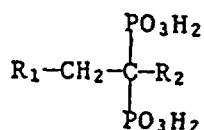


The invention relates to novel substituted alkanediphosphonic acids, especially heteroarylalkanediphosphonic acids of the formula



wherein  $\text{R}_1$  is an imidazolyl, 2H-1,2,3-, 1H-1,2,4- or 4H-1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl or thiadiazolyl radical which is unsubstituted or C-mono- or di-substituted by lower alkyl, by lower alkoxy, by phenyl which may in turn be mono- or di-substituted by lower alkyl, lower alkoxy and/or halogen, by hydroxy, by di-lower alkylamino, by lower alkylthio and/or by halogen and is N-substituted at a substitutable N-atom by lower alkyl or by phenyl-lower alkyl which may in turn be mono- or di-substituted in the phenyl moiety by lower alkyl, lower alkoxy and/or halogen, alk is lower alkylene, and  $\text{R}_2$  is hydrogen, hydroxy, amino, lower alkylthio or halogen, lower radicals having up to and including 7 C-atoms, with the provisos that  $\text{R}_1$  is other than imidazol-4-yl, 2-methylthiazol-4-yl, 2-methylthiazol-5-yl and 1,2,5-thiadiazol-4-yl when  $\text{R}_2$  is hydrogen, that  $\text{R}_1$  is other than imidazol-2-yl, 5(4)-methylimidazol-4(5)-yl, 2H-1,2,3-triazol-4-yl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl, 5-ethoxy-, 5-ethoxy-2-methyl-, 2-chloro-, 5-methoxy- and 2,5-dimethyl-oxazol-4-yl, 3-methyl- and 3-phenyl-isoxazol-5-yl, 3-methyl-1,2,5-oxadiazol-4-yl, 2-methyl-1,3,4-oxadiazol-5-yl, 3-phenyl-1,2,4-oxadiazol-5-yl, 2-chloro- and 2-methyl-thiazol-5-yl, 1,2,3- and 1,2,5-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl, 4-methyl-1,2,3-thiadiazol-5-yl and 3-methyl- and 3-phenyl-1,2,4-thiadiazol-5-yl when  $\text{R}_2$  is hydroxy, and that  $\text{R}_1$  is other than imidazol-4-yl when  $\text{R}_2$  is amino or dimethylamino, and to salts thereof, to a process for the preparation of the compounds according to

the invention, to pharmaceutical compositions contain them, and to the use thereof as active ingredients in medicaments.

Imidazolyl is, for example, imidazol-1-yl, -2-yl or -4-yl; thiazolyl is, for example, thiazol-2-yl or -4-yl; oxazolyl is, for example, oxazol-2-yl or -4-yl; isoxazolyl is, for example, isoxazol-3-yl or -4-yl; triazolyl is, for example, 1H-1,2,4-triazol-1-yl, 4H-1,2,4-triazol-3-yl or -4-yl or 2H-1,2,3-triazol-4-yl; tetrazolyl is, for example, tetrazol-5-yl; thiadiazolyl is, for example, 1,2,5-thiadiazol-3-yl; and oxadiazolyl is, for example, 1,3,4-oxadiazol-2-yl. The radicals mentioned may contain one or two identical or different substituent(s) selected from those mentioned at the beginning. Radicals  $R_1$  that are unsubstituted or substituted as indicated are, for example, imidazol-2-yl or -4-yl radicals which are unsubstituted or C-substituted by phenyl which is unsubstituted\* or substituted as indicated; or which are C- or N-substituted by  $C_1$ - $C_4$ alkyl, such as methyl, for example imidazol-2-yl, 1- $C_1$ - $C_4$ alkylimidazol-2-yl, such as 1-methylimidazol-2-yl, or 2- or 5- $C_1$ - $C_4$ alkylimidazol-4-yl, such as 2- or 5-methylimidazol-4-yl, unsubstituted thiazolyl radicals, for example thiazol-2-yl, or 1H-1,2,4-triazolyl radicals which are unsubstituted or substituted by  $C_1$ - $C_4$ alkyl, such as methyl, for example 1- $C_1$ - $C_4$ alkyl-1H-1,2,4-triazol-5-yl, such as 1-methyl-1H-1,2,4-triazol-5-yl, or imidazol-1-yl, pyrazol-1-yl, 1H-1,2,4-triazol-1-yl, 4H-1,2,4-triazol-4-yl or tetrazol-1-yl radicals which are unsubstituted or C-substituted by phenyl which is unsubstituted or substituted as indicated or by  $C_1$ - $C_4$ alkyl, such as methyl, for example imidazol-1-yl, 2-, 4- or 5- $C_1$ - $C_4$ alkylimidazol-1-yl, such as 2-, 4-

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\*Translator's note: It is assumed that the expression "im Phenylteil", which would result in "unsubstituted in the phenyl moiety", is redundant.

or 5-methylimidazol-1-yl, pyrazol-1-yl, 3- or 4-C<sub>1</sub>-C<sub>4</sub>-alkylpyrazol-1-yl, such as 3- or 4-methylpyrazol-1-yl, 1H-1,2,4-tetrazol-1-yl, 3-C<sub>1</sub>-C<sub>4</sub>alkyl-1H-1,2,4-triazol-1-yl, such as 3-methyl-1H-1,2,4-triazol-1-yl, 4H-1,2,4-triazol-4-yl, 3-C<sub>1</sub>-C<sub>4</sub>alkyl-4H-1,2,4-triazol-4-yl, such as 3-methyl-4H-1,2,4-triazol-4-yl, or 1H-tetrazol-1-yl.

Hereinbelow, there is to be understood by lower radicals and compounds, for example, those containing up to and including 7, especially up to and including 4, C-atoms. In addition, the general terms have, for example, the following meanings:

Lower alkyl is, for example, C<sub>1</sub>-C<sub>4</sub>alkyl, such as methyl, ethyl, propyl or butyl, or also iso-, sec- or tert-butyl, but may also be a C<sub>5</sub>-C<sub>7</sub>alkyl group, such as a pentyl, hexyl or heptyl group.

Phenyl-lower alkyl is, for example, phenyl-C<sub>1</sub>-C<sub>4</sub>alkyl, especially 1-phenyl-C<sub>1</sub>-C<sub>4</sub>alkyl, such as benzyl.

Lower alkoxy is, for example, C<sub>1</sub>-C<sub>4</sub>alkoxy, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy or tert-butoxy.

Di-lower alkylamino is, for example, di-C<sub>1</sub>-C<sub>4</sub>alkylamino, such as dimethylamino, diethylamino, N-ethyl-N-methylamino, dipropylamino, N-methyl-N-propylamino or dibutylamino.

Lower alkylthio is, for example, C<sub>1</sub>-C<sub>4</sub>alkylthio, such as methylthio, ethylthio, propylthio or butylthio, or also iso-, sec- or tert-butylthio.

Halogen is, for example, halogen having an atomic number of up to and including 35, such as fluorine, chlorine or

bromine.

