyclohexyl, imidazolyl and indolyl, such as in amino acids, lysine and arginine being excluded, especially glutamic acid or aspartic acid in the (D)-, (L)- or (D,L)-form, preferably the (D)- or (L)-form, by substituted amino or substituted amino and carboxy and/or by one or two radicals selected independently from mercapto (also in oxidised form as the corresponding disulfide consisting of two molecules of the corresponding mercaptan), methylmercapto, hydroxy, phenyl, 4-hydroxyphenyl, naphthyl, cyclohexyl, imidazolyl and indolyl, such as in amino acids, for example in N-mono- or N,N-di-lower alkylamino acids, such as N-methyl-glycine, or in N-lower alkanoylamino acids, such as acetylaminoacetic acid (N-acetyl-glycine), N-acetylasparagine or N-acetylcystine, by oxo, such as in pyruvic acid or acetoacetic acid, by phospho and amino, such as in phosphoserine, or by phospho and hydroxy, such as in 2- or 3-glycerophosphoric acid, glucose-6-phosphoric acid, glucose-1-phosphoric acid or fructose-1,6-bisphosphoric acid. Amino acids are especially α -amino acids which may be in the (D)-, (L)- or (D,L)-form, preferably the (L)- or (D)-form, and, when other centres of asymmetry are present, they may also be in the form of other isomers, for example selected from glycine (H-Gly-OH), alanine (H-Ala-OH), valine (H-Val-OH), norvaline (α -aminovaleric acid), leucine (H-Leu-OH), isoleucine (H-Ile-OH), norleucine (α -aminohexanoic acid, H-Nle-OH), serine (H-Ser-OH), homoserine (α -amino- γ -hydroxy-

butyric acid), threonine (H-Thr-OH), methionine (H-Met-OH), cysteine (H-Cys-OH) (which may also be present in oxidised form as cystine), phenylalanine (H-Phe-OH), tyrosine (H-Tyr-OH), β -phenylserine (β -hydroxyphenylalanine), phenylglycine, α -naphthylalanine (H-Nal-OH), cyclohexylalanine (H-Cha-OH), cyclohexylglycine, tryptophan (H-Trp-OH), aspartic acid (H-Asp-OH), asparagine (H-Asn-OH), amino-malonic acid, glutamic acid (H-Glu-OH), glutamine (H-Gln-OH), histidine (H-HisOH), δ -hydroxylysine, ornithine (α,δ -diaminovaleric acid), α,γ -diaminobutyric acid and α,β -diaminopropionic acid, and, unless otherwise indicated, from arginine (H-Arg-OH) and lysine (H-Lys-OH). Especially preferred amino acids are glycine, serine, cystine, aspartic acid and glutamic acid, especially aspartic acid and glutamic acid. Amino acids may also be omitted from the definition of substituted alkanoic acids.

Alkenoic acids are, for example, C_2 - C_{10} alkenoic di-acids that are unsubstituted, such as maleic acid, or substituted, preferably by hydroxy, such as in hydroxymaleic acid (tautomer: oxalacetic acid), or lower alkyl, for example methyl, such as in methylmaleic acid. Unsubstituted fumaric acid is excluded.

Cycloalkylcarboxylic acids are preferably C_4 - C_{12} cycloalkylcarboxylic acids wherein the cycloalkyl radical is mono-, bi- or tri-cyclic, preferably monocyclic or tricyclic, for example cyclopentyl, cyclohexyl, cycloheptyl or adamantyl, and is, for example, unsubstituted, such as in cyclohexanecarboxylic acid or adamantanecarboxylic acid.

In arylcarboxylic acids, the aryl radical has, for example, from 6 to 20, preferably from 6 to 14, carbon atoms, and is selected, for example, from phenyl, 1- or 2-naphthyl and indane, and is unsubstituted, such as in benzoic acid, or substituted, preferably by from 1 to 3 radicals selected independently from lower alkyl, such as methyl, halogen, such as fluorine, chlorine or bromine, hydroxy, lower alkoxy, for example methoxy, phenoxy, lower alkanoyloxy, such as acetoxy, amino and carboxy, such as in salicylic acid, 1- or 3-hydroxynaphthyl-2-carboxylic acid, 3,4,5-trimethoxybenzoic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, 4-aminosalicylic acid or phthalic acid.

In aryl-lower alkylcarboxylic acids, aryl is as last defined for arylcarboxylic acids and is unsubstituted or substituted as defined there, and lower alkyl is preferably methyl or ethyl, lower alkyl being unsubstituted, such as in phenylacetic acid, or substituted, for example by hydroxy, such as in mandelic acid.

In aryl-lower alkenylcarboxylic acids, aryl is as last defined for arylcarboxylic acids, and lower alkenyl has preferably from 2 to 4 carbon atoms, such as in cinnamic acid.

Heterocyclylcarboxylic acids contain, for example, heterocyclyl comprising from one to three rings, preferably one or two rings, that is saturated or partially or completely unsaturated, preferably saturated or unsaturated, and has from 5 to 12 ring atoms, preferably from 5 to 7 ring atoms, which are selected from carbon and up to three hetero atoms, preferably one or two hetero atoms being present, especially oxygen, nitrogen and/or sulfur, especially oxygen and nitrogen, heterocyclyl being, for example, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, pyrazinyl, pyrimidinyl, indolyl, quinolyl, isoquinolyl, quinoxalinyll or a completely or partially saturated derivative of those radicals, or pyranlyl or furanyl, and being unsubstituted, such as in nicotinic acid or isonicotinic acid, or from mono- to penta-substituted, preferably by hydroxy and/or by hydroxy-lower alkyl, for example hydroxy or hydroxymethyl, such as in glucuronic acid or galacturonic acid.

Alkylsulfonic acids are especially C_2 - C_{20} alkylsulfonic acids, preferably C_2 - C_7 alkylsulfonic acids, such as ethanesulfonic acid, that are unsubstituted or substituted, preferably by one or two radicals selected from hydroxy and sulfo, such as in 2-hydroxyethanesulfonic acid, or alkanedisulfonic acids, for example lower alkanedisulfonic acids, such as ethane-1,2-disulfonic acid. Methylsulfonic acid is excluded.

In arylsulfonic acids, aryl is, for example, as defined for arylcarboxylic acids and is unsubstituted, such as in benzenesulfonic acid or 2-naphthalenesulfonic acid, or is substituted as in arylcarboxylic acids, especially by lower alkyl, for example methyl, such as in 2-, 3- or 4-methylbenzenesulfonic acid, or by a further sulfonyl radical, such as in 1,3-benzenedisulfonic acid or naphthalene-1,5-disulfonic acid, such as, especially, in 1,5-naphthalenedisulfonic acid.

Alkylsulfuric acids are especially C_1 - C_{20} alkylsulfuric acids, especially lower alkylsulfuric acids, such as methylsulfuric acid or ethylsulfuric acid, or dodecylsulfuric acid.

N-substituted sulfamic acids are, for example, N-cycloalkylsulfamic acids, wherein cycloalkyl is preferably C_4 - C_{12} cycloalkyl and the cycloalkyl radical is mono-, bi- or tri-cyclic, for example cyclopentyl, cyclohexyl, cycloheptyl or adamantyl, preferably monocyclic, such as in N-cyclohexylsulfamic acid, or N-alkylsulfamic acids, preferably N-lower alkylsulfamic acid, such as methyl-, ethyl- or propyl-sulfamic acid.

Organic acids without carboxy, sulfo, sulfate or phospho groups contain, for example, acidic hydroxy groups, such as in ascorbic acid.

Important acids are carbonic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, 2-hydroxybutyric acid, gluconic acid, glucose monocarboxylic acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, glucaric acid, galactaric acid, glutamic acid, aspartic acid, N-methylglycine, acetylaminoacetic acid, N-acetylasparagine, N-acetylcystine, pyruvic acid, acetoacetic acid, phosphoserine, 2- or 3-glycerophosphoric acid, glucose-6-phosphoric acid, glucose-1-phosphoric acid, fructose-1,6-bisphosphoric acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantane-carboxylic acid, benzoic acid, salicylic acid, 1- or 3-hydroxynaphthyl-2-carboxylic acid, 3,4,5-trimethoxybenzoic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, 4-amino-salicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, nicotinic acid, isonicotinic acid, glucuronic acid, galacturonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalene-sulfonic acid, 1,5-naphthalenedisulfonic acid, 2-, 3- or 4-methylbenzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, N-cyclohexylsulfamic acid, methyl-, ethyl- or propyl-sulfamic acid, or ascorbic acid.

Very important acids are octanoic acid, succinic acid, adipic acid, salicylic acid, benzenesulfonic acid, 1,5-naphthalenesulfonic acid or N-cyclohexylsulfamic acid, very especially salicylic acid or, more especially, adipic acid or benzenesulfonic acid.

Very important acids are equally tartaric acid, especially L-tartaric acid, or citric acid.

The mentioned acids, especially if they contain several acidic groups of differing acidity that can dissociate protons, may also be in the form of mixed salts with cations, for example alkali metal cations, such as sodium or potassium ions, alkali metal salts, such as magnesium salts, or zinc salts, the mentioned mixed salts containing at least one other dissociable proton at the acid component, or they may be present in the resulting salts in a form in which not all protons are freed, but at least one proton has been transferred to the relevant base of formula I. For example, carbonic acid can be used in the form of a hydrogen carbonate salt, such as sodium or potassium hydrogen carbonate.

The acid addition salts of a base of formula I with an acid [PA] may also be in the form of hydrates. Crystals may also include other solvents used for crystallisation.

Depending on structural factors, the acid addition salts of the present invention may be in the form of isomeric mixtures or in the form of pure isomers. If, for example, R_2 is a substituent other than hydrogen, the corresponding acid addition salts of formula I may be in the form of racemic salts or enantiomerically pure salts or also in the form of diastereoisomeric salts, for example in the presence of acids S having centres of asymmetry, such as the mentioned amino acids, lactic acid or tartaric acid.

The aim of the present invention is to provide novel acid addition salts of pharmacologically acceptable compounds, which salts have a good solubility in physiological liquids and/or liquids that are similar to physiological liquids, such as physiological saline solution, mannitol solution or phosphate buffers, and/or good absorbability in the case of enteral, such as oral, administration, for example the formation of ion pairs, such as lipophilic ion pairs.

The acid addition salts according to the invention have valuable pharmacologically exploitable properties. They exhibit, especially, a strong, specific inhibitory action on the enzyme S-adenosylmethionine decarboxylase (SAMDC). As a key enzyme, SAMDC plays an important role in polyamine synthesis, which takes place in practically all cells of mammals, including humans. SAMDC regulates the concentration of polyamine in the cell. Inhibition of the enzyme SAMDC results in a reduction in polyamine concentration. Because a reduction in polyamine concentration brings about inhibition of cell growth, it is possible, by administering SAMDC-inhibiting substances, to inhibit the growth of both eukaryotic and prokaryotic cells and even to kill cells or to inhibit the onset of cell differentiation.

Inhibition of the enzyme SAMDC can be demonstrated, for example, using the method of H.G. Williams-Ashmann and A. Schenone, *Biochem. Biophys. Res. Commun.* **46**, 288 (1972). The acid addition salts of the invention in this case exhibit IC_{50} values as low as $0.005 \mu M$ or lower.

A further advantage of the acid addition salts according to the invention is that, compared with their strong inhibitory action on SAMDC, they inhibit diaminoxidase to only a slight extent and are well tolerated. According to J. Jaenne and D.R. Morris, *Biochem.*

J. 218, 974 (1984), inhibition of diaminoxidase is unfavourable because it can lead to the accumulation of putrescine and indirect SAMDC-activation.

The acid addition salts of formula I can accordingly be used, for example, in the treatment of benign and malignant tumours. They can induce tumour regression and can also prevent the spread of tumour cells resulting in metastase formation, and also the growth of micro-metastases. They can also be used, for example, in the treatment of protozoa infections, such as, for example, trypanosomiasis, malaria or pulmonary inflammation caused by *Pneumocystis carinii*.

As selective SAMDC-inhibitors, the acid addition salts of bases of formula I with an acid [PA] can be used alone or also in combination with other pharmacologically active substances. A possible combination is, for example, one with (a) inhibitors of other enzymes of polyamine biosynthesis, for example ornithine decarboxylase inhibitors, (b) inhibitors of protein kinase C, (c) inhibitors of tyrosine protein kinase, (d) cytokinins, (e) negative growth regulators, (f) aromatase inhibitors, (g) antioestrogens or (h) conventional cytostatic active substances.

The invention relates preferably to the acid addition salts of a base of formula I wherein A is a direct bond or $-(CH_2)_n-$, n being 1 or 2; X is a radical $-C(=Y)-NR_6R_7$; Y is NR_8 , O or S; Z is NR_9 , O or S; each of R_1 and R_2 , independently of the other, is hydrogen or one or two substituents selected from the group consisting of lower alkyl, trifluoromethyl, cyclo-alkyl, aryl-lower alkyl, hydroxy, lower alkoxy, aryl-lower alkoxy, aryloxy, lower alkanoyloxy, halogen, amino, N-lower alkylamino, N,N-di-lower alkylamino, lower alkanoylamino, nitro, lower alkanoyl, arylcarbonyl, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N-arylcarbamoyl, cyano, mercapto, lower alkylthio, lower alkylsulfonyl, sulfamoyl, N-lower alkylsulfamoyl and N,N-di-lower alkylsulfamoyl, aryl being phenyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen or by trifluoromethyl; each of the radicals R_3 , R_4 , R_6 , R_8 and R_9 , independently of the others, is hydrogen or lower alkyl; and each of R_5 and R_7 , independently of the other, is hydrogen, lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, amino, lower alkylamino, di-lower alkylamino, lower alkyleneamino or oxa-, thia- or aza-lower alkyleneamino;

with an acid [PA] that is a mono- or poly-protic acid selected from carbonic acid, alkanolic acids that are unsubstituted or mono- or poly-substituted, with the exception of formic

acid, unsubstituted acetic acid, lysine and arginine; alkenoic acids that are unsubstituted or substituted, with the exception of fumaric acid; cycloalkylcarboxylic acids, arylcarboxylic acids, aryl-lower alkylcarboxylic acids, wherein lower alkyl is unsubstituted or substituted, aryl-lower alkenylcarboxylic acids, heterocyclylcarboxylic acids, alkylsulfonic acids that are unsubstituted or substituted, with the exception of methylsulfonic acid; aryl-sulfonic acids, alkylsulfuric acids, N-substituted sulfamic acids, organic acids without carboxy, sulfo, sulfate or phospho groups, and also selected from pyrophosphoric acid and hydriodic acid, for example one of the acids defined above as being important, for example one of the acids defined as being very important,

or tautomers thereof.

Especially preferred are the acid addition salts of a base of formula I wherein A is a direct bond or $-(CH_2)_n-$, wherein n is 1 or 2; X is a radical $-C(=Y)-NR_6R_7$; Y is NH, O or S; Z is NH, O or S; each of R_1 and R_2 , independently of the other, is hydrogen or one or two substituents selected from the group consisting of lower alkyl, trifluoromethyl, phenyl-lower alkyl, hydroxy, lower alkoxy and halogen; the radicals R_3 , R_4 and R_6 are hydrogen; and each of R_5 and R_7 , independently of the other, is hydrogen, lower alkyl, hydroxy or amino; with an acid [PA] that is a mono- or poly-protic acid selected from carbonic acid, alkenoic acids that are unsubstituted or mono- or poly-substituted, with the exception of formic acid, unsubstituted acetic acid, lysine and arginine; alkenoic acids that are unsubstituted or substituted, with the exception of fumaric acid; cycloalkylcarboxylic acids, arylcarboxylic acids, aryl-lower alkylcarboxylic acids, wherein lower alkyl is unsubstituted or substituted, aryl-lower alkenylcarboxylic acids, heterocyclylcarboxylic acids, alkylsulfonic acids that are unsubstituted or substituted, with the exception of methylsulfonic acid; arylsulfonic acids, alkylsulfuric acids, N-substituted sulfamic acids, organic acids without carboxy, sulfo, sulfate or phospho groups, and also selected from pyrophosphoric acid and hydriodic acid, for example one of the acids defined above as being important, for example one of the acids defined as being very important;

or tautomers thereof.

More especially preferred are the acid addition salts of a base of formula I wherein A is a direct bond or $-CH_2-$; X is a radical $-C(=Y)-NR_6R_7$; Y is NH or S; Z is NH; R_1 is hydrogen or one or two substituents selected from the group consisting of lower alkyl, hydroxy, lower alkoxy and halogen; R_2 is hydrogen or lower alkyl; the radicals R_3 , R_4 and

R_6 are hydrogen; and each of R_5 and R_7 , independently of the other, is hydrogen, lower alkyl or hydroxy; with an acid [PA] that is as defined above, for example one of the acids defined above as being important, for example one of the acids defined as being very important; or tautomers thereof.

Most especially preferred are the acid addition salts of bases of formula I wherein A is a direct bond; X is a radical $-C(=NH)-NH_2$; Z is NH; R_1 is hydrogen or one or two substituents selected from the group consisting of lower alkyl, hydroxy and lower alkoxy; the radicals R_2 , R_3 and R_4 are hydrogen; and R_5 is hydrogen or hydroxy; with an acid [PA] that is as defined above, for example one of the acids defined above as being important, especially one of the acids defined as being very important; or tautomers thereof.

As sub-groups of a group of acid addition salts of bases of formula I with acids [PA], attention is drawn to:

(a) acid addition salts of bases of formula I wherein A is a direct bond; (b) acid addition salts of bases of formula I wherein X is a radical $-C(=NH)-NH_2$; (c) acid addition salts of bases of formula I wherein Z is NH, R_4 is hydrogen, and R_5 is hydrogen or hydroxy; and (d) acid addition salts of bases of formula I wherein R_1 and R_2 are hydrogen; each of the other radicals being as defined; with acids [PA] selected from one of the groupings mentioned above, for example from the acids defined above as being very important; or tautomers thereof.

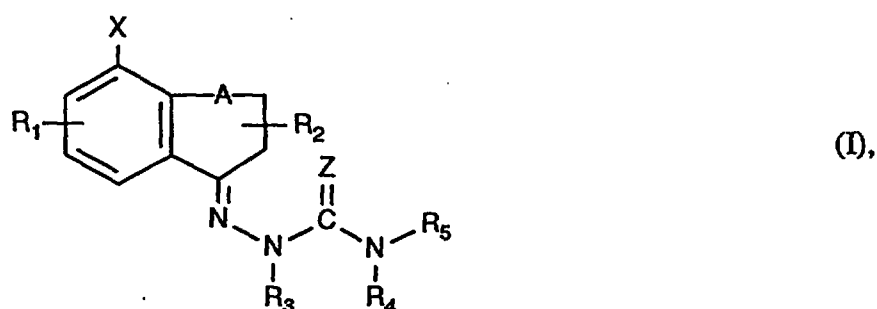
The invention relates more especially to the acid addition salts of bases of formula I wherein A is a direct bond; X is a radical $-C(=NH)-NH_2$; Z is NH; and each of R_1 , R_2 , R_3 , R_4 and R_5 is hydrogen; and [PA] is selected from the above-mentioned acids, or is preferably one of the acids defined above as being important, for example one of the acids defined as being very important, for example an acid selected from N-cyclohexylsulfamic acid, octanoic acid, salicylic acid and benzenesulfonic acid, such as salicylic acid.

The invention relates more especially also to the acid addition salts of bases of formula I wherein A is a direct bond; X is a radical $-C(=NH)-NH_2$; Z is NH; and each of R_1 , R_2 , R_3 , R_4 and R_5 is hydrogen; and [PA] is preferably one of the acids defined above as being very important, especially selected from tartaric acid, more especially L-tartaric acid, and citric acid.

Most strongly preferred are the acid addition salts of bases of formula I mentioned in the Examples with an acid [PA].

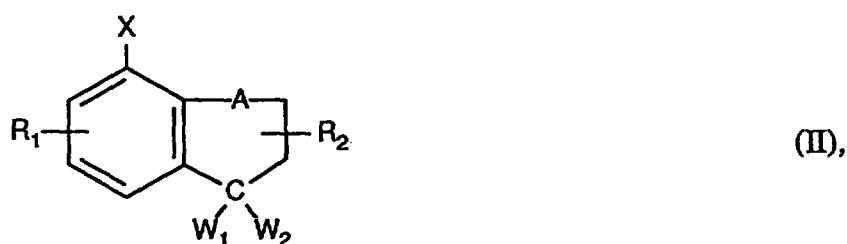
The acid addition salts of bases of formula I with an acid [PA] are prepared in accordance with processes known per se, for example as follows:

a) a base of formula I



wherein the radicals are as defined for acid addition salts of bases of formula I, is reacted with an acid [PA], [PA] being as defined above, or

b) a compound of the formula

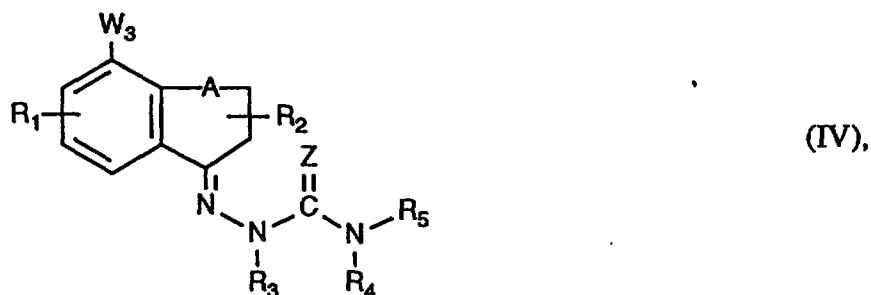


wherein the group CW_1W_2 is carbonyl, functionally modified carbonyl or protected carbonyl and A, X, R_1 and R_2 are as defined for acid addition salts of formula I, is condensed with an amine of the formula



wherein Z, R₃, R₄ and R₅ are as defined for acid addition salts of bases of formula I, in the presence of an acid [PA] that is as defined, or

c) in a compound of the formula



wherein W₃ is a radical that can be converted into a group X in a base of formula I and A, Z, R₁, R₂, R₃, R₄ and R₅ are as defined under formula I, the radical W₃ is converted into the group X in the presence of an acid [PA] that is as defined above; or

d) any desired acid addition salt of a base of formula I with an acid that does not fall within the definition of [PA] is converted into an acid addition salt of a base of formula I with an acid [PA] that is as defined above;

and, if desired, a resulting acid addition salt of a base of formula I with an acid [PA] is converted into a different acid addition salt of a base of formula I with an acid [PA], and/or, if desired, isomeric mixtures are separated into the individual isomers.

In the following more detailed description of processes a)-d), each of the symbols A, X, Y, Z, R₁-R₉ and [PA] is as defined in the definition of the acid addition salts of bases of formula I with acids [PA], unless otherwise indicated.

Process a)

The reaction of a base of formula I with an acid [PA] to form the corresponding acid addition salt is carried out in accordance with methods known per se for the formation of acid addition salts of basic compounds.

The reaction to form the acid addition salt takes place, for example, in solvents, especially

in organic solvents, more especially in polar organic solvents, most especially in esters, for example lower alkanoyl-lower alkyl esters, such as acetic acid ethyl ester, in amides, for example N,N-di-lower alkyl-lower alkanoylamides, such as dimethylformamide, in alcohols, for example hydroxy-lower alkanes, such as methanol, ethanol, ethylene glycol or glycerol, or aryl alcohols, such as phenols, for example phenol, or in dimethyl sulfoxide, in the absence or presence of water, preferably in the absence of water. The reaction in alcohols, such as the last-mentioned hydroxy-lower alkanes, is especially preferred.

The reaction takes place, for example, in free solution but may also be carried out using chromatographic columns, for example by gel filtration, or using ion exchangers, or via semi-permeable membranes by osmotic processes.

The reaction is carried out at temperatures from the freezing point to the boiling point of the solutions concerned, preferably at from 0 to 50°C, especially from 20 to 40°C, for example at room temperature, in the presence or absence of a protective gas, such as nitrogen or argon.

The compounds of formula I and the acids [PA] are used in suitable molar ratios, or the acid [PA] is used in excess. The individual components are used preferably in the molar ratio corresponding to the ratio of the molarity of the base of formula I and the acid [PA] in the acid addition salts according to the invention.

The resulting salts precipitate, for example, spontaneously, in some cases only after cooling, or they are precipitated by the addition of solvents, especially non-polar solvents, for example ethers, such as diethyl ether, or water and/or are obtained by partial or complete concentration by evaporation.

Process b)

There may be mentioned as functionally modified or protected carbonyl CW_1W_2 , for example: di-lower alkoxymethyl, C_1 - C_2 alkylenedioxymethyl, dihalomethyl, di-lower alkylthiomethyl or C_1 - C_2 alkylenedithiomethyl.

The group CW_1W_2 in the compounds of formula II is preferably in the form of free carbonyl.

The condensation reaction according to Process b) is effected under the conditions known per se for the formation of hydrazones and is carried out in the presence of an acid [PA] that at the same time acts as a catalyst. The amount of [PA] is preferably such that the reacting amino group in the compound of formula III is protonated to such a slight extent that it is still reactive. For that purpose, the starting compounds, provided they contain salt-forming groups, are used especially preferably in the form of salts of the acid [PA] which are, if necessary, formed in situ either from the free compounds or salts of readily volatile acids, such as hydrohalic acids, for example HBr or HCl, formic acid, acetic acid or carbonic acid (in the form of the carbonate salt or hydrogen carbonate salt), it also being possible for the reaction to take place, for example, in the presence of a catalytically active small excess of the acid [PA]. The solvent used is preferably one of the solvents mentioned under Process a), especially an aqueous solvent, such as water, at preferred temperatures of from 20°C up to the boiling point of the reaction mixture concerned, especially at the boiling point of the mixture concerned, in the presence or absence of a protective gas, such as nitrogen or argon. Suitable for compounds of formula II are those protected carbonyl groups CW_1W_2 that pass over into free carbonyl under the conditions of the condensation reaction.

For the preparation of acid addition salts from a base of formula I wherein R_5 is amino, and from an acid [PA], it is expedient to use the compound of formula III in excess.

Process c)

In the intermediates of formula IV, W_3 is, for example, free or functionally modified carboxy, especially halocarbonyl, cyano, imino-lower alkoxycarbonyl, imino-lower alkylthiolcarbonyl or thiocarbamoyl.