Salts of compounds of formula I are especially the salts thereof with pharmaceutically acceptable bases, such as non-toxic metal salts derived from metals of groups Ia, Ib, IIa and IIb, for example alkali metal salts, especially sodium or potassium salts, alkaline earth metal salts, especially calcium or magnesium salts, copper, aluminium or zinc salts, or ammonium salts with ammonia or organic amines or quaternary ammonium bases, such as free or C-hydroxylated aliphatic amines, especially mono-, di- or tri-lower alkylamines, for example methyl-, ethyl-, dimethyl- or diethyl-amine, mono-, di- or tri-(hydroxy-lower alkyl)-amines, such as ethanol-, di-ethanol- or triethanol-amine, tris(hydroxymethyl)amino-methane or 2-hydroxy-tert-butylamine, or N-(hydroxy-lower alkyl)-N,N-di-lower alkylamines or N-(polyhydroxy-lower alkyl)-N-lower alkylamines, such as 2-(dimethylamino)-ethanol or D-glucamine, or quaternary aliphatic ammonium hydroxides, for example tetrabutylammonium hydroxide.

It should also be mentioned in this connection that the compounds of formula I may also be in the form of internal salts, provided the group  $R_1$  is sufficiently basic. These compounds can accordingly be converted into the corresponding acid addition salts by treatment with a strong protic acid, such as a hydrohalic acid, sulfuric acid, sulfonic acid, for example methanesulfonic acid or p-toluenesulfonic acid, or sulfamic acid, for example N-cyclohexylsulfamic acid.

The compounds of formula I and salts thereof have valuable pharmacological properties. In particular, they exhibit a pronounced regulatory action on the calcium metabolism of warm-blooded animals. In particular, they effect pronounced inhibition of bone resorption in rats,

as can be demonstrated both in the experimental procedure described in *Acta. Endocrinol.* 78, 613-24 (1975) by means of the PTH-induced increase in the serum calcium level after subcutaneous administration of doses of from approximately 0.01 to approximately 1.0 mg/kg, and in the TPTX (thyroparathyroidectomised) rat model by means of the experimental hypercalcaemia, induced by vitamin D<sub>3</sub>, after the administration of doses of approximately from 0.0003 to 1.0 mg s.c.. The tumour hypercalcaemia induced by Walker-256-tumours is likewise inhibited after peroral administration of from approximately 1.0 to approximately 100 mg/kg. In addition, when administered subcutaneously in doses of approximately from 0.001 to 1.0 mg/kg in the experimental procedure according to Newbould, *Brit. J. Pharmacology* 21, 127 (1963) and according to Kaibara *et al.*, *J. Exp. Med.* 159, 1388-96 (1984), they exhibit a marked inhibition of the progression of chronic arthritic processes in rats with adjuvant arthritis. They are therefore eminently suitable as active ingredients in medicaments for the treatment of diseases associated with disorders of the calcium metabolism, for example inflammatory processes in joints, degenerative processes in articular cartilage, of osteoporosis, periodontitis, hyperparathyroidism and of calcium deposits in blood vessels or on prosthetic implants. Favourable results are also achieved both in diseases in which an anomalous deposition of sparingly soluble calcium salts is to be observed, such as those from the among the forms of arthritis, for example ankylosing spondylitis, neuritis, bursitis, periodontitis and tendinitis, fibrodysplasia, osteoarthritis and arteriosclerosis, and in those diseases in which an anomalous degeneration of hard body tissue is the principal symptom, such as hereditary hypophosphatasia, degenerative processes in articular cartilage, osteoporoses of various origins, Paget's disease and osteodystrophia fibrosa, and also in osteo-

lytic processes induced by tumours.

There were already known from DE-A-3 203 307 and EP-A-84 822 1-hydroxy-2-(pyrazol-3-yl)-ethane-1,1-diphosphonic acids substituted in the 1,4-position of the pyrazole moiety by unsubstituted or substituted phenyl radicals and, from EP-A-170 228, C<sub>3</sub>-C<sub>9</sub>alkane-1,1-diphosphonic acids substituted in the  $\omega$ -position by an imidazole, oxazole or isoxazole radical and unsubstituted or substituted in the 1-position by hydroxy, amino or lower alkylamino, which compounds have a regulatory action on the calcium metabolism. In addition, EP-A-258 618, which was not prior-published, describes alkanediphosphonic acids substituted in the  $\omega$ -position by a heteroaromatic radical and unsubstituted or substituted in the 1-position by hydroxy, amino or lower alkylamino, which have similar properties.

The invention relates especially to compounds of formula I wherein R<sub>1</sub> is an imidazolyl, 2H-1,2,3-triazolyl or 4H-1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl or thiadiazolyl radical which is unsubstituted or C-mono- or di-substituted by lower alkyl, lower alkoxy, phenyl which is unsubstituted or mono- or di-substituted by lower alkyl, lower alkoxy and/or halogen, hydroxy, di-lower alkylamino, lower alkylthio and/or halogen, and/or is N-substituted at a substitutable N-atom by lower alkyl or phenyl-lower alkyl which is unsubstituted or mono- or di-substituted by lower alkyl, lower alkoxy and/or halogen, and R<sub>2</sub> is hydrogen, hydroxy, amino, lower alkylthio or halogen, and salts thereof, especially internal salts thereof and pharmaceutically acceptable salts thereof with bases.

The invention preferably relates, on the one hand, to compounds of formula I wherein R<sub>1</sub> is an imidazol-2-yl or

imidazol-4-yl radical which is unsubstituted or C-substituted by phenyl or C- or N-substituted by C<sub>1</sub>-C<sub>4</sub>alkyl, such as methyl, for example imidazol-2-yl, 1-C<sub>1</sub>-C<sub>4</sub>alkyl-imidazol-2-yl, such as 1-methylimidazol-2-yl, or 2- or 5-C<sub>1</sub>-C<sub>4</sub>alkylimidazol-4-yl, such as 2- or 5-methylimidazol-4-yl, or is a 1H-1,2,4-triazolyl radical which is unsubstituted or substituted by C<sub>1</sub>-C<sub>4</sub>alkyl, such as methyl, and R<sub>2</sub> is hydroxy or, less preferably, hydrogen, and salts thereof, especially pharmaceutically acceptable salts thereof.

The invention preferably relates, on the other hand, to compounds of formula I wherein R<sub>1</sub> is 2-, 4- or 5-C<sub>1</sub>-C<sub>4</sub>-alkylimidazol-1-yl, such as 2-, 4- or 5-methylimidazol-1-yl, 3-C<sub>1</sub>-C<sub>4</sub>alkyl-1H-1,2,4-triazol-1-yl, such as 3-methyl-1H-1,2,4-triazol-1-yl, 4H-1,2,4-triazol-4-yl, 3-C<sub>1</sub>-C<sub>4</sub>-alkyl-4H-1,2,4-triazol-4-yl, such as 3-methyl-4H-1,2,4-triazol-4-yl, or 1H-tetrazol-1-yl, and R<sub>2</sub> is hydroxy or, less preferably, hydrogen, and salts thereof, especially pharmaceutically acceptable salts thereof.