In the preparation of amidines of formula I ($Y \hat{=} NR_8$), the group W_3 in a compound of formula IV may be, for example: an acid addition salt of an imino-lower alkyl ester ($\hat{=}$ imino-lower alkyl ether) or imino-lower alkyl thiol ester with one of the mentioned acids S, for example $-C(=NH)-OC_2H_5 \cdot [PA]$ or $-C(=NH)-SC_2H_5 \cdot [PA]$, respectively, also thio-carbamoyl or cyano.

By reacting an imino-lower alkyl ester of formula IV (in the form of a salt of one of the acids [PA], as defined above) with ammonia or primary or secondary amines, the unsub-

stituted or mono- or di-substituted acid addition salts, respectively, of the corresponding amidines according to formula I are obtained. Cyano compounds of formula IV can be converted, for example, by reaction with a primary or secondary (di-)lower alkyl-ammonium salt of one of the mentioned acids [PA] into an unsubstituted or mono- or di-substituted acid addition salt of an amidine of formula I.

In the preparation of carbamoyl-substituted bases of formula I ($Y \hat{=} O$) as constituents of acid addition salts with acids [PA], the group W_3 in a compound of formula IV may be, for example: carboxy, halocarbonyl (for example $-COCl$) or lower alkoxy carbonyl. The formation of unsubstituted or mono- or di-substituted carbamoyl-substituted bases of formula I as constituents of acid addition salts with an acid [PA] from corresponding intermediates of formula IV, wherein W_3 is carboxy, halocarbonyl or lower alkoxy carbonyl, by reaction with ammonia or primary or secondary amines, respectively, is known per se. The corresponding acid addition salts of the bases of formula I can be obtained directly from the reaction mixture by precipitation, that is to say, by acidifying a, for example, alkaline or neutral reaction mixture with one of the mentioned acids [PA].

In the preparation of acid addition salts with carbamoyl-substituted bases of formula I ($Y \hat{=} O$), the group W_3 in a compound of formula IV may be, for example, cyano. Intermediates of formula IV wherein W_3 is cyano can be converted, for example, by partial hydrolysis in the manner of a Graf-Ritter reaction, or by way of carboxylic acid ester imide salts of the relevant acids [PA], into unsubstituted or mono- or di-substituted carbamoyl-substituted bases of formula I as constituents of acid addition salts. The conditions of the hydrolysis of the cyano intermediates may be so chosen that the reaction is discontinued at the stage of the amide. Especially suitable for that purpose is hydrolysis with one of the acids [PA], as defined above, especially with the stronger of the acids mentioned there having a pK_A of ≤ 5 , at room temperature or with heating, for example to the boiling temperature or up to $150^\circ C$, in the presence of a non-aqueous solvent or of a solvent containing a stoichiometric amount of water.

Using the Graf-Ritter reaction it is also possible to prepare the acid addition salts of N-substituted amides of formula I from nitriles of formula IV. To that end, the nitriles are reacted in the presence of a, preferably relatively strong (pK_A of ≤ 5), acid [PA] with compounds that can form carbenium ions in the acidic medium, that is to say, for example, with olefins, such as propylene, or alcohols, such as ethanol.

The carboxylic acid ester imides are obtained, for example, by acid-catalysed addition of alcohols to the nitriles of formula IV. The acid addition salts of the amides of formula I are obtained from the ester imides in the manner of a Pinner cleavage by thermal decomposition of the ester imide salts with acids [PA] at temperatures above approximately 80°C.

Acid addition salts of bases of formula I, wherein X is a radical $-C(=NH)-NR_6R_7$, with acids [PA] can also be obtained by reacting compounds of formula IV or the acid addition salts thereof with one of the above-mentioned acids [PA] wherein W_3 is the radical $-C(=S)-NH_2$, with S-alkylation, for example with tri-lower alkyloxonium tetrafluoroborate, and subsequent reaction with an ammonia salt of one of the mentioned acids [PA] or with a corresponding acid addition salt of an amine of the formula NHR_6R_7 and one of the mentioned acids [PA].

The reactions indicated under c) can, unless otherwise indicated, be carried out under reaction conditions known per se, in the absence or, generally, in the presence of solvents or diluents, preferably those that are inert towards the reagents used and dissolve those reagents, in the absence or presence of catalysts, condensation agents or neutralising agents, depending on the type of reaction and/or reactants, at reduced, normal or elevated temperature, for example in a temperature range of from approximately -70°C to approximately 190°C, preferably from approximately -20°C to approximately 150°C, for example at room temperature or at the boiling point of the solvent used in the reaction mixture concerned, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under a nitrogen atmosphere.

Process d)

The reaction of any desired acid addition salt of a base of formula I with an acid that does not fall within the definition of [PA] is carried out in accordance with the customary methods for converting salts.

Acids that do not fall within the definition of [PA] include all other protic acids, for example organic acids that do not fall within the definition of [PA], such as formic acid, acetic acid and methylsulfonic acid, or inorganic acids, such as sulfuric acid, hydrohalic acids, such as HF, HCl, HBr or HI, also hydrazoic acid or phosphoric acid. The salts of hydrohalic acids are especially preferred.

The reaction of such salts of acids that do not fall within the definition of [PA] to form the acid addition salt of an acid [PA] is carried out, for example, in solvents, especially in organic solvents, more especially in polar organic solvents, most especially in esters, for example lower alkanoyl-lower alkyl esters, such as acetic acid ethyl ester, in amides, for example N,N-di-lower alkyl-lower alkanoylamides, such as dimethylformamide, in alcohols, for example hydroxy-lower alkanes, such as methanol, ethanol, ethylene glycol or glycerol, or aryl alcohols, such as phenols, for example phenol, or in dimethyl sulfoxide, in the absence or presence of water, preferably in the absence of water. The reaction in alcohols, such as the last-mentioned hydroxy-lower alkanes, is especially preferred.

The reaction can also be carried out by way of the free bases of formula I which are prepared, for example, by converting the acid salt, used as starting material, of a base of formula I with an acid that does not fall within the definition of [PA], with the aid of a base, for example a hydroxy base, such as an alkali hydroxide, for example NaOH or KOH, in aqueous solution in the presence or absence of an organic solvent, such as defined under a), into the free base; the subsequent conversion of the free base is carried out, for example, as described under Process a).

The compounds of formula I and the acids [PA] are used in the mentioned reactions in suitable molar ratios, or the acid [PA] is used in excess. The individual components are used preferably in the molar ratio corresponding to the ratio of the molarity of the base of formula I and the acid [PA] in the acid addition salts according to the invention.

The reaction is carried out at temperatures from the freezing point to the boiling point of the solutions concerned, preferably at from 0 to 50°C, especially from 20 to 40°C, for example at room temperature, in the presence or absence of a protective gas, such as nitrogen or argon.

The resulting salts precipitate, for example, spontaneously, in some cases only after cooling, or they are precipitated by the addition of solvents, especially non-polar solvents, for example ethers, such as diethyl ether, or water and/or are obtained by partial or complete concentration by evaporation.

Additional process measures

Acid addition salts of a base of formula I with an acid [PA] can be converted into acid addition salts of other bases of formula I and/or of other acids [PA], processes known per se being used.

That can be effected, for example, by converting the acid [PA], the base of formula I or both components of the acid addition salt.

For example, the acid component [PA] can be exchanged, either directly by conversion into the free base in the presence of the acid [PA] to be introduced, which may, for example, be used in excess, or indirectly by converting the base of formula I contained in the acid addition salt used as starting material into the free base, for example by reacting the acid addition salt, used as starting material, of the base of formula I with a base, especially a hydroxy base, such as an alkali hydroxide, for example NaOH or KOH, in aqueous solution in the presence or, preferably, absence of an organic solvent, as defined under a), and by subsequent conversion of the free base in accordance with Process a) into a different acid addition salt of formula I, also by dialysis, by means of ion exchangers or by gel chromatography.

Also the base of formula I within an acid addition salt comprising a base of formula I and an acid [PA] can be converted into a different base according to formula I.

For example, the bases of formula I wherein X is a radical $-C(=S)-NH_2$ can be converted by S-alkylation, for example with tri-lower alkylloxonium tetrafluoroborate, and subsequent reaction with an ammonium salt from the acid [PA], contained in the original acid addition salt, and ammonia itself or an amine of the formula NHR_6R_7 into other bases of formula I wherein X is a radical $-C(=NH)-NR_6R_7$, the acid component in the resulting acid addition salts being the same as before.

A base of formula I within acid addition salts with an acid [PA] wherein X is a radical of the formula $-C(=NH)-NH-OH$ can be converted by reaction in the presence of a base, such as triethylamine, and an oxidisable reagent, such as iron pentacarbonyl, in an organic solvent, such as tetrahydrofuran, at elevated temperatures, preferably the boiling point of the reaction mixture, and subsequent reaction of the resulting product with the same acid [PA] into acid addition salts of a base of formula I wherein X is the radical $-C(=NH)-NH_2$,

[PA] being unchanged with respect to the starting salt.

Isomeric mixtures obtainable according to the invention can be separated in a manner known per se into the individual isomers. For example, racemates can be separated by the formation of salts with optically pure salt-forming reagents and separation of the diastereoisomeric mixture so obtainable, for example by means of fractional crystallisation or by chromatography on optically active column materials.

In the process of the present invention, it is preferable to use those starting materials that lead to the acid addition salts described at the beginning as being especially valuable.

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

Pharmaceutical compositions:

The present invention relates also to pharmaceutical compositions that comprise as active ingredient one of the pharmacologically active acid addition salts of a base of formula I with an acid [PA]. Compositions for enteral, especially oral, and parenteral administration are especially preferred. The compositions comprise the active ingredient alone or, preferably, together with at least one pharmaceutically acceptable carrier. The dose of the active ingredient depends on the disorder to be treated and on the species and its age, weight and individual condition, and also on the method of administration.

The pharmaceutical compositions comprise from approximately 0.1 % to approximately 95 % active ingredient, single dosage forms of administration comprising preferably from approximately 1 % to approximately 90 % and non-single dosage forms of administration comprising preferably from approximately 0.1 % to approximately 20 % active ingredient. Unit dose forms, such as dragées, tablets or capsules, comprise from approximately 1 mg to approximately 500 mg of the active ingredient.

The pharmaceutical compositions of the present invention are prepared in a manner known per se, for example by means of conventional mixing, granulating, confectioning,

dissolving or lyophilising processes. For example, pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with one or more solid carriers, optionally granulating a resulting mixture, and processing the mixture or granules, if desired or necessary after the addition of further excipients, to form tablets or dragée cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, cross-linked polyvinylpyrrolidone, alginic acid or a salt thereof, such as sodium alginate.

Further excipients are especially flow-conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

Dragée cores may be provided with suitable enteric or non-enteric coatings, there being used, inter alia, concentrated sugar solutions that may contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, coating solutions in suitable organic solvents or solvent mixtures or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colourings or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Orally administrable pharmaceutical compositions are also dry-filled capsules consisting of gelatin, and also soft sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders and/or glidants, such as talc or magnesium stearate, and optionally stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols, to which stabilisers may also be added.

Further oral forms of administration are, for example, syrups prepared in customary manner that comprise the active ingredient, for example, in suspended form and in a concentration of approximately from 0.1 % to 10 %, preferably approximately 1 % or in a similar concentration that, for example, on measuring off 5 or 10 ml, gives a suitable individual dose. Also suitable are, for example, pulverulent or liquid concentrates for the preparation of shakes, for example in milk. Such concentrates can also be packed in amounts for individual doses.

Suitable rectally administrable pharmaceutical compositions are, for example, suppositories that consist of a combination of the active ingredient and a suppository base. Suitable as suppository base are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.

Suitable for parenteral administration are especially aqueous solutions of an active ingredient in water-soluble form, for example a water-soluble salt, or aqueous injection suspensions containing viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran and optionally stabilisers. The active ingredient, optionally together with excipients, may also be in the form of a lyophilisate and may be dissolved before parenteral administration by the addition of suitable solvents. An isotonic solution for infusion can be prepared especially by the addition of suitable salts, such as NaCl, buffers, such as phosphate buffers, for example with sodium as counter-ion, and/or sugar alcohols, such as mannitol, it being optionally possible for others of the mentioned excipients also to be present.

Solutions, as used, for example, for parenteral administration, may also be used in the form of infusion solutions.

The invention relates also to a method of treating the above-mentioned diseased states, caused especially by a lack of S-adenosylmethionine decarboxylase-inhibition, which respond to treatment with an inhibitor of S-adenosylmethionine decarboxylase. The acid addition salts of the present invention may be administered prophylactically or therapeutically, especially in amounts that are suitable for inhibiting S-adenosylmethionine decarboxylase, and they are used preferably in the form of pharmaceutical compositions. In the case of a body weight of approximately 70 kg, a daily dose, especially one that is effective against the mentioned diseases, of from approximately 1 mg to approximately 1000 mg, preferably approximately from 25 to 100 mg in the case of oral administration or

approximately from 2 to 50 mg in the case of parenteral administration, of an acid addition salt of the present invention is administered, for example to a warm-blooded animal, such as a human, that is in need of such treatment because it is suffering from a protozoa infection or from tumours.