The invention further relates to compounds of formula I wherein R<sub>1</sub> is an imidazolyl, 4H-1,2,4-triazol-4-yl or thiazolyl radical which is unsubstituted or C-mono- or di-substituted by C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, phenyl, hydroxy, di-C<sub>1</sub>-C<sub>4</sub>alkylamino, C<sub>1</sub>-C<sub>4</sub>alkylthio and/or halogen having an atomic number of up to and including 35, and/or is N-substituted by C<sub>1</sub>-C<sub>4</sub>alkyl or phenyl-C<sub>1</sub>-C<sub>4</sub>alkyl, and R<sub>2</sub> is hydroxy, hydrogen or amino, and salts thereof.

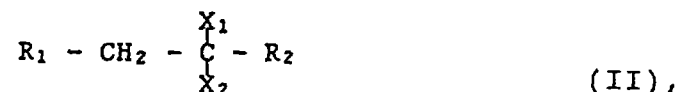
The invention further relates also to the compounds of formula I wherein R<sub>1</sub> is an imidazol-2-yl or imidazol-4-yl radical which is unsubstituted or C-substituted by phenyl or C- or N-substituted by C<sub>1</sub>-C<sub>4</sub>alkyl, or is an unsubstituted thiazolyl radical or a 1H-1,2,4-triazolyl

radical which is unsubstituted or N-substituted by C<sub>1</sub>-C<sub>4</sub>alkyl, and R<sub>2</sub> is hydroxy or hydrogen, and salts thereof, and to the compounds according to claim 1 wherein R<sub>1</sub> is imidazol-1-yl, 2-, 4- or 5-C<sub>1</sub>-C<sub>4</sub>alkylimidazol-1-yl, 3-C<sub>1</sub>-C<sub>4</sub>alkyl-1H-1,2,4-triazol-1-yl, 4H-triazol-4-yl, 3-C<sub>1</sub>-C<sub>4</sub>alkyl-4H-1,2,4-triazol-4-yl or 1H-tetrazol-1-yl, and alk and R<sub>2</sub> are as defined in claim 1, and salts thereof.

The invention relates specifically to the compounds of formula I mentioned in the Examples and to salts thereof, especially internal salts thereof and pharmaceutically acceptable salts thereof with bases.

The invention further relates to a process, based on methods known per se, for the preparation of compounds of formula I and salts thereof, which process comprises

a) in a compound of formula



wherein X<sub>1</sub> is a functionally modified phosphono group and X<sub>2</sub> is a free or functionally modified phosphono group, which compound may be temporarily protected at a substitutable N-atom of the radical R<sub>1</sub>, converting X<sub>1</sub> and, if appropriate, X<sub>2</sub> into the free phosphono group, or

b) reacting a compound of formula



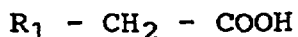
wherein X<sub>3</sub> is a carboxy, carbamoyl, imino ether, imino ester or cyano group, which compound may be temporarily

protected at a substitutable N-atom of the radical  $R_1$ , with phosphorous acid and phosphorus trichloride, and, where a start is made from a compound of formula III wherein  $X_3$  is a carbamoyl, imino ether, imino ester or cyano group, there is obtained, upon working up by hydrolysis, a compound of formula I wherein  $R_2$  is amino, and, if desired, converting a resultant compound into another compound of formula I and/or a resultant free compound into a salt or a resultant salt into the free compound or into another salt.

Functionally modified phosphono groups that are to be converted into phosphono according to process variant a) are, for example, in the form of an ester, especially in the form of a diester of formula  $-P(=O)(OR)_2$  (IV) wherein OR is, for example, lower alkoxy, or a phenoxy group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl and/or by hydroxy.

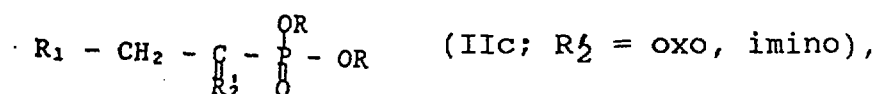
The conversion of a functionally modified phosphono group into a free phosphono group is effected in conventional manner by hydrolysis, for example in the presence of a mineral acid, such as hydrobromic acid, hydrochloric acid or sulfuric acid, or by reaction with a tri-lower alkyl-halosilane, for example with trimethylchlorosilane in the presence of sodium iodide, or especially with trimethyl-iodosilane or trimethylbromosilane, preferably with cooling, for example in a temperature range of from approximately  $0^\circ$  to approximately  $25^\circ\text{C}$ .

The starting materials of formula II wherein  $R_2$  is hydroxy or amino can be prepared, for example, by reacting a compound of formula

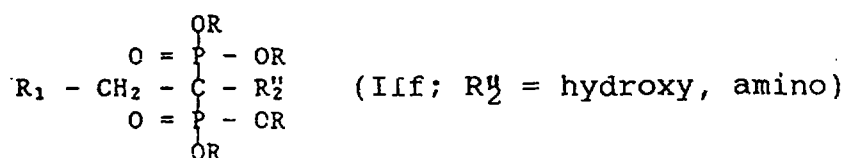


(IIa)

or preferably the nitrile or acid chloride thereof, with a suitable triphosphite of formula  $P(OR)_3$  (IIb), wherein R is, for example, lower alkyl, in the presence of a tri-lower alkylamine, for example triethylamine, to give an intermediate, presumably a compound of formula



and subsequently reacting said compound with a diphosphite of formula  $H-P(=O)(OR)_2$  (IIId) or  $P(OH)(OR)_2$  (IIe), wherein R is, for example, lower alkyl, in the presence of a di-lower alkylamine, for example diethylamine, or of an alkali metal lower alkanolate, for example sodium methanolate, to give the corresponding compound of formula



Compounds of formula IIa are obtained, for example, by converting a suitable compound of formula



with a strong base, for example one of the metal bases mentioned in process variant a), into a carbeniate salt, and reacting said salt with carbon dioxide, or by converting a compound of formula



wherein Y is reactive esterified hydroxy, especially halogen, such as bromine, with an alkali metal cyanide, for example with sodium or potassium cyanide, into the corresponding nitrile (IIg; Y = CN), and hydrolysing the nitrile to the acid, especially under basic conditions.

Starting materials of formula II wherein R<sub>2</sub> is hydrogen are obtained, for example, by reacting a compound of formula



wherein Y is reactive esterified hydroxy, especially halogen, such as bromine, in the presence of a metal base, such as the hydride, an amide or a hydrocarbon compound of an alkali metal, for example sodium hydride, sodium amide, ditrimethylsilyl sodium amide or butyllithium, with a methanediphosphonate, for example of formula



wherein R is, for example, lower alkyl.

Starting materials of formula II wherein the radical R<sub>1</sub> is bonded through a N-atom and R<sub>2</sub> is hydrogen or hydroxy can also be prepared by reacting an appropriate compound of formula



in the presence of a strong metal base, such as an alkali metal hydride or alkaline earth metal hydride, for

example sodium hydride, with a compound of formula



wherein  $\text{X}_1$  and  $\text{X}_2$  are especially groups of formula IV.

Compounds of formula II wherein  $\text{R}_2$  is lower alkylthio or halogen can be prepared, for example, starting from the corresponding compounds of formula II wherein  $\text{R}_2$  is hydrogen, by converting these with a strong base, for example one of the metal bases mentioned above, into the carbeniate salt and subsequently reacting said salt with a lower alkylthio donor, for example a di-lower alkyl disulfide or a lower alkanesulfenyl chloride, or with a halogen donor, for example a halogen, for example chlorine or bromine, perchloryl fluoride ( $\text{FClO}_3$ ) or the like.