The invention relates also to a pharmaceutical composition that is suitable for administration to a mammal, for example a human, for the prevention or treatment of a disease that responds to treatment with an inhibitor of S-adenosylmethionine decarboxylase, especially a tumour disease or a protozoa infection, which composition comprises an amount of an acid addition salt of formula I, or tautomers thereof, that is effective in the inhibition of S-adenosylmethionine decarboxylase, and a pharmaceutically acceptable carrier.

Starting Compounds:

The protic acids [PA] are known, can be prepared in accordance with processes known per se or are commercially available.

The starting compounds of formula I are prepared in accordance with processes known per se, for example as follows:

(i) a compound of formula II as defined under Process a) is condensed with an amine of formula III as defined under Process a), or

(ii) in a compound of formula IV as defined under Process c), the radical W_3 is converted into the group X,

and, if desired, a resulting compound of formula I is converted into a different compound of formula I, and/or, if desired, a resulting salt is converted into the free compound or into a different salt, and/or, if desired, a resulting free compound of formula I having salt-forming properties is converted into a salt.

In the following more detailed description of Processes i)-ii), each of the symbols A, X, Y, Z, R_1 - R_9 and [PA] occurring in formulae is as defined for acid addition salts of bases of formula I with acids [PA], unless otherwise indicated.

Process (i):

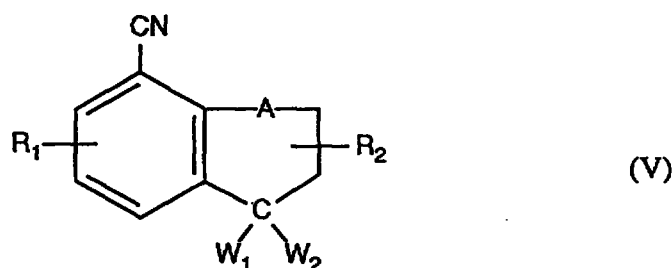
There may be mentioned as functionally modified or protected carbonyl CW_1W_2 , for example: di-lower alkoxymethyl, C_1 - C_2 alkylenedioxymethyl, dihalomethyl, di-lower alkylthiomethyl or C_1 - C_2 alkylenedithiomethyl.

The group CW_1W_2 in the compounds of formula II is preferably in the form of free carbonyl.

The condensation reaction according to Process a) is carried out under the conditions known per se for the formation of hydrazones. It is preferably catalysed by an acid. In compounds of formula II, suitable protected carbonyl groups CW_1W_2 are those that pass over into free carbonyl under the conditions of the condensation reaction.

For the preparation of compounds of formula I wherein R_5 is amino, it is expedient to use the compound of formula III in excess.

The intermediates of formula I wherein Y in the radical X is NH are obtained, for example, by first converting a compound of formula V



into the corresponding thiocarboxamide $[-C(=S)-NH_2]$ by treatment with hydrogen sulfide. The thiocarboxamide can also be obtained by other methods starting from the analogous carboxamide $[-C(=O)-NH_2]$, for example by reaction with Lawesson's reagent [2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane]. The thiocarboxamides are S-alkylated, for example, with lower alkyl iodide or tri-lower alkyloxonium tetrafluoroborate, and thus converted into imino-lower alkylthiol ester hydroiodides $[-C(=NH)S-alkyl \cdot HI]$ or tetrafluoroborates, respectively, which can be readily converted into the desired carboximidamides of formula I by reaction with ammonia or amines of the formula NHR_6R_7 , respectively, [see S. Patai (Ed.), The Chemistry of Amidines and

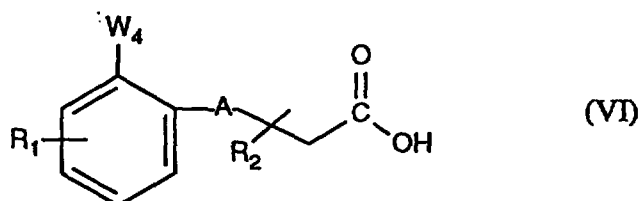
Imidates, Wiley, London etc. 1975, p. 303-304].

The preparation of the carboxamides of formula II from the cyano compounds of formula V takes place analogously to the preparation, described below in connection with Process (ii), of carboxamides of formula I from cyano compounds of formula IV and is described in detail there.

Another possible method of preparing the compounds of formula II is to treat a compound of formula V, wherein the group CW_1W_2 is as defined under formula II, for example with ethanol and hydrochloric acid in, for example, chloroform or diethyl ether, to form the corresponding iminoethyl ester hydrochloride which can be converted into the desired carboximidamide of formula II, for example, by reaction with ammonia or a primary or secondary amine of the formula NHR_6R_7 and, for example, methanol. That method may, however, fail in some cases owing to steric hindrance by the group A or R_1 .

The starting compounds of formula V are known per se or are prepared analogously to the known compounds.

The compounds of formula V can be prepared, for example, by intramolecular Friedel-Crafts acylation of ω -phenyl-lower alkanolic acids of formula VI,

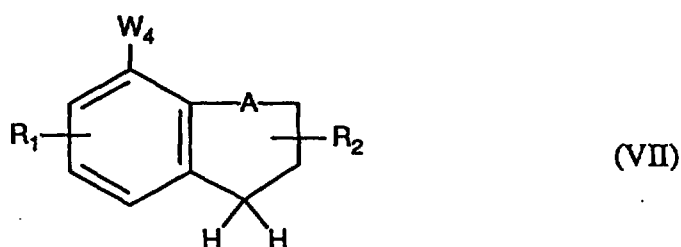


wherein W_4 is cyano or a cyano precursor, or acid derivatives thereof, for example acid chlorides or acid anhydrides. There may be used as catalysts in the case of free acids, for example, polyphosphoric acid, and, in the case of acid chlorides or acid anhydrides, for example $AlCl_3$.

In that reaction it is preferable to use compounds of formula VI wherein W_4 is not cyano but a precursor of cyano, for example halogen, especially bromine, or protected amino, for example acetylamino. After the cyclisation step, the cyano precursors can be converted into cyano in a manner known per se, for example: bromine can be converted by reaction

with copper(I) cyanide, or acetylamino can be converted by removal of the acetyl-protecting group, diazotisation and reaction with copper(I) cyanide.

Compounds of formula V wherein the group CW_1W_2 is carbonyl can also be prepared, for example, by oxidation, for example with chromium trioxide (CrO_3), from the corresponding non-carbonyl compounds of formula VII



wherein W_4 is cyano or a cyano precursor as defined above. If a cyano precursor is used, it is again to be converted, after completion of oxidation, into cyano, for example as indicated above.

Another possible method of preparing the compounds of formula V wherein the group CW_1W_2 is carbonyl is to start from compounds of formula II wherein X is hydrogen and to introduce the cyano group, for example, by a reaction sequence analogous to US Patent 3 956 363, Example 10, which comprises nitration, reduction of the nitro group to amino, diazotisation and reaction with copper(I) cyanide (Sandmeyer reaction).

The preparation of amino-guanidines, -ureas and -thioureas of formula III is known *per se*. Amino(thio)ureas [$\hat{=}$ semi(thio)carbazines] are prepared, for example, in a manner analogous to corresponding simple (thio)ureas, there being used, for example, instead of amines, the corresponding hydrazines of the formula H_2N-NHR_3 , which are reacted, for example, with an isocyanate of the formula $R_4N=C=O$ or $R_5N=C=O$, an isothiocyanate of the formula $R_4N=C=S$ or $R_5N=C=S$, a carbamoyl chloride of the formula $R_4R_5N-COCl$ or a thiocarbamoyl chloride of the formula $R_4R_5N-CSCl$. Also possible is, for example, the reaction of a hydrazine of the formula H_2N-NHR_3 with an acyl isothiocyanate, for example acetyl isothiocyanate, and subsequent acidic hydrolysis.

Aminoguanidines of formula III wherein Z is NR_9 and R_3 , R_4 , R_5 and R_9 are as defined under formula I are known *per se* and can be prepared, for example, from corresponding aminothioureas of formula III by converting the latter by alkylation, for example with an

alkyl p-toluenesulfonate or an alkyl halide, into the corresponding S-alkylisothiuronium salts and reacting those salts with an amine of the formula NHR_4R_5 .

Process (ii):

In the intermediates of formula IV, W_3 is, for example, free or functionally modified carboxy, especially halocarbonyl, cyano, imino-lower alkoxycarbonyl, imino-lower alkylthiolcarbonyl or thiocarbamoyl.

In the preparation of amidines of formula II ($\text{Y} \hat{=} \text{NR}_8$), the group W_3 in a compound of formula IV may be, for example: an acid addition salt of an imino-lower alkyl ester ($\hat{=}$ imino-lower alkyl ether) or imino-lower alkylthiol ester, for example $-\text{C}(=\text{NH})-\text{OC}_2\text{H}_5 \cdot \text{HCl}$ or $-\text{C}(=\text{NH})-\text{SC}_2\text{H}_5 \cdot \text{HI}$, respectively, or cyano.

By reacting an imino-lower alkyl ester of formula IV (in the form of a salt) with ammonia or primary or secondary amines, the unsubstituted or mono- or di-substituted amidines, respectively, of formula I are obtained. Cyano compounds of formula IV can be converted, for example, by reaction with an alkali metal amide, for example KNH_2 , or by reaction with a primary or secondary (di-)lower alkylammonium halide, for example

$\oplus\text{NH}_3\text{CH}_3 \text{ Cl}^\ominus$, into an unsubstituted or mono- or di-substituted amidine of formula I.

In the preparation of carbamoyl compounds of formula I ($\text{Y} \hat{=} \text{O}$), the group W_3 in a compound of formula IV may be, for example: carboxy, halocarbonyl (for example $-\text{COCl}$), lower alkoxycarbonyl or cyano. The formation of unsubstituted or mono- or di-substituted carbamoyl compounds of formula I from corresponding intermediates of formula IV, wherein W_3 is carboxy, halocarbonyl or lower alkoxycarbonyl, by reaction with ammonia or primary or secondary amines, respectively, is known per se. Intermediates of formula IV wherein W_3 is cyano can be converted, for example, by partial hydrolysis, in the manner of a Graf-Ritter reaction, or by way of carboxylic acid ester imide salts, into unsubstituted or mono- or di-substituted carbamoyl compounds of formula I. In the hydrolysis of the cyano intermediates, the conditions may be so chosen that the reaction is discontinued at the amide stage. Suitable for that purpose is especially hydrolysis with acids, for example with 80 % sulfuric acid (with heating), polyphosphoric acid (at 110-150°C), hydrobromic acid/glacial acetic acid (at room temperature, in the presence of formic acid or without further solvent) or HCl gas in ethereal solution

followed by the addition of water or aqueous hydrochloric acid, or reaction with boron halides.

Using the Graf-Ritter reaction it is also possible to produce N-substituted amides from nitriles of formula IV. To that end, the nitriles are reacted in the presence of a strong acid, especially 85-90 % sulfuric acid, or also polyphosphoric acid, formic acid, boron trifluoride or other Lewis acids, with the exception of aluminium chloride, with compounds that can form carbenium ions in the acidic medium, that is to say, for example, with olefins, such as propylene, or alcohols, such as ethanol.

The carboxylic acid ester imides are obtained, for example, by acid-catalysed addition of alcohols to the nitriles of formula IV. The amides are obtained from the ester imides in the manner of a Pinner cleavage by thermal decomposition of the ester imide salts at temperatures above approximately 80°C.

Compounds of formula IV wherein W_3 is cyano can be prepared, for example, by reacting a compound of formula V with a compound of formula III in accordance with Process ii). The other compounds of formula IV wherein W_3 is free carboxy or carboxy functionally modified in another manner can be prepared from compounds of formula IV wherein W_3 is cyano in a manner known per se or as described above.

Compounds of formula I wherein X is a radical $-C(=NH)-NR_6R_7$ can also be obtained by reacting compounds of formula IV wherein W_3 is a radical $-C(=S)-NH_2$, with S-alkylation, for example with tri-lower alkyloxonium tetrafluoroborate, and by subsequent reaction with ammonia or an amine of the formula NHR_6R_7 or a corresponding ammonium salt, for example the chloride.

Compounds of formula I can be converted into different compounds of formula I.

For example, compounds of formula I wherein X is a radical $-C(=S)-NH_2$ can be converted by S-alkylation, for example with tri-lower alkyloxonium tetrafluoroborate, and subsequent reaction with ammonia or an amine of the formula NHR_6R_7 , or especially with a corresponding ammonium salt thereof, into compounds of formula I wherein X is a radical $-C(=NH)-NR_6R_7$.

Compounds of formula I wherein X is an N-hydroxyamidino radical $-C(=NR_8)-NHOH$

can be converted, for example, by reaction with iron pentacarbonyl $[\text{Fe}(\text{CO})_5]$ into different compounds of formula I wherein X is an analogous amidino radical $-\text{C}(=\text{NR}_8)-\text{NH}_2$ (see, for example, J. Chem. Soc. Chem. Commun. 1975, 761).

Free compounds of formula I that have salt-forming properties and that are obtainable in accordance with the process can be converted in a manner known *per se* into their salts: for example, compounds having basic properties can be converted by treatment with acids, either with the protic acids [PA] themselves or preferably with other protic acids, for example organic acids that do not fall within the definition of [PA], such as formic acid, acetic acid and methylsulfonic acid, or inorganic acids, such as sulfuric acid, hydrohalic acids, such as HF, HCl, HBr or HI, also hydrazoic acid or phosphoric acid. Hydrohalic acids are especially preferred. The reaction takes place, for example, analogously to Process a) for the preparation of acid addition salts of bases of formula I with acids [PA].

The acid addition salts of bases of formula I, especially those with protic acids other than [PA], can also be converted into the free compounds. That can be effected, for example, by conversion into the free base, for example by reaction of the salt of a compound of formula I used as starting material with a hydroxy base, such as an alkali metal hydroxide, for example NaOH or KOH, in aqueous solution in the presence or, preferably, absence of an organic solvent, as defined under a), also by dialysis, using ion exchangers or by gel chromatography.

The preparation of starting compounds of formulae II, III and IV is carried out as indicated in the more detailed description of Processes i) and ii).

Owing to the close relationship between the compounds of formulae I, II, III, IV and also V, VI and VII in free form and, insofar as the mentioned compounds contain salt-forming groups, in the form of salts, hereinbefore and hereinafter the free compounds and their salts are also to be understood as being the corresponding salts, for example acid addition salts or also salts with bases, and the free compounds, respectively, where appropriate and where the context so allows.

The preparation of salts, for example of the compounds of formulae II, III and IV having salt-forming groups, is carried out analogously to the preparation of salts of the bases of formula I (Process a)).

The compounds, including their salts, can also be obtained in the form of hydrates, or their crystals may include, for example, the solvent used for crystallisation.

Isomeric mixtures obtainable in accordance with Process i) or ii) can be separated in a manner known per se into the individual isomers. For example, racemates can be separated by the formation of salts with optically pure salt-forming reagents and separation of the diastereoisomeric mixture so obtainable, for example by means of fractional crystallisation.

The above reactions given under Process i) or ii) can be carried out under reaction conditions known per se, in the absence or, generally, presence of solvents or diluents, preferably those that are inert towards the reagents used and dissolve those reagents, in the absence or presence of catalysts, condensation agents or neutralising agents, depending on the type of reaction and/or the reactants at reduced, normal or elevated temperature, for example in a temperature range of from approximately -70°C to approximately 190°C, preferably from approximately -20°C to approximately 150°C, for example at room temperature or at the boiling point of the solvent used in the reaction mixture concerned, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under a nitrogen atmosphere.

The preparation of some starting compounds of formula I is described below for purely illustrative purposes. Temperatures are given in degrees Celsius. The following abbreviations are used: abs. = absolute (anhydrous); D₂O = deuterised water; DMF = N,N-dimethylformamide; DMSO-d₆ = perdeuterised dimethyl sulfoxide; ether = diethyl ether; ethyl acetate = acetic acid ethyl ester; IR = infrared spectroscopy; m.p. = melting point; THF = tetrahydrofuran; MS (FAB) = mass spectrum ("Fast Atom Bombardment").

1) Starting Compound A:

4-Amino-1-indanone-2'-amidinohydrazone dihydrochloride

A solution of 3.8 g (27.9 mmol) of aminoguanidine hydrogen carbonate in 200 ml of water and 14.7 ml of 2N hydrochloric acid is heated to 60° and, with stirring, a solution of 5.85 g (27.8 mmol) of 4-amidino-1-indanone hydrochloride in 200 ml of methanol is added over the course of 30 min. The reaction mixture is boiled under reflux for 24 h and, after cooling, is concentrated to dryness by evaporation. The residue is suspended in 50 ml of ethanol, filtered, washed with ethanol and ether and dried to yield the title compound which contains 1 mol of water of crystallisation, m.p. >330°; MS(FAB): (M+H)⁺=231;

¹H-NMR (D₂O): δ =8.08 (d,1H); 7.75 (d,1H); 7.58 (t,1H); 3.35 (m,2H); 2.96 (m,2H).

The precursors are prepared as follows:

(a) 4-Thiocarbamoyl-1-indanone

A solution of 12.1 g (77 mmol) of 4-cyano-1-indanone [Coll. Czechoslov. Chem. Commun. **43**, 3227 (1978)] in 220 ml of pyridine and 10.6 ml (77 mmol) of triethylamine is saturated for 3 h at 40° with hydrogen sulfide and stirred for a further 16 h at that same temperature. After cooling, the reaction mixture is concentrated to dryness by evaporation and 300 ml of water are added to the residue. The yellow product which crystallises out is filtered off with suction, washed with water, dried and recrystallised from ethyl acetate to yield the title compound, m.p. 197° (decomposition).

(b) 4-Amidino-1-indanone hydrochloride

10.8 g (54 mmol) of triethyloxonium tetrafluoroborate are added at room temperature and under argon to a solution of 9.8 g (51.3 mmol) of 4-thiocarbamoyl-1-indanone in 500 ml of abs. methylene chloride. After 16 h, a mixture of 4.2 g of potassium carbonate and 4.2 ml of water is added to the reaction solution. The reaction mixture is then stirred briefly and filtered and the filtrate is washed with water. The organic phase is dried over magnesium sulfate, filtered and concentrated by evaporation. The resulting crude ethylthioimino ether is dissolved in 160 ml of abs. ethanol; 3.3 g (60 mmol) of ammonium chloride are added and the reaction mixture is heated under reflux for 20 h. After cooling, it is concentrated to dryness by evaporation and the title compound is purified by chromatography on 1000 ml of Amberlite[®] ER-180 resin (water as eluant) and recrystallised from ethanol/ether, m.p. 215-218° (decomposition).

2) **Starting Compound B:**

4-Amidino-1-indanone-2'-(N-hydroxyamidino)-hydrazone dihydrochloride

A solution of 394 mg (1.5 mmol) of 1-amino-3-hydroxyguanidine-4-toluenesulfonate in 6 ml of water and 0.75 ml (1.5 mmol) of 2N hydrochloric acid is added to a solution of 316 mg (1.5 mmol) of 4-amidino-1-indanone hydrochloride (see precursor 1 b) under Starting Compound A) in 7 ml of methanol and the reaction mixture is heated for 2 h under reflux and stirred for 16 h at room temperature. It is then concentrated by evaporation and the residue is purified by chromatography (Pharmacia column SR-28-100) on silica gel OPTI-UP C₁₂[®] (water as eluant, 5 ml-fractions, rate of flow 27.5 ml/h). The contents of fractions 58-78 are combined and concentrated by evaporation and the residue

is crystallised from ethanol to yield the title compound in the form of wax-like crystals, MS (FAB): $(M+H)^+ = 247$; $^1\text{H-NMR}$ (D_2O): $\delta=8.06$ (d,1H); 7.73 (d,1H); 7.58 (t,1H); 3.36 (m,2H); 2.98 (m,2H).

3) Starting Compound C:

5-Amidino-1-tetralone-2'-amidinohydrazone dihydrochloride

0.675 g (3 mmol) of 5-amidino-1-tetralone hydrochloride is added to a solution of 0.41 g (3 mmol) of aminoguanidine hydrogen carbonate in 31.5 ml of 0.1N hydrochloric acid and the batch is heated for 72 h under reflux. After cooling, it is concentrated to dryness by evaporation and the title compound is recrystallised from methanol/ether, m.p. $>250^\circ$; MS (FAB): $(M+H)^+ = 245$; $^1\text{H-NMR}$ (DMSO-d_6): $\delta=11.3$ (s, 1H); 9.5 (m,4H); 8.65 (d,1H); 7.92 (m,3H); 7.52 (d,1H); 7.46 (t,1H); 2.7-2.85 (m,4H); 1.9 (m,4H).

The precursors are prepared as follows:

(a) 5-Cyano-1-tetralone

0.41 g (4.5 mmol) of copper(I) cyanide is added to a solution of 1.0 g (4.4 mmol) of 5-bromo-1-tetralone [J. Org. Chem. **49**, 4226 (1984)] in 1.3 ml of DMF and the reaction mixture is stirred for 6 h at 160° . It is then cooled to 80° and a solution of 1.6 g of iron(III) chloride hexahydrate in 2.5 ml of water and 0.44 ml of concentrated hydrochloric acid is added. The reaction mixture is then stirred for 45 minutes, cooled, diluted with water and extracted with toluene. The organic phase is washed with water, dried over magnesium sulfate, filtered and concentrated by evaporation to yield the title compound in the form of yellow-orange crystals, IR (CH_2Cl_2): 2220, 1690 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3): $\delta = 8.26$ (q,1H); 7.81 (q,1H); 7.43 (t,1H); 3.21 (t,2H); 2.72 (t,2H); 2.23 (m,2H).

(b) 5-Thiocarbamoyl-1-tetralone

Analogously to the process described for Starting Compound A under 1 a), 10.6 g (62 mmol) of 5-cyano-1-tetralone in 200 ml of pyridine and 8.6 ml of triethylamine are treated with hydrogen sulfide and worked up to yield the title compound in the form of yellow crystals, m.p. $200-205^\circ$.

(c) 5-Amidino-1-tetralone hydrochloride

Analogously to the process described for Starting Compound A under 1 b), 8.6 g (42 mmol) of 5-thiocarbamoyl-1-tetralone are treated with 8.8 g (44 mmol) of triethyl-oxonium tetrafluoroborate and 2.6 g (49 mmol) of ammonium chloride to yield the title

compound in the form of pale pink crystals, MS (FAB): $(M+H)^+ = 189$.

4) Starting Compound D:

4-Thiocarbamoyl-1-indanone-2'-amidinohydrazone hydrochloride

1.36 g (10 mmol) of aminoguanidine hydrogen carbonate and 10 ml of 2N hydrochloric acid are added to a solution of 1.9 g (10 mmol) of 4-thiocarbamoyl-1-indanone (prepared as described under Starting Compound A, 1 a)) in 50 ml of ethanol and the reaction mixture is heated under reflux for 24 h. After cooling, it is concentrated to dryness by evaporation to yield the title compound.

5) Starting Compound E:

4-(N-Hydroxyamidino)-1-indanone-2'-amidinohydrazone dihydrochloride

0.2 g (3 mmol) of hydroxylamine hydrochloride is suspended in 1 ml of abs. ethanol, and 2 ml of a 1N sodium ethoxide solution in ethanol are added. The mixture is stirred for 1 h and filtered. A solution of 0.26 g (1 mmol) of 4-cyano-1-indanone-2'-amidinohydrazone hydrochloride (see below under 18 a)) in 2 ml of water is added to the filtrate, and the reaction mixture is heated under reflux for 6 h. After cooling, it is concentrated by evaporation and the title compound is crystallised from water, m.p. $>250^\circ$; $^1\text{H-NMR}$ ($\text{DMSO-d}_6 + \text{D}_2\text{O}$): $\delta = 8.12$ (m, 1H); 7.55 (m, 2H); 3.22 (m, 2H); 2.83 (m, 2H).

6) Starting Compound F:

4-Amidino-2-methyl-1-indanone-2'-amidinohydrazone dihydrochloride

A solution of 1.0 g (5.0 mmol) of 4-amidino-2-methyl-1-indanone hydrochloride and 0.68 g (5.0 mmol) of aminoguanidine hydrogen carbonate in 10 ml of 0.5N hydrochloric acid is stirred for 120 h at 25° . The product which crystallises out is filtered off with suction, washed with a small amount of water and dried to yield the title compound, m.p. $>250^\circ$; MS (FAB): $(M + H)^+ = 245$; $^1\text{H-NMR}$ (D_2O): $\delta = 7.95$ (d, 1H); 7.66 (d, 1H); 7.48 (t, 1H); 3.45 (m, 2H); 2.85 (d, 1H); 1.12 (d, 3H).

The precursors are prepared as follows:

(a) 4-Thiocarbamoyl-2-methyl-1-indanone

Analogously to the process described for Starting Compound A under 1 a), 11.1 g (65 mmol) of 4-cyano-2-methyl-1-indanone [see US Patent 3 956 363] in 200 ml of pyridine and 9.7 ml of triethylamine are treated with hydrogen sulfide and worked up to yield the title compound in the form of yellow crystals, m.p. $195-198^\circ$ (decomposition);

$^1\text{H-NMR}$ ($\text{DMSO-}d_6$): δ = 9.61 (s,1H); 7.71 (m,2H); 7.48 (m,1H); 3.48 (m,1H); 2.81 (m,2H); 1.23 (s,3H); 1.19 (s,3H).

(b) 4-Amidino-2-methyl-1-indanone hydrochloride

Analogously to the process described for Starting Compound A under 1 b), 10.2 g (50 mmol) of 4-thiocarbamoyl-2-methyl-1-indanone are treated with 11.0 g (55 mmol) of triethyloxonium tetrafluoroborate and 3.2 g (60 mmol) of ammonium chloride to yield the title compound in the form of pink crystals, which is further reacted directly.

7) Starting Compound G:

5-Amidino-6-methoxy-1-tetralone-2'-amidinohydrazone dihydrochloride

Analogously to Starting Compound A under 1) the title compound is prepared starting from 5-cyano-6-methoxy-1-tetralone [Chem. Pharm. Bull. 31, 2329 (1983)].

8) Starting Compound H:

4-Amidino-6-methoxy-7-methyl-1-indanone-2'-amidinohydrazone dihydrochloride

Analogously to Starting Compound C, the title compound is prepared starting from 4-bromo-6-methoxy-7-methyl-1-indanone (J. Chem. Soc. Perkin Trans. 1 1974, 1911).