In starting materials of formula III for process variant b), imino ether and imino ester groups are, for example, those of formula  $-\text{C}(=\text{NH})-\text{X}_3$  (III'), wherein  $\text{X}_3$  is etherified or esterified hydroxy, such as lower alkoxy, a phenoxy group, lower alkanoyloxy, a benzoyloxy group or a halogen atom, for example chlorine. Compounds of formula III wherein  $\text{X}_3$  is one of the mentioned groups III' may also be in the form of salts, such as mineral acid salts, for example hydrohalides.

The reaction of compounds of formula III with phosphorous acid and phosphorus trichloride is carried out in conventional manner, the phosphorous acid component preferably being formed in situ by reacting excess phosphorus trichloride with aqueous phosphoric acid, for example with commercial phosphoric acid having a strength of about 75 % to 95 %, preferably of about 85 %. The reaction is advantageously carried out with heating, for

example to from approximately 70° to approximately 120°C, in a suitable solvent, such as tetrachloroethane, trichloroethane, chlorobenzene, chlorotoluene or paraffin oil, and with working up by hydrolysis.

The starting materials of formula III, if not known, can be prepared, for example, by converting an appropriate compound of formula



with a strong base, for example with one of the metal bases mentioned in process variant a), into the carbeniate salt and reacting said salt with carbon dioxide or with a compound of formula  $Y-X_3$  (IIIb) wherein Y is halogen, such as chlorine or bromine, for example with a carbamoyl halide, imino ether halide or, especially, a cyanogen halide, such as cyanogen chloride.

For the temporary protection of the a substitutable N-atom of the radical  $R_1$  there are suitable the customary N-protecting groups and methods of introducing and removing the same, for example di-lower alkoxymethyl groups, such as dimethoxymethyl, which can be removed by treatment with an acid, and 2,2,2-trihaloethoxycarbonyl radicals, such as 2,2,2-triiodo-, 2,2,2-tribromo- or 2,2,2-trichloro-ethoxycarbonyl radicals, which may be removed, for example, by treatment with zinc in acetic acid,  $\alpha$ -phenyl-lower alkoxycarbonyl radicals, such as benzyloxycarbonyl or trityl, which can be removed, for example, by catalytic hydrogenation, and lower alkane-sulfonyl groups, such as methanesulfonyl, which can be removed, for example, by treatment with bis(2-methoxyethoxy) sodium aluminium hydride, and also  $\alpha$ -phenylalkyl or alkyl groups the removal of which is discussed below.

Compounds of formula I obtained by the process of this invention or by other processes known per se can be converted into other compounds of formula I in a manner known per se.

Thus, for example, compounds of formula I wherein  $R_2$  is amino can be converted by treatment with nitrous acid into the corresponding compounds of formula I wherein  $R_2$  is hydroxy. The treatment with nitrous acid is effected in conventional manner with formation of same in aqueous solution from a salt thereof, for example from sodium nitrite, by treatment with an acid, for example by the action of hydrochloric acid, to form a corresponding unstable diazonium salt, for example diazonium chloride, which splits off nitrogen with the introduction of the  $\alpha$ -hydroxy group.

In compounds of formula I wherein the radical  $R_1$  is N-substituted by lower alkyl or by phenyl-lower alkyl which is unsubstituted or substituted by lower alkyl, lower alkoxy and/or by halogen, it is also possible to remove the N-substituent; lower alkyl, for example, by treatment with a haloformate, such as a lower alkyl bromoformate or lower alkyl chloroformate, and subsequent hydrolysis of the resultant carbamate, and  $\alpha$ -phenyl-lower alkyl radicals, for example, by hydrogenolysis, for example by treatment with hydrogen in the presence of a hydrogenation catalyst, for example palladium-on-carbon and/or platinum oxide, or by reduction with a metal, for example treatment with an alkali metal in ammonia.

Resulting free compounds of formula I, including the internal salts thereof of formula I, can be converted into basic salts by partial or complete neutralisation with one of the basis mentioned at the beginning. Analogously, it is also possible to convert acid addition

salts into the corresponding free compounds or their internal salts.

Conversely, resulting free compounds of formula I can be converted into acid addition salts of formula I" by treatment with one of the protic acids mentioned at the beginning.

Resulting salts can be converted in a manner known per se into the free compounds, for example by treatment with an acid reagent, such as a mineral acid, or a base, for example an alkali metal hydroxide solution.

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

Owing to the close relationship between the novel compounds in free form and in the form of their salts, hereinbefore and hereinafter any reference to the free compounds or their salts is to be understood as meaning, where appropriate and expedient, also the corresponding salts or free compounds, respectively.

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

The starting materials that are used in the process of the present invention are preferably those which result in the compounds described at the beginning as being especially valuable. The invention relates also to novel

starting materials and to processes for the preparation thereof.

The pharmaceutical compositions according to the invention, which contain compounds of formula I or pharmaceutically acceptable salts thereof, are for enteral, such as oral or rectal, and parenteral administration and contain the pharmacological active ingredient on its own or together with a pharmaceutically acceptable carrier.

The novel pharmaceutical compositions contain, for example, from approximately 10 % to approximately 80 %, preferably from approximately 20 % to approximately 60 %, active ingredient. Pharmaceutical compositions according to the invention for enteral and parenteral administration are, for example, those in unit dosage form, such as dragées, tablets, capsules or suppositories, and also ampoules. These 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 solid carriers, if desired granulating a resulting mixture and processing the mixture or granulate, if desired or necessary after the addition of suitable excipients, into 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, and binders, such as starch pastes using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, carboxymethyl starch, crosslinked

polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow-regulating and lubricating agents, for example silica, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable coatings which may be resistant to gastric juices, there being used, inter alia, concentrated sugar solution which may contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, shellac solutions in suitable organic solvents or solvent mixtures, or, for the preparation of coatings that are resistant to gastric juices, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colourings or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Other pharmaceutical compositions for oral administration are 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 lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and, if desired, stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, to which stabilisers can also be added.

Suitable pharmaceutical compositions for rectal administration are, for example, suppositories that consist of a combination of the active ingredient with a suppository base. Suitable suppository bases are, for example,

natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. It is also possible to use gelatin rectal capsules that contain a combination of the active ingredient with a base material; suitable base materials are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

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

The present invention relates also to the use of the compounds of the formula I and salts thereof, preferably for the treatment of inflammatory conditions, especially diseases that can be attributed to calcium metabolism disorders, for example of the rheumatic type, and especially of osteoporoses.

Dosages under 0.001 mg/kg of body weight have only a negligible effect on pathological calcification and the degeneration of hard tissue. At dosages above 100 mg/kg of body weight, toxic side-effects may occur in long-term use. The compounds of formula I and salts thereof can be administered both orally and, in the form of a hypertonic solution, subcutaneously, intramuscularly or intravenously. The preferred daily doses for these kinds of

administration are in the range of approximately from 0.1 to 5 mg/kg in the case of oral administration, in the range of approximately from 0.1 to 1 mg/kg in the case of subcutaneous and intramuscular administration and in the range of approximately from 0.01 to 2 mg/kg in the case of intravenous administration.

The dosage of the compounds used is, however, variable and depends on the particular conditions, such as nature and severity of the disease, duration of treatment and on the particular compound. Single doses contain, for example, from 0.01 to 10 mg, unit dosage forms for parenteral, such as intravenous, administration contain, for example, from 0.01 to 0.1 mg, preferably from 0.02 to 0.08 mg, and oral unit dosage forms contain, for example, from 0.2 to 2.5 mg, preferably from 0.3 to 1.5 mg, per kg of body weight. The preferred single dosage for oral administration is from 10 to 100 mg and, for intravenous administration, from 0.5 to 5 mg. It is, however, possible to administer up to 4 single doses per day. The higher dosages in the case of oral administration are necessary on account of the limited absorption. In the case of long-term treatments, the dosage can normally be reduced to a lower level after an initially higher dosage in order to maintain the desired effect.

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

Example 1: With stirring and under reflux, 8.6 g (0.053 mole) 0.05 mole of (1-methylimidazol-4-yl)acetic acid, 7.1 ml of 85 % phosphoric acid and 25 ml of chlorobenzene are heated to 100°. Then 13.9 ml of phosphorus trichloride are added dropwise at 100° where-

upon evolution of gas occurs. Over the course of 30 minutes, a dense mass precipitates from the reaction mixture. The batch is heated at 100° for a further 3 hours, and the supernatant chlorobenzene is then decanted off. With stirring and under reflux, the viscous mass remaining is heated to the boil for 3 hours with 40 ml of 9N hydrochloric acid. The batch is filtered hot with the addition of carbon, and the filtrate is diluted with acetone, whereupon the crude 2-(1-methylimidazol-4-yl)-1-hydroxyethane-1,1-diphosphonic acid precipitates. This product is recrystallised from water, m.p. 261° (decomp.).

Example 2: With stirring and under reflux, 19.7 g (0.1 mole) of 1-benzylimidazol-2-ylacetonitrile, 13.4 ml of 85 % phosphoric acid and 50 ml of chlorobenzene are heated to 100°. Then 27 ml of phosphorus trichloride are added dropwise at 100°, whereupon evolution of gas occurs. Over the course of 30 minutes, a dense mass precipitates from the reaction mixture. The batch is heated at 100° for a further 3 hours, and the supernatant chlorobenzene is then decanted off. With stirring and under reflux, the viscous mass remaining is heated to the boil for 3 hours with 100 ml of 9N hydrochloric acid. The batch is filtered hot with the addition of carbon and the filtrate is cooled, whereupon 1-amino-2-(1-benzylimidazol-2-yl)-ethane-1,1-diphosphonic acid precipitates.

Example 3: In a manner analogous to that described in Example 2 and starting from 0.1 mole of (1-methylimidazol-4-yl)acetonitrile, 1-amino-2-(1-methylimidazol-4-yl)ethane-1,1-diphosphonic acid and salts thereof, for example disodium salts, are also obtained.

Example 4: Reaction of 1-methylimidazol-2-ylmethyl bromide, benzylimidazol-2-ylmethyl chloride, (imidazole-

1-methyl)toluenesulfonate, imidazol-4-ylmethyl chloride and thiazol-2-ylmethyl bromide with tetraethyl methane-diphosphonate and hydrolysis of the initially obtained ethanediphosphonate analogously to Example 7 or 10 gives also

2-(1-methylimidazol-2-yl)ethane-1,1-diphosphonic acid, m.p. 295° (decomp.);

2-(1-benzylimidazol-2-yl)ethane-1,1-diphosphonic acid monohydrate, m.p. 181-183°;

2-(imidazol-1-yl)ethane-1,1-diphosphonic acid, m.p. 255° (decomp.);

2-(imidazol-4-yl)ethane-1,1-diphosphonic acid and

2-(thiazol-2-yl)ethane-1,1-diphosphonic acid, m.p. 259° (decomp.),

and salts thereof, for example disodium salts.

Example 5: In a manner analogous to that described in Example 1 and starting from 1-methylimidazole-2-acetic acid hydrochloride, 2-(1-methylimidazol-2-yl)-1-hydroxyethane-1,1-diphosphonic acid monohydrate, m.p. 261° (decomp.), is obtained.

The starting material can be prepared, for example, as follows: 5.0 g (0.032 mole) of 1-methyl-2-cyanomethylimidazole hydrochloride, 15 ml of glacial acetic acid and 15 ml of 36 % hydrochloric acid are boiled under reflux for 24 hours. The reaction mixture is then concentrated by evaporation to dryness under reduced pressure, the residue is taken up in 30 ml of hot glacial acetic acid and undissolved ammonium chloride is removed by filtration. The filtrate is concentrated by evaporation and acetone is added to the residue to yield 1-methyl-2-carboxymethylimidazole hydrochloride, m.p. 163-164°C (yield: 91 % of the theoretical yield).

Example 6: In a manner analogous to that described in

Example 1 and starting from 1-benzylimidazole-2-acetic acid hydrochloride and 1-methylimidazole-2-acetic acid hydrochloride, there are respectively obtained 2-(1-benzylimidazol-2-yl)-1-hydroxyethane-1,1-diphosphonic acid, m.p. 171° (decomp.) and 2-(1-methylimidazol-2-yl)-1-hydroxyethane-1,1-diphosphonic acid monohydrate, m.p. 261° (decomp.), and salts thereof, for example sodium salts. The starting material 1-benzylimidazole-2-acetic acid hydrochloride, m.p. 124-125°, can be prepared in a manner analogous to that described in Example 2.

Example 7: 14.8 g (0.051 mole) of tetraethyl methane-diphosphonate are added dropwise to a suspension of 2.4 g of sodium hydride in 35 ml of absolute tetrahydrofuran, and the reaction mixture is stirred at room temperature until the evolution of gas has ceased. Then 11.3 g (0.0465 mole) of 1-benzyl-2-chloromethylimidazole hydrochloride are added in portions. With stirring and under reflux, the reaction mixture is heated to the boil for 20 hours. The sodium chloride which has separated is then removed by filtration and the filtrate is concentrated by evaporation under reduced pressure to give crude tetraethyl (1-benzyl-imidazol-2-ylmethyl)-methanediphosphonate. 3.0 g (0.065 mole) of tetraethyl (1-benzyl-imidazol-2-yl)ethane-1,1-diphosphonate and 12 ml of 36 % hydrochloric acid are then heated to the boil under reflux for 20 hours. Concentration by evaporation and crystallisation of the residue from aqueous methanol yield 2-(1-benzylimidazol-2-yl)ethane-1,1-diphosphonic acid monohydrate, m.p. 181-183° (yield: 30 % of the theoretical yield).

Example 8: Analogously to Example 7 there are obtained from

1-methyl-2-chloromethylimidazole hydrochloride and 2-chloromethylthiazole hydrochloride by reaction to give the corresponding tetraethyl ethane-diphosphonates and subsequent cleavage of the esters with trimethylbromosilane in the manner described: 2-(1-methylimidazol-1-yl)ethane-1,1-diphosphonic acid, m.p. 295° (decomp.) and 2-(thiazol-2-yl)ethane-1,1-diphosphonic acid, m.p. 259° (decomp.), respectively, and salts thereof, for example disodium salts, and hydrates.