9) Starting Compound I:

4-Amidino-6,7-dimethyl-1-indanone-2'-amidinohydrazone dihydrochloride

Analogously to Starting Compound A under 1), the title compound is prepared starting from 4-amidino-6,7-dimethyl-1-indanone hydrochloride, m.p. $>240^\circ\text{C}$; MS (FAB): $(\text{M}+\text{H})^{\oplus} = 259$; $^1\text{H-NMR}$ (D_2O): δ = 7.43 (s,1H); 3.12 (m,2H); 2.75 (m,2H); 2.43 (s,3H); 2.24 (s,3H).

The precursors are prepared as follows:

(a) 4-Cyano-6,7-dimethyl-1-indanone

A mixture of 17.8 g (74.5 mmol) of 4-bromo-6,7-dimethyl-1-indanone [J. Het. Chem. 24, 677 (1987)] and 7.3 g (82 mmol) of copper(I) cyanide in 18 ml of DMF is stirred for 6 h at 170° . The reaction mixture is then cooled to 100° and 200 ml of toluene and a solution of 31.2 g of iron(III) chloride hexahydrate in 47 ml of water and 8.2 ml of concentrated hydrochloric acid are added in succession. The reaction mixture is stirred for 20 min at 70° , cooled and diluted with toluene and water. The organic phase is separated off, washed with water, a semi-saturated sodium hydrogen carbonate solution and again with water,

dried and concentrated by evaporation. The residue is crystallised from ethyl acetate and ether and corresponds to the title compound. Beige crystals are obtained of m.p. 160-163°; IR (CH₂Cl₂): 2220, 1710 cm⁻¹.

(b) 4-Thiocarbamoyl-6,7-dimethyl-1-indanone

Analogously to the process described for Starting Compound A under 1 a), 10 g (54.1 mmol) of 4-cyano-6,7-dimethyl-1-indanone in 200 ml of pyridine and 7.5 ml of triethylamine are treated with hydrogen sulfide and worked up to yield the title compound in the form of yellow crystals, m.p. 207-208°; ¹H-NMR (DMSO-d₆): δ = 10.03 (s,1H); 9.49 (s,1H); 7.49 (s,1H); 3.12 (m,2H); 2.61 (m,2H); 2.54 (s,3H); 2.29 (s,3H).

(c) 4-Amidino-6,7-dimethyl-1-indanone hydrochloride

Analogously to the process described for Starting Compound A under 1 b), 4.4 g (20 mmol) of 4-thiocarbamoyl-6,7-dimethyl-1-indanone are treated with 4.26 g (21 mmol) of triethyloxonium tetrafluoroborate and 1.2 g (24 mmol) of ammonium chloride to yield the title compound in the form of beige crystals.

10) Starting Compound J:

4-Amidino-7-hydroxy-3-methyl-1-indanone-2'-amidinohydrazone dihydrochloride

Analogously to Starting Compound C, the title compound is prepared starting from 4-bromo-7-hydroxy-3-methyl-1-indanone [Indian J. Chem. Sect. B 24B, 1061 (1985)].

11) Starting Compound K:

4-(Methylamidino)-1-indanone-2'-amidinohydrazone dihydrochloride

Analogously to the process described for Starting Compound A under 1 b), 4-thiocarbamoyl-1-indanone-2'-amidinohydrazone hydrochloride (Starting Compound D) is reacted with triethyloxonium tetrafluoroborate and methylammonium chloride to yield the title compound.

12) Starting Compound L:

4-Amidino-6,7-dimethoxy-1-indanone-2'-amidinohydrazone dihydrochloride

0.73 g (2.7 mmol) of 4-amidino-6,7-dimethoxy-1-indanone hydrochloride is added to a solution of 0.4 g (3 mmol) of aminoguanidine hydrogen carbonate in 6 ml of 0.5N hydrochloric acid and the batch is stirred for 24 h at 50°. After cooling, the product which crystallises out is filtered off with suction, washed with a small amount of water and dried to yield the title compound, m.p. >220°; MS (FAB): (M + H)⁺ = 291; ¹H-NMR (D₂O):

$\delta = 7.45$ (s,1H); 3.97 (s,6H); 3.27 (m,2H); 2.98 (m,2H).

The precursors are prepared as follows:

(a) 4-Cyano-6,7-dimethoxy-1-indanone

A mixture of 6.57 g (24.2 mmol) of 4-bromo-6,7-dimethoxy-1-indanone [Can. J. Chem. 57, 1603 (1979)] and 2.5 g (28 mmol) of copper(I) cyanide in 7 ml of DMF is stirred for 5.75 h at 170°. The reaction mixture is then cooled to 100° and 70 ml of toluene and a solution of 9.7 g (36 mmol) of iron(III) chloride hexahydrate in 15.6 ml of water and 3.5 ml of concentrated hydrochloric acid are added in succession. The reaction mixture is then stirred for 30 min at 80°, cooled and diluted with toluene and water. The organic phase is separated off, washed with water, a semi-saturated sodium hydrogen carbonate solution and again with water, dried and concentrated by evaporation. The residue is distilled at 150-160°/0.1 mbar in a bulb tube distilling apparatus and corresponds to the title compound, m.p. 150°; IR (CH₂Cl₂): 2220, 1710 cm⁻¹; ¹H-NMR (CDCl₃): $\delta = 7.33$ (s,1H); 4.12 (s,3H); 3.90 (s,3H); 3.19 (m,2H); 2.76 (m,2H).

(b) 4-Thiocarbamoyl-6,7-dimethoxy-1-indanone

Analogously to the process described for Starting Compound A under 1 a), 3.7 g (17 mmol) of 4-cyano-6,7-dimethoxy-1-indanone in 100 ml of pyridine and 2.4 ml of triethylamine are treated with hydrogen sulfide and worked up to yield the title compound in the form of pale yellow crystals, m.p. 196-199°; ¹H-NMR (DMSO-d₆): $\delta = 10.06$ (s,1H); 9.50 (s,1H); 7.41 (s,1H); 3.84 (s,6H); 3.13 (m,2H); 2.63 (m,2H).

(c) 4-Amidino-6,7-dimethoxy-1-indanone hydrochloride

Analogously to the process described for Starting Compound A under 1 b), 3.3 g (13 mmol) of 4-thiocarbamoyl-6,7-dimethoxy-1-indanone are treated with 2.8 g (14 mmol) of triethylxonium tetrafluoroborate and 0.8 g (15 mmol) of ammonium chloride to yield the title compound in the form of beige crystals, m.p. 188° (with decomposition); ¹H-NMR (DMSO-d₆): $\delta = 9.4$ (s,3H); 7.63 (s,1H); 3.92 (s,3H); 3.89 (s,3H); 3.18 (m,2H); 2.68 (m,2H).

13) Starting Compound M:

4-Amidino-6-methyl-1-indanone-2'-amidinohydrazone dihydrochloride

Analogously to Starting Compound C, the title compound is prepared starting from 4-bromo-6-methyl-1-indanone (Bull. Soc. Chim. France 1964, 3103), m.p. > 250°C;

MS (FAB): $(M + H)^+ = 245$; $^1\text{H-NMR}$ (D_2O): $\delta = 7.89$ (s, 1H); 7.62 (s, 1H); 3.34 (t, 2H); 2.96 (t, 2H); 2.45 (s, 3H).

14) Starting Compound N:

4-Amidino-3-methyl-1-indanone-2'-amidinohydrazone dihydrochloride

300 mg (2.3 mmol) of aminoguanidine hydrogen carbonate in 4 ml of 0.5N hydrochloric acid are added to a solution of 300 mg (1.3 mmol) of 4-amidino-3-methyl-1-indanone hydrochloride in 6 ml of water and the reaction mixture is stirred for 24 h at 80°. It is then cooled and concentrated by evaporation and the residue is purified by chromatography on 180 ml of Amberlite® ER-180 resin using water as eluant. The title compound is recrystallised from methanol/ether, m.p. >250°; $R_f = 0.18$ (silica gel, methylene chloride/-methanol/concentrated ammonia 5:3:1); MS (FAB): $(M + H)^+ = 245$; $^1\text{H-NMR}$ (D_2O): $\delta = 7.97$ (d, 1H); 7.64 (d, 1H); 7.49 (t, 1H); 3.86 (m, 1H); 3.17 (q, 1H); 2.49 (d, 1H); 1.24 (d, 3H).

The precursors are prepared as follows:

(a) 4-Cyano-3-methyl-1-indanone

A mixture of 2.6 g (11.5 mmol) of 4-bromo-3-methyl-1-indanone [J. Org. Chem. 22, 1019 (1957)] and 1.14 g (12.7 mmol) of copper(I) cyanide in 2.5 ml of DMF is stirred for 6 h at 170°. The reaction mixture is then cooled to 100° and 50 ml of toluene and a solution of 4.5 g (16.5 mmol) of iron(III) chloride hexahydrate in 7 ml of water and 1.7 ml of concentrated hydrochloric acid are added in succession. The reaction mixture is then stirred for 20 min at 70°, cooled and diluted with toluene and water. The organic phase is separated off, washed with water, a semi-saturated sodium hydrogen carbonate solution and again with water, dried and concentrated by evaporation. The residue is distilled at 100-120°/-0.05 mbar in a bulb tube distilling apparatus and corresponds to the title compound, m.p. 109-111°; IR (CH_2Cl_2): 2220, 1710 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3): $\delta = 7.92$ (m, 2H); 7.52 (t, 1H); 3.73 (m, 1H); 3.03 (q, 1H); 2.40 (q, 1H); 1.55 (d, 3H).

(b) 4-Thiocarbamoyl-3-methyl-1-indanone

Analogously to the process described for Starting Compound A under 1 a), 1.45 g (8.47 mmol) of 4-cyano-3-methyl-1-indanone in 25 ml of pyridine and 1.2 ml of triethylamine are treated with hydrogen sulfide and worked up to yield the title compound in the form of pale yellow crystals, m.p. 198-200°; $^1\text{H-NMR}$ (DMSO-d_6): $\delta = 9.78$ (s, 1H); 7.65 (m, 2H); 7.46 (m, 1H); 3.98 (m, 1H); 2.95 (q, 1H); 2.26 (q, 1H); 1.25 (d, 3H).

(c) 4-Amidino-3-methyl-1-indanone hydrochloride

Analogously to the process described for Starting Compound A under 1 b), 0.96 g (4.68 mmol) of 4-thiocarbamoyl-3-methyl-1-indanone is treated with 1.0 g (4.93 mmol) of triethyloxonium tetrafluoroborate and 0.3 g (6 mmol) of ammonium chloride to yield the title compound in the form of beige crystals, $^1\text{H-NMR}$ (DMSO-d_6): $\delta = 9.59$ (s, 4H); 7.65 (m, 2H); 7.46 (m, 1H); 3.98 (m, 1H); 2.95 (q, 1H); 2.26 (q, 1H); 1.25 (d, 3H).

15) Starting Compound O:

4-Amidino-2-ethyl-1-indanone-2'-amidinohydrazone dihydrochloride

3-(2-bromophenyl)-2-ethylpropionic acid (German Patent 2 733 868) is cyclised at elevated temperature with polyphosphoric acid to form the corresponding 1-indanone which is converted into the title compound analogously to the process described for Starting Compound C. M.p. $>250^\circ\text{C}$; MS (FAB): $(\text{M}+\text{H})^+ = 259$; $^1\text{H-NMR}$ (D_2O): $\delta = 7.96$ (d, 1H); 7.65 (d, 1H); 7.48 (t, 1H); 2.95-3.48 (m, 3H); 1.3-1.8 (m, 2H); 0.83 (t, 3H).

16) Starting Compound P:

4-Amidino-2-n-butyl-1-indanone-2'-amidinohydrazone dihydrochloride

3-(2-bromophenyl)-2-n-butylpropionic acid (German Patent 2 733 868) is cyclised at elevated temperature with polyphosphoric acid to form the corresponding 1-indanone which is converted into the title compound analogously to the process described for Starting Compound C.

Further processes for the preparation of Starting Compound A) (4-amidino-1-indanone-2'-amidinohydrazone dihydrochloride):

17) Analogously to the process described for Starting Compound A under 1 b), 4-thiocarbamoyl-1-indanone-2'-amidinohydrazone hydrochloride (Starting Compound D) is reacted with triethyloxonium tetrafluoroborate and ammonium chloride to yield Starting Compound A, m.p. $>330^\circ$; MS (FAB): $(\text{M}+\text{H})^+ = 231$; $^1\text{H-NMR}$ (D_2O): $\delta = 8.08$ (d, 1H); 7.75 (d, 1H); 7.58 (t, 1H); 3.35 (m, 2H); 2.96 (m, 2H).

18) 1.2 ml of a 1N sodium methoxide solution in methanol are added to a solution of 0.26 g (1 mmol) of 4-cyano-1-indanone-2'-amidinohydrazone hydrochloride in 5 ml of abs. methanol and the reaction mixture is heated under reflux for 16 h. After cooling, 0.16 g (3 mmol) of solid ammonium chloride is added to the reaction mixture and stirring

is effected for 1 h at 60°. The reaction mixture is then concentrated by evaporation and the residue is crystallised from dilute ethanol to yield Starting Compound A, m.p. >330°.