The starting material 1-methyl-5-chloromethyl-1H-1,2,4-triazole hydrochloride can be prepared as follows:

11.1 g (0.10 mole) of 5-hydroxymethyl-1-methyl-1H-1,2,4-triazole are dissolved in 25 ml of dichloromethane. While cooling with ice and stirring, 29.7 g of thionyl chloride are added dropwise. The reaction mixture is then stirred for one hour at room temperature and thereafter for 20 minutes at boiling temperature under reflux. The resulting precipitate is filtered with suction, washed with diethyl ether and dried in vacuo. M.p. 136-137°C.

Example 9: In a manner analogous to that described in Example 1 and starting from 1-imidazoleacetic acid hydrochloride, 1-pyrazoleacetic acid hydrochloride, \* and 2-(imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid, m.p. 239° (decomp.) are obtained.

Example 10: 3.3 g (0.0072 mole) of tetraethyl 2-(1-benzylimidazol-2-yl)ethane-1,1-diphosphonate are dissolved in 50 ml of liquid ammonia and, with stirring, 1.0 g of sodium is added gradually in small pieces until

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\*Translator's note: There appears to be an omission in the German text at this point.

the blue colour of the solution is maintained for some time. Then 2.35 g of ammonium chloride are added in portions. The ammonia is then removed by evaporation, and the residue is taken up in diethyl ether and filtered, and the filtrate is concentrated by evaporation to yield tetraethyl 2-(imidazol-2-yl)ethane-1,1-diphosphonate in the form of a colourless oil.

2.3 g (0.0062 mole) of tetraethyl 2-(imidazol-2-yl)ethane-1,1-diphosphonate are dissolved in 20 ml of methylene chloride, and 4.8 ml of trimethylbromosilane are added thereto and the reaction mixture is left to stand at room temperature for 24 hours. It is then concentrated by evaporation under reduced pressure, and 10 ml of methanol and 1 ml of water are added to the residue, yielding 2-(imidazol-2-yl)ethane-1,1-diphosphonic acid, m.p. 279-282° (decomp.).

Example 11: With stirring and under reflux, 8.6 g (0.053 mole) of imidazol-1-ylacetic acid hydrochloride, 7.1 ml of 85 % phosphoric acid and 25 ml of chlorobenzene are heated to 100°. Then 13.9 ml of phosphorus trichloride are added dropwise at 100°, whereupon evolution of gas occurs. Over the course of 30 minutes, a dense mass precipitates from the reaction mixture. The batch is heated at 100° for a further 3 hours and the supernatant chlorobenzene is then decanted off. With stirring and under reflux, the viscous mass remaining is heated to the boil with 40 ml of 9N hydrochloric acid for 3 hours. The batch is filtered hot with the addition of carbon, and the filtrate is diluted with acetone, whereupon the crude 2-(imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid precipitates. This product is recrystallised from water, m.p. 239° (decomp.), (yield: 41 % of the theoretical yield).

Example 12: Analogously to Example 10 and starting from tetraethyl 2-(imidazol-1-yl)ethane-1,1-diphosphonate, there is obtained, by treatment with trimethylbromosilane and working up with aqueous methanol, 2-(imidazol-1-yl)ethane-1,1-diphosphonic acid, m.p. 255° (decomp.).

The starting ester can be prepared, for example, as follows: 0.10 g of sodium hydride is suspended in 4.0 ml of absolute tetrahydrofuran. A solution of 0.27 g (0.04 mole) of imidazole in 2.0 ml of tetrahydrofuran is slowly added dropwise. 1.2 g of tetraethyl vinylidene-diphosphonate are added the clear reaction solution and the batch is kept at room temperature for 24 hours. Then 2 ml of 2N ethanolic hydrochloric acid are added. The sodium chloride which separates is removed by filtration and the filtrate is concentrated by evaporation.

Example 13: In a manner analogous to that described in Example 11 and starting from 0.05 mole of 4H-1,2,4-triazol-4-ylacetic acid, 2-(4H-1,2,4-triazol-4-yl)-1-hydroxyethane-1,1-diphosphonic acid and salts thereof, for example disodium salts, are obtained.

Example 14: By reaction of (imidazol-1-ylmethyl)-p-toluenesulfonate with tetraethyl methanediphosphonate and hydrolysis of the initially obtained ethanediphosphonate analogously to Example 5, it is also possible to prepare 2-(imidazol-1-yl)ethane-1,1-diphosphonic acid, m.p. 255° (decomp.), and salts thereof, for example the disodium salt thereof.

Example 15: Analogously to Example 5 there is obtained from 1-benzyl-2-cyanomethylimidazole 1-benzyl-2-carboxymethylimidazole hydrochloride, m.p. 124-125°.

Analogously to Example 11, there is obtained from 1-

benzyl-2-carboxymethylimidazole hydrochloride 2-(1-benzylimidazol-2-yl)-1-hydroxyethane-1,1-diphosphonic acid, m.p. 171° (decomp.).

Example 16: 3.59 g (0.01 mole) of 1-amino-2-(1-benzylimidazol-2-yl)ethane-1,1-diphosphonic acid are dissolved in 20 ml of 1N sodium hydroxide solution, 0.82 g of sodium nitrite is added, and the solution is cooled to 0°. With stirring, 18 ml of 2N hydrochloric acid are slowly added dropwise. Stirring is then continued for 1 hour at 0-10° and the product which precipitates is filtered. Recrystallisation from water yields 2-(1-benzylimidazol-2-yl)-1-hydroxyethane-1,1-diphosphonic acid, m.p. 171° (decomp.), yield 47 %.

Example 17: In a manner analogous to that described in Examples 1 to 16 it is also possible to prepare 2-[2-phenylimidazol-4(5)-yl]ethane-1,1-diphosphonic acid; 2-(4,5-dimethylimidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid and 2-(2-methylimidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid, m.p. 245-246°, and salts thereof, for example disodium salts.

Example 18: Tablets containing 100 mg of active ingredient, for example 2-(imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid or a salt, for example the disodium salt, thereof can be prepared as follows:

Constituents (for 1000 tablets)

|                    |         |
|--------------------|---------|
| active ingredient  | 100.0 g |
| lactose            | 100.0 g |
| wheat starch       | 47.0 g  |
| magnesium stearate | 3.0 g   |

Procedure: All the solid constituents are sieved through

a sieve having a mesh size of 0.6 mm. The active ingredient is then mixed with the lactose, talcum, magnesium stearate and half of the starch. The other half of the starch is suspended in 40 ml of water and the suspension is added to a boiling solution of polyethylene glycol in 100 ml of water, and the mixture is granulated, if necessary with the addition of water. The granules are dried overnight at 35°, forced through a sieve having a mesh size of 1.2 mm and compressed into tablets of approximately 6 mm diameter which are concave on both sides.

In an analogous manner, it is also possible to prepare tablets each containing 100 mg of another of the compounds of formula I mentioned in Examples 1 to 17, which compounds may also be in the form of salts and bases, for example in the form of the sodium salt.