The precursor is prepared as follows:

(a) 4-Cyano-1-indanone-2'-amidinohydrazone hydrochloride

Analogously to the process mentioned for Starting Compound A under 1), 314 mg (2 mmol) of 4-cyano-1-indanone are dissolved in 20 ml of methanol. A solution of 272 mg (2 mmol) of aminoguanidine hydrogen carbonate in 9 ml of water and 1 ml of 2N hydrochloric acid is added and the reaction mixture is stirred under reflux for 4 days. After cooling, it is concentrated to dryness by evaporation and the residue is crystallised from water to yield the title compound, m.p. >230°; ¹H-NMR (DMSO-d₆/D₂O): δ=8.16 (d,1H); 7.9 (d,1H); 7.55 (t,1H); 3.28 (m,2H); 2.9 (m,2H); IR (Nujol (paraffin)): 2190 cm⁻¹ (CN).

19) 9.45 g (44.9 mmol) of 4-amidino-1-indanone hydrochloride (see under Starting Compound A, 1 b)) are added to a solution of 6.12 g (45 mmol) of aminoguanidine hydrogen carbonate in 100 ml of water and 46 ml of 1N hydrochloric acid and the batch is stirred for 24 h at 24°. The product which crystallises out is filtered off with suction, washed with a small amount of water and recrystallised from 300 ml of water to yield Starting Compound A, which contains 1 mol of water of crystallisation, m.p. >330°; MS (FAB): (M + H)⁺ = 231; ¹H-NMR (D₂O): δ = 8.08 (d,1H); 7.75 (d,1H); 7.58 (t,1H); 3.35 (m,2H); 2.96 (m,2H).

20) A mixture of 0.32 g (1 mmol) of 4-(N-hydroxyamidino)-1-indanone-2'-amidinohydrazone dihydrochloride (Starting Compound E), 0.36 ml (2 mmol) of triethylamine and 0.2 g (1 mmol) of iron pentacarbonyl in 10 ml of abs. THF is boiled under reflux for 16 h. The reaction mixture is then concentrated by evaporation and the residue is crystallised from dilute hydrochloric acid to yield Starting Compound A, m.p. >330°.

21) Starting Compound Q:

4-Amidino-2-propylindanone-1-amidinohydrazone dihydrochloride

Analogously to Starting Compound O, the title compound is prepared starting from 2-bromobenzyl bromide and malonic acid diethyl ester, m.p. >250°C; MS (FAB): (M+H)⁺ = 273; ¹H-NMR (D₂O): δ=7.98 (d,1H); 7.67 (m,1H); 7.49 (t,1H); 3.44 (m,2H); 3.01 (m,1H); 1.1-1.75 (m,4H); 0.81 (t,3H).

Examples

The following Examples serve to illustrate the invention but do not limit the scope thereof in any way.

Temperatures are given in degrees Celsius (°C). If no temperature is indicated, the reaction concerned is carried out at room temperature. If concentration by evaporation is carried out, a rotary evaporator is used unless otherwise indicated.

The values for proton nuclear magnetic resonance spectroscopy are given in ppm ("parts per million") based on tetramethylsilane ($\delta = 0$) as the internal standard. d = doublet, s = singlet, t = triplet, m = multiplet.

In the case of elemental analyses, the empirical formula, the molecular weight, and calculated and found analysis values are indicated.

The shortened forms and abbreviations used have the following meanings:

anal.	elemental analysis
calc.	calculated
D ₂ O	dideuterium oxide
DMSO-d ₆	completely deuterised dimethyl sulfoxide
¹ H-NMR	proton nuclear magnetic resonance spectroscopy
m.p.	melting point
decomp.	with decomposition

Example 1: 4-Amidino-1-indanone-2'-amidinohydrazone dicyclamate

A solution of 717 mg (4 mmol) of N-cyclohexylsulfamic acid in 20 ml of methanol is added to a solution of 460 mg (2 mmol) of 4-amidinoindanone-1-amidinohydrazone in 80 ml of methanol and the batch is concentrated to dryness by evaporation. The residue is dissolved in ethanol and crystallised by the addition of diethyl ether to yield the title compound, m.p. 210° (decomp.); ¹H-NMR (D₂O): δ 7.97 (d,1H); 7.64 (d,1H); 7.47 (t,1H); 3.25 (m,2H); 2.9 (m,4H); 1-2 (m,20H); anal. for C₂₃H₄₀N₈O₆S₂ (588.75): calc. 46.92% C, 6.85% H, 19.03% N, found 46.5% C, 6.9% H, 19.0% N.

The starting material is prepared as follows:

a) 4-Amidino-1-indanone-2'-amidinohydrazone

9.63 g (30 mmol) of 4-amidino-1-indanone-2'-amidinohydrazone dihydrochloride (Starting Compound A, prepared in accordance with one of the processes described under "Starting Compounds", for example in accordance with 16)) are dissolved in 900 ml of distilled water heated to 70-80°C and cooled to 10°C. 30 ml of 2N sodium hydroxide solution are added dropwise to the resulting solution with stirring. The product which separates out is filtered off with suction, washed with a small amount of ice-water and dried to yield the title compound, m.p. 250° (decomp.).

Example 2: 4-Amidino-1-indanone-2'-amidinohydrazone dioctanoate

631 µl (4 mmol) of octanoic acid are added to a solution of 460 mg (2 mmol) of 4-amidinoindanone-1-amidinohydrazone (Example 1 a)) in 80 ml of methanol and the batch is concentrated to dryness by evaporation. The residue is dissolved in ethanol and crystallised by the addition of diethyl ether to yield the title compound, m.p. 190° (decomp.); ¹H-NMR (DMSO-d₆): δ 8.03 (d,1H); 7.52 (d,1H); 7.47 (t,1H); 3.19 (m,2H); 2.85 (m,2H); 1.98 (t,4H); 1.42 (m,4H); 1.19 (s,24H); 0.81 (t,6H); anal. for C₂₇H₄₆N₆O₄ (518.70): calc. 62.52% C, 8.94% H, 16.20% N, found 62.3% C, 8.9% H, 16.2% N.

Example 3: 4-Amidino-1-indanone-2'-amidinohydrazone disalicylate

A solution of 830 mg (6 mmol) of salicylic acid in 50 ml of ethanol is added to a solution of 690 mg (3 mmol) of 4-amidinoindanone-1-amidinohydrazone (Example 1 a)) in 100 ml of methanol and the reaction mixture is concentrated to half the volume by evaporation. 70 ml of water are added to the solution, whereupon the title compound crystallises out, m.p. 206-9° (decomp.); anal. for C₂₅H₂₆N₆O₆ (507.1): calc. 59.13% C, 5.19% H, 16.55% N, found 59.3% C, 5.2% H, 16.8% N.

Example 4: 4-Amidino-1-indanone-2'-amidinohydrazone dibenzenesulfonate

A solution of 975 mg (3 mmol) of benzenesulfonic acid in 50 ml of methanol is added to a solution of 690 mg (3 mmol) of 4-amidinoindanone-1-amidinohydrazone (Example 1 a)) in 100 ml of methanol and the batch is concentrated to dryness by evaporation. The residue is crystallised from ethanol to yield the title compound, m.p. >250° (decomp.); ¹H-NMR (D₂O): δ 7.38-7.95 (m,16H); 3.21 (m,2H); 2.78 (m,2H); anal. for C₂₃H₂₆N₆O₆S₂ (546.63): calc. 50.54% C, 4.79% H, 15.37% N, found 50.4% C, 4.8% H, 15.6% N.

Example 5: further salts

Example 5a: 4-Amidinoindanone-1-amidinohydrazone succinate

A solution of 472 mg (4 mmol) of succinic acid in 120 ml of methanol is added to a solution of 920 mg (4 mmol) of 4-amidinoindanone-1-amidinohydrazone in 120 ml of methanol. The product which crystallises out is filtered off with suction, washed with a small amount of methanol and dried to yield the title compound, m.p. 200° (decomp.); anal. for $C_{15}H_{20}N_6O_4 \cdot 1.04 H_2O$ (367.10): calc. 49.08% C, 6.06% H, 22.89% N, found 49.13% C, 6.07% H, 23.04% N.

Example 5b: 4-Amidinoindanone-1-amidinohydrazone adipate

A solution of 146 mg (1 mmol) of adipic acid in 25 ml of ethanol is added to a solution of 230 mg (1 mmol) of 4-amidinoindanone-1-amidinohydrazone in 30 ml of methanol. The product which crystallises out is filtered off with suction, washed with a small amount of ethanol and dried to yield the title compound, m.p. 200° (decomp.); anal. for $C_{17}H_{24}N_6O_4 \cdot 0.25 H_2O$ (380.92): calc. 53.60% C, 6.48% H, 22.06% N, found 53.79% C, 6.73% H, 21.93% N.

Example 5c: 4-Amidinoindanone-1-amidinohydrazone-1,5-naphthalene di-sulfonate

A solution of 1.49 g (4 mmol) of 1,5-naphthalene disulfonic acid in 100 ml of methanol is added to a solution of 920 mg (4 mmol) of 4-amidinoindanone-1-amidinohydrazone in 120 ml of methanol. The product which crystallises out is filtered off with suction, washed with a small amount of methanol and dried to yield the title compound, m.p. >250°; anal. for $C_{21}H_{22}N_6O_6S_2 \cdot 2.36 H_2O$ (561.09): calc. 44.95% C, 4.80% H, 14.98% N, found 45.06% C, 4.98% H, 15.21% N.

Example 5d: 4-Amidinoindanone-1-amidinohydrazone ethane disulfonate

Analogously to any one of the Examples given hereinbefore and hereinafter, 4-amidino-1-indanone-2'-amidinohydrazone is converted into the title compound using 1,2-ethanedisulfonic acid.

Example 5e: 4-Amidinoindanone-1-amidinohydrazone L-tartrate

A solution of 600 mg (4 mmol) of L-(+)-tartaric acid in 100 ml of methanol is added to a solution of 920 mg (4 mmol) of 4-amidinoindanone-1-amidinohydrazone in

120 ml of methanol. The product which crystallises out is filtered off with suction, washed with a small amount of methanol and dried to yield the title compound, m.p. 190° (decomp.); anal. for $C_{15}H_{20}N_6O_6 \cdot 0.26 H_2O$ (385.04): calc. 46.79% C, 5.37% H, 21.83% N, found 46.83% C, 5.43% H, 21.87% N.

Example 5f: 4-Amidinoindanone-1-amidinohydrazone citrate

A solution of 210 mg (1 mmol) of citric acid in 10 ml of methanol is added to a solution of 230 mg (1 mmol) of 4-amidinoindanone-1-amidinohydrazone in 30 ml of methanol. The product which crystallises out is filtered off with suction, washed with a small amount of methanol and dried to yield the title compound, m.p. >220° (decomp.); anal. for $C_{17}H_{22}N_6O_7$ (422.40): calc. 48.34% C, 5.25% H, 19.90% N, found 48.23% C, 5.33% H, 20.07% N.

Example 6:

Analogously to any one of the above Examples, the following starting compounds can be converted into the acid addition salts of octanoic acid, succinic acid, adipic acid, salicylic acid, cyclohexylsulfamic acid, ethanedisulfonic acid, benzenesulfonic acid, citric acid, tartaric acid and 1,5-naphthalenedisulfonic acid:

- a) 4-amidino-1-indanone-2'-(N-hydroxyamidino)-hydrazone dihydrochloride (Starting Compound B);
- b) 5-Amidino-1-tetralone-2'-amidinohydrazone dihydrochloride (Starting Compound C);
- c) 4-Thiocarbamoyl-1-indanone-2'-amidinohydrazone hydrochloride (Starting Compound D);
- d) 4-(N-Hydroxyamidino)-1-indanone-2'-amidinohydrazone dihydrochloride (Starting Compound E);
- e) 4-Amidino-2-methyl-1-indanone-2'-amidinohydrazone dihydrochloride (Starting Compound F);
- f) 5-Amidino-6-methoxy-1-tetralone-2'-amidinohydrazone dihydrochloride (Starting Compound G);

- g) 4-Amidino-6-methoxy-7-methyl-1-indanone-2'-amidinohydrazone dihydrochloride (Starting Compound H);
- h) 4-Amidino-6,7-dimethyl-1-indanone-2'-amidinohydrazone dihydrochloride (Starting Compound I);
- i) 4-Amidino-7-hydroxy-3-methyl-1-indanone-2'-amidinohydrazone dihydrochloride (Starting Compound J);
- j) 4-(Methylamidino)-1-indanone-2'-amidinohydrazone dihydrochloride (Starting Compound K);
- k) 4-Amidino-6,7-dimethoxy-1-indanone-2'-amidinohydrazone dihydrochloride (Starting Compound L);
- l) 4-Amidino-6-methyl-1-indanone-2'-amidinohydrazone dihydrochloride (Starting Compound M);
- m) 4-Amidino-3-methyl-1-indanone-2'-amidinohydrazone dihydrochloride (Starting Compound N);
- n) 4-Amidino-2-ethyl-1-indanone-2'-amidinohydrazone dihydrochloride (Starting Compound O);
- o) 4-Amidino-2-n-butyl-1-indanone-2'-amidinohydrazone dihydrochloride (Starting Compound P).
- p) 4-Amidino-2-n-propyl-indanone-1-amidinohydrazone (Starting Compound Q).

Example 7: Capsules, each containing 0.25 g of active ingredient, for example one of the acid addition salts of Examples 1-6, can be prepared as follows:

Composition (for 5000 capsules)

active ingredient	1250 g
talc	180 g
wheat starch	120 g

magnesium stearate	80 g
lactose	20 g

The pulverulent substances are forced through a sieve having a mesh size of 0.6 mm and mixed. 0.33 g portions of the mixture are introduced into gelatin capsules by means of a capsule-filling machine.

Example 8: 10 000 tablets, each comprising 5 mg of active ingredient, for example one of the acid addition salts prepared in Examples 1-6, are prepared:

Composition:

active ingredient	50.00 g
lactose	2535.00 g
corn starch	125.00 g
polyethylene glycol 6000	150.00 g
magnesium stearate	40.00 g
purified water	quantum satis

Method: All of the pulverulent constituents are passed through a sieve having a mesh size of 0.6 mm. The active ingredient, the lactose, the magnesium stearate and half of the starch are then mixed in a suitable mixer. The other half of the starch is suspended in 65 ml of water and the resulting suspension is added to a boiling solution of the polyethylene glycol in 260 ml of water. The resulting paste is added to the powder mixture and granulated, where appropriate with the addition of more water. The granules are dried overnight at 35°C, forced through a sieve having a mesh size of 1.2 mm and compressed to form tablets having a breaking notch.

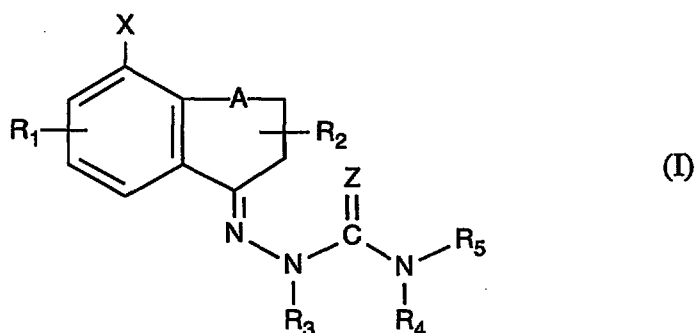


4-18815/A

Europe

What is claimed is:

1. An acid addition salt of a base of formula I



wherein A is a direct bond or $-(CH_2)_n-$, wherein n is 1, 2 or 3; X is a radical $-C(=Y)-NR_6R_7$; Y is NR_8 , O or S; Z is NR_9 , O or S; each of R_1 and R_2 , independently of the other, is hydrogen or one or more substituents other than hydrogen; each of the radicals R_3 , R_4 , R_6 , R_8 and R_9 , independently of the others, is hydrogen or lower alkyl; and each of R_5 and R_7 , independently of the other, is hydrogen, lower alkyl, hydroxy, etherified or esterified hydroxy or unsubstituted or mono- or di-substituted amino;

with an acid [PA] that is a mono- or poly-protic acid selected from carbonic acid, alkanolic acids that are unsubstituted or mono- or poly-substituted, with the exception of formic acid, unsubstituted acetic acid, lysine and arginine; alkenoic acids that are unsubstituted or substituted, with the exception of unsubstituted fumaric acid; cycloalkylcarboxylic acids, arylcarboxylic acids, aryl-lower alkylcarboxylic acids, wherein lower alkyl is unsubstituted or substituted, aryl-lower alkenylcarboxylic acids, heterocyclylcarboxylic acids, alkanesulfonic acids that are unsubstituted or substituted, with the exception of unsubstituted methanesulfonic acid; aromatic sulfonic acids, alkylsulfuric acids, N-substituted sulfamic acids, organic acids without carboxy, sulfo, sulfate or phospho groups, and also selected from pyrophosphoric acid and hydriodic acid, or a tautomer thereof.



2. An acid addition salt according to claim 1 of a base of formula I wherein A is a direct bond; X is a radical $-C(=NH)-NH_2$; Z is NH; and each of R_1 , R_2 , R_3 , R_4 and R_5 is hydrogen; with an acid [PA] that is a mono- or poly-protic acid selected from carbonic acid, alkanolic acids that are unsubstituted or mono- or poly-substituted, with the exception of formic acid, unsubstituted acetic acid, lysine and arginine; alkenolic acids that are unsubstituted or substituted, with the exception of unsubstituted fumaric acid; cycloalkyl-carboxylic acids, arylcarboxylic acids, aryl-lower alkylcarboxylic acids, wherein lower alkyl is unsubstituted or substituted, aryl-lower alkenylcarboxylic acids, heterocyclyl-carboxylic acids, alkanesulfonic acids that are unsubstituted or substituted, with the exception of unsubstituted methanesulfonic acid; aromatic sulfonic acids, alkylsulfuric acids, N-substituted sulfamic acids, organic acids without carboxy, sulfo, sulfate or phospho groups, and also selected from pyrophosphoric acid and hydriodic acid, or a tautomer thereof.

3. An acid addition salt according to claim 1 of a base of formula I wherein A is a direct bond; X is a radical $-C(=NH)-NH_2$; Z is NH; and each of R_1 , R_2 , R_3 , R_4 and R_5 is hydrogen; with an acid [PA] that is carbonic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, 2-hydroxybutyric acid, gluconic acid, glucose monocarboxylic acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, glucaric acid, galactaric acid, glutamic acid, aspartic acid, N-methylglycine, acetaminic acid, N-acetylasparagine, N-acetylcystine, pyruvic acid, acetoacetic acid, phosphoserine, 2- or 3-glycerophosphoric acid, glucose-6-phosphoric acid, glucose-1-phosphoric acid, fructose-1,6-bisphosphoric acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantanecarboxylic acid, benzoic acid, salicylic acid, 1- or 3-hydroxynaphthyl-2-carboxylic acid, 3,4,5-trimethoxybenzoic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, 4-aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, nicotinic acid, isonicotinic acid, glucuronic acid, galacturonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalenedisulfonic acid, 2-, 3- or 4-methylbenzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or ascorbic acid, or a tautomer thereof.

4. An acid addition salt according to claim 1 of a base of formula I wherein A is a direct



bond; X is a radical $-C(=NH)-NH_2$; Z is NH; and each of R_1 , R_2 , R_3 , R_4 and R_5 is hydrogen; with an acid [PA] that is N-cyclohexylsulfamic acid, octanoic acid, salicylic acid or benzenesulfonic acid.

5. An acid addition salt according to claim 1 of a base of formula I wherein A is a direct bond; X is a radical $-C(=NH)-NH_2$; Z is NH; and each of R_1 , R_2 , R_3 , R_4 and R_5 is hydrogen; with an acid [PA] that is selected from citric acid, lactic acid and tartaric acid.

6. An acid addition salt according to claim 1 of a base of formula I wherein A is a direct bond; X is a radical $-C(=NH)-NH_2$; Z is NH; and each of R_1 , R_2 , R_3 , R_4 and R_5 is hydrogen; with an acid [PA] that is selected from succinic acid, adipic acid and 1,5-naphthalenedisulfonic acid.

7. An acid addition salt according to claim 1 of a base of formula I wherein A is a direct bond; X is a radical $-C(=NH)-NH_2$; Z is NH; and each of R_1 , R_2 , R_3 , R_4 and R_5 is hydrogen; with an acid [PA] that is succinic acid, adipic acid, ethanedisulfonic acid or 1,5-naphthalenedisulfonic acid.

8. The acid addition salt according to claim 1 of a base of formula I wherein A is a direct bond; X is a radical $-C(=NH)-NH_2$; Z is NH; and each of R_1 , R_2 , R_3 , R_4 and R_5 is hydrogen; with the acid [PA] that is selected from adipic acid and benzenesulfonic acid.

9. A pharmaceutical composition comprising an acid addition salt according to any one of claims 1 to 8 and at least one pharmaceutically acceptable carrier.

10. An acid addition salt according to any one of claims 1 to 8 for use in a method for the therapeutic treatment of the animal or human body.

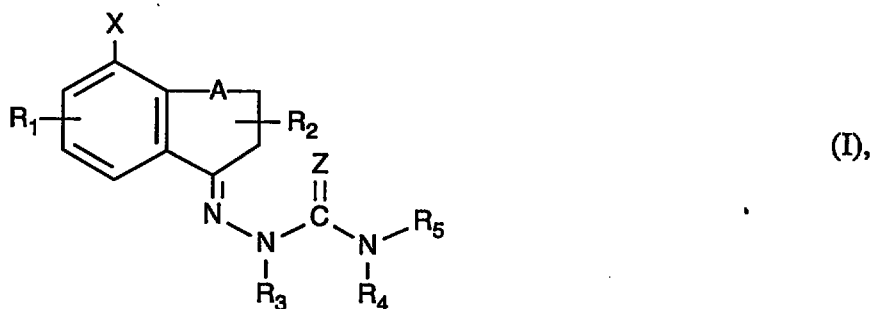
11. An acid addition salt according to any one of claims 1 to 8 for use in the treatment of diseases that respond to inhibition of the enzyme S-adenosylmethionine decarboxylase.

12. Use of an acid addition salt according to any one of claims 1 to 8 for the preparation of a pharmaceutical composition for the treatment of diseases that respond to inhibition of the enzyme S-adenosylmethionine decarboxylase.

13. A process for the preparation of an acid addition salt according to claim 1, wherein

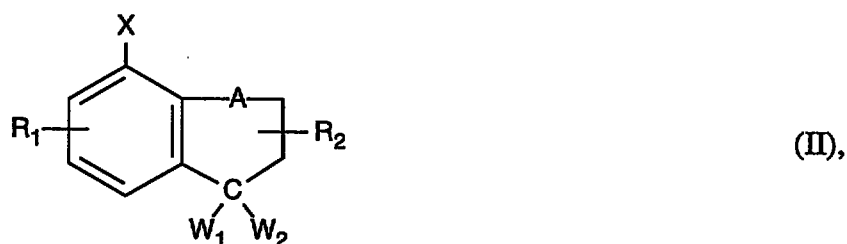


a) a base of formula I



wherein the radicals are as defined for acid addition salts of bases of formula I, is reacted with an acid [PA], [PA] being as defined above, or

b) a compound of the formula



wherein the group CW_1W_2 is carbonyl, functionally modified carbonyl or protected carbonyl and A, X, R_1 and R_2 are as defined for acid addition salts of formula I, is condensed with an amine of the formula

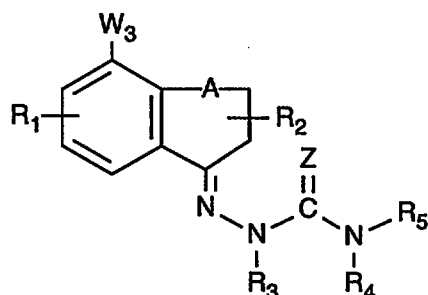


wherein Z, R_3 , R_4 and R_5 are as defined for acid addition salts of bases of formula I, in the presence of an acid [PA] that is as defined, or

c) in a compound of the formula



- 50 -



(IV),

wherein W_3 is a radical that can be converted into a group X in a base of formula I and A, Z, R_1 , R_2 , R_3 , R_4 and R_5 are as defined under formula I, the radical W_3 is converted into the group X in the presence of an acid [PA] that is as defined above; or

d) any desired acid addition salt of a base of formula I with an acid that does not fall within the definition of [PA] is converted into an acid addition salt of a base of formula I with an acid [PA] that is as defined above;

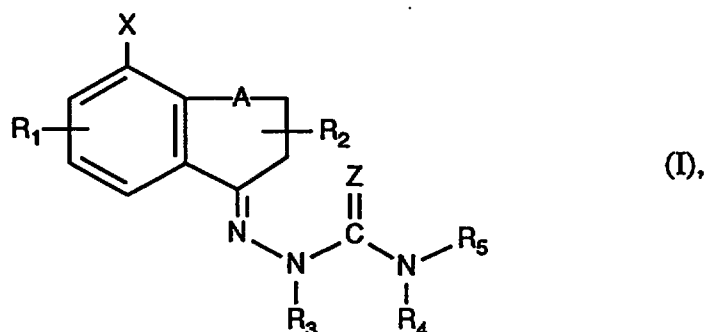
and, if desired, a resulting acid addition salt of a base of formula I with an acid [PA] is converted into a different acid addition salt of a base of formula I with an acid [PA], and/or, if desired, isomeric mixtures are separated into the individual isomers.

4-18815/A

Salts of hydrazones

Abstract

The invention relates to acid addition salts of bases of formula I



wherein A, R₁, R₂, R₃, R₄, R₅, X and Z are as defined in the description, with an acid [PA] that is a mono- or poly-protic acid selected from carbonic acid, alkanolic acids that are unsubstituted or mono- or poly-substituted, with the exception of formic acid, unsubstituted acetic acid, lysine and arginine; alkenolic acids that are unsubstituted or substituted, with the exception of unsubstituted fumaric acid; cycloalkylcarboxylic acids, aryl-carboxylic acids, aryl-lower alkylcarboxylic acids, wherein lower alkyl is unsubstituted or substituted, aryl-lower alkenylcarboxylic acids, heterocyclylcarboxylic acids, alkyl-sulfonic acids that are unsubstituted or substituted, with the exception of unsubstituted methylsulfonic acid; arylsulfonic acids, alkylsulfuric acids, N-substituted sulfamic acids, organic acids without carboxy, sulfo, sulfate or phospho groups, and also selected from pyrophosphoric acid and hydriodic acid; and tautomers thereof. The acid addition salts are used in the treatment of disorders that respond to inhibition of S-adenosylmethionine decarboxylase.