Example 19: Lozenges containing 75 mg of active ingredient, for example 2-(imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid or a salt, for example the disodium salt, thereof can be prepared, for example, as follows:

Composition: (for 1000 lozenges)

|                      |         |
|----------------------|---------|
| active ingredient    | 75.0 g  |
| mannitol             | 230.0 g |
| lactose              | 100.0 g |
| talcum               | 21.0 g  |
| glycine              | 12.5 g  |
| stearic acid         | 10.0 g  |
| saccharine           | 1.5 g   |
| 5 % gelatin solution | q.s.    |

Procedure: All the solid ingredients are first forced through a sieve having a mesh size of 0.25 mm. The mannitol and the lactose are mixed, granulated with the

addition of gelatin solution, forced through a sieve having a mesh size of 2 mm, dried at 50° and again forced through a sieve having a mesh size of 1.7 mm. The active ingredient, glycine and saccharine are carefully mixed together, the mannitol, lactose granules, stearic acid and the talcum are added and the whole is thoroughly mixed and compressed into lozenges of approximately 10 mm diameter which are concave on both sides and provided with a breaking notch on the upper side.

In an analogous manner, it is also possible to prepare lozenges each containing 75 mg of another of the compounds of formula I mentioned in Examples 1 to 17, which compounds may be in the form of salts with bases, for example in the form of the sodium salt.

Example 20: Tablets containing 10 mg of active ingredient, for example 2-(imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid or a salt, for example the disodium salt, thereof can be prepared as follows:

Composition (for 1000 tablets)

|                          |         |
|--------------------------|---------|
| active ingredient        | 10.0 g  |
| lactose                  | 115.7 g |
| corn starch              | 17.5 g  |
| polyethylene glycol 6000 | 5.0 g   |
| talcum                   | 5.0 g   |
| magnesium stearate       | 4.0 g   |
| demineralised water      | q.s.    |

Procedure: The solid ingredients are first sieved through a sieve having a mesh size of 0.6 mm. the active ingredient is then mixed with the lactose, talcum, magnesium stearate and half of the starch. The other half of the starch is suspended in 65 ml of water and the suspension is added to a boiling solution of the polyethylene glycol

in 260 ml of water. The resultant paste is added to the powdered substances and the whole is mixed and granulated, if necessary with the addition of water. The granules are dried overnight at 35°, forced through a sieve having a mesh size of 1.2 mm and compressed into tablets of approximately 10 mm diameter which are concave on both sides and provided with a breaking notch on the upper side.

In an analogous manner, it is also possible to prepare tablets containing 10 mg of another of the compounds of formula I mentioned in Examples 1 to 17, which compounds may be in the form of salts with bases, for example in the form of the sodium salt.

Example 21: Gelatin dry-filled capsules containing 100 mg of active ingredient, for example 2-(imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid or a salt, for example the disodium salt, thereof can be prepared as follows:

Composition (for 1000 capsules)

|                            |         |
|----------------------------|---------|
| active ingredient          | 350.0 g |
| microcrystalline cellulose | 30.0 g  |
| sodium lauryl sulfate      | 2.0 g   |
| magnesium stearate         | 8.0 g   |

The sodium lauryl sulfate is added to the active ingredient (lyophilised) through a sieve having a mesh size of 0.2 mm and the two components are intimately mixed for 10 minutes. Then the microcrystalline cellulose is sieved in through a sieve having a mesh size of 0.9 mm and the ingredients are again intimately mixed for 10 minutes. Finally, the magnesium stearate is sieved in through a sieve having a mesh size of 0.8 mm and, after being further mixed for 3 minutes, the mixture is

introduced into size 0 dry-filled gelatin capsules (elongated) in portions of 390 mg each.

In an analogous manner, it is also possible to prepare capsules containing 100 mg of another of the compounds of formula I mentioned in Examples 1 to 17, which compounds may be in the form of salts with bases, for example in the form of the disodium salt.

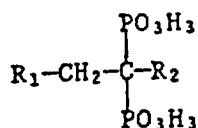
Example 22: A 0.2 % injection or infusion solution can be prepared, for example, as follows:

|                                                                                                                                          |              |
|------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| active ingredient, for example 2-(imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid or a salt, for example the disodium salt, thereof | 5.0 g        |
| sodium chloride                                                                                                                          | 22.5 g       |
| phosphate buffer pH = 7.4                                                                                                                | 300.0 g      |
| demineralised water                                                                                                                      | to 2500.0 ml |

The active ingredient is dissolved in 1000 ml of water and the solution is filtered through a micro-filter. The buffer solution is added, followed by the addition of water to make up to 2500 ml. To prepare unit dosage forms, 1.0 or 2.5 ml are introduced into glass ampoules (each containing respectively 2.0 or 5.0 mg of active ingredient).

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

1. A substituted alkanediphosphonic acid, especially a heteroarylalkanediphosphonic acid of formula



wherein  $\text{R}_1$  is an imidazolyl, 2H-1,2,3-, 1H-1,2,4- or 4H-1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl or thiadiazolyl radical which is unsubstituted or C-mono- or di-substituted by lower alkyl, by lower alkoxy, by phenyl which may in turn be mono- or di-substituted by lower alkyl, lower alkoxy and/or halogen, by hydroxy, by di-lower alkylamino, by lower alkylthio and/or by halogen and is N-substituted at a substitutable N-atom by lower alkyl or by phenyl-lower alkyl which may in turn be mono- or di-substituted in the phenyl moiety by lower alkyl, lower alkoxy and/or halogen, alk is lower alkylene, and  $\text{R}_2$  is hydrogen, hydroxy, amino, lower alkylthio or halogen, lower radicals having up to and including 7 C-atoms, with the provisos that  $\text{R}_1$  is other than imidazol-4-yl, 2-methylthiazol-4-yl, 2-methylthiazol-5-yl and 1,2,5-thiadiazol-4-yl when  $\text{R}_2$  is hydrogen, that  $\text{R}_1$  is other than imidazol-2-yl, 5(4)-methylimidazol-4(5)-yl, 2H-1,2,3-triazol-4-yl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl, 5-ethoxy-, 5-ethoxy-2-methyl-, 2-chloro-, 5-methoxy- and 2,5-dimethyl-oxazol-4-yl, 3-methyl- and 3-phenyl-isoxazol-5-yl, 3-methyl-1,2,5-oxadiazol-4-yl, 2-methyl-1,3,4-oxadiazol-5-yl, 3-phenyl-1,2,4-oxadiazol-5-yl, 2-chloro- and 2-methyl-thiazol-5-yl, 1,2,3- and 1,2,5-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl, 4-methyl-1,2,3-thiadiazol-5-yl and 3-methyl- and 3-phenyl-1,2,4-thiadiazol-5-yl when  $\text{R}_2$  is hydroxy, and that  $\text{R}_1$  is other than imidazol-4-yl when



R<sub>2</sub> is amino or dimethylamino, or a salt thereof.

2. A compound of formula I wherein R<sub>1</sub> is an imidazolyl, 2H-1,2,3-triazolyl or 4H-1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl or thiadiazolyl radical which is unsubstituted or C-mono- or di-substituted by lower alkyl, lower alkoxy, phenyl which is unsubstituted or mono- or di-substituted by lower alkyl, lower alkoxy and/or halogen, hydroxy, di-lower alkyl-amino, lower alkylthio and/or halogen, and/or is N-substituted at a substitutable N-atom by lower alkyl or phenyl-lower alkyl which is unsubstituted or mono- or di-substituted by lower alkyl, lower alkoxy and/or halogen, and R<sub>2</sub> is hydrogen, hydroxy, amino, lower alkylthio or halogen, or a salt thereof.

3. A compound of formula I wherein R<sub>1</sub> is an imidazolyl, 4H-1,2,4-triazol-4-yl or thiazolyl radical which is unsubstituted or C-mono- or di-substituted by C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, phenyl, hydroxy, di-C<sub>1</sub>-C<sub>4</sub>alkylamino, C<sub>1</sub>-C<sub>4</sub>alkylthio and/or halogen having an atomic number of up to and including 35, and/or is N-substituted by C<sub>1</sub>-C<sub>4</sub>alkyl or phenyl-C<sub>1</sub>-C<sub>4</sub>alkyl, and R<sub>2</sub> is hydroxy, hydrogen or amino, or a salt thereof.

4. A compound of formula I wherein R<sub>1</sub> is an imidazol-2-yl or imidazol-4-yl radical which is unsubstituted or C-substituted by phenyl or C- or N-substituted by C<sub>1</sub>-C<sub>4</sub>-alkyl, or is an unsubstituted thiazolyl radical or a 1H-1,2,4-triazolyl radical which is unsubstituted or N-substituted by C<sub>1</sub>-C<sub>4</sub>alkyl, and R<sub>2</sub> is hydroxy or hydrogen, or a salt thereof.

5. A compound according to claim 1 wherein R<sub>1</sub> is imidazol-1-yl, 2-, 4- or 5-C<sub>1</sub>-C<sub>4</sub>alkylimidazol-1-yl, 3-C<sub>1</sub>-C<sub>4</sub>alkyl-1H-1,2,4-triazol-1-yl, 4H-triazol-4-yl, 3-



C<sub>1</sub>-C<sub>4</sub>alkyl-4H-1,2,4-triazol-4-yl or 1H-tetrazol-1-yl, and alk and R<sub>2</sub> are as defined in claim 1, or a salt thereof.

6. A compound of formula I wherein R<sub>1</sub> is an imidazol-1-yl, 4H-1,2,4-triazol-4-yl or tetrazol-1-yl radical which is unsubstituted or C-substituted by phenyl or by C<sub>1</sub>-C<sub>4</sub>-alkyl, and R<sub>2</sub> is hydroxy or hydrogen, or a salt thereof.

7. 2-(1-Methylimidazol-2-yl)-1-hydroxyethane-1,1-diphosphonic acid or a salt thereof.

8. 2-(1-Benzylimidazol-2-yl)-1-hydroxyethane-1,1-diphosphonic acid or a salt thereof.

9. 2-(1-Methylimidazol-4-yl)-1-hydroxyethane-1,1-diphosphonic acid or a salt thereof.

10. 1-Amino-2-(1-methylimidazol-4-yl)ethane-1,1-diphosphonic acid or a salt thereof.

11. 1-Amino-2-(1-benzylimidazol-4-yl)ethane-1,1-diphosphonic acid or a salt thereof.

12. 2-(1-Methylimidazol-2-yl)ethane-1,1-diphosphonic acid or a salt thereof.

13. 2-(1-Benzylimidazol-2-yl)ethane-1,1-diphosphonic acid or a salt thereof.

14. 2-(Imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid or a salt thereof.

15. 2-(Imidazol-1-yl)ethane-1,1-diphosphonic acid or a salt thereof.

16. 2-(4H-1,2,4-triazol-4-yl)-1-hydroxyethane-1,1-



diphosphonic acid or a salt thereof.

17. 2-(Thiazol-2-yl)ethane-1,1-diphosphonic acid or a salt thereof.

18. 2-(Imidazol-2-yl)ethane-1,1-diphosphonic acid or a salt thereof.

19. 2-[2-Methylimidazol-4(5)-yl]ethane-1,1-diphosphonic acid or a salt thereof.

20. 2-[2-Phenylimidazol-4(5)-yl]ethane-1,1-diphosphonic acid or a salt thereof.

21. 2-(4,5-Dimethylimidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid or a salt thereof.

22. 2-(2-Methylimidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid or a salt thereof.

23. A compound according to any one of claims 1, 4, 5 and 17 to 22 for use in a method for the therapeutic treatment of the human or animal body, for example as an agent that regulates calcium metabolism and/or as an anti-arthritic agent.

24. A compound according to any one of claims 2, 3 and 6 to 16 for use in a method for the therapeutic treatment of the human or animal body, for example as an agent that regulates calcium metabolism and/or as an anti-arthritic agent.

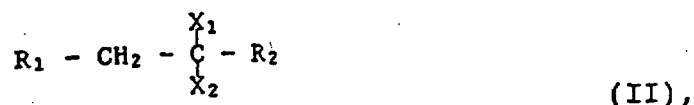
25. A pharmaceutical composition comprising a compound according to any one of claims 1, 4, 5 and 17 to 23, together with conventional pharmaceutical excipients.



26. A pharmaceutical composition comprising a compound according to any one of claims 2, 3, 6 to 16 and 24.

27. A process for the preparation of a compound according to claim 1 or a salt thereof, which comprises

a) in a compound of formula



wherein  $X_1$  is a functionally modified phosphono group and  $X_2$  is a free or functionally modified phosphono group, which compound may be temporarily protected at a substitutable N-atom of the radical  $R_1$ , converting  $X_1$  and, if appropriate,  $X_2$  into the free phosphono group, or

b) reacting a compound of formula

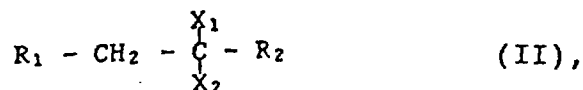


wherein  $X_3$  is a carboxy, carbamoyl, imino ether, imino ester or cyano group, which compound may be temporarily protected at a substitutable N-atom of the radical  $R_1$ , with phosphorous acid and phosphorus trichloride, and, where a start is made from a compound of formula IV wherein  $X_3$  is a carbamoyl, imino ether, imino ester or cyano group, there is obtained, upon working up by hydrolysis, a compound of formula I wherein  $R_2$  is amino, and, if desired, converting a resultant compound into another compound of formula I and/or a resultant free compound into a salt or a resultant salt into the free compound or into another salt.

28. A process according to claim 27, which comprises

a) in a compound of formula





wherein  $X_1$  is a functionally modified phosphono group and  $X_2$  is a free or functionally modified phosphono group, converting  $X_1$  and, if appropriate,  $X_2$  into the free phosphono group, or

b) reacting a compound of formula



wherein  $X_3$  is carboxy or cyano, with phosphorous acid and phosphorus trichloride, and, where a start is made from a compound of formula III wherein  $X_3$  is cyano, there is obtained, with working up by hydrolysis, a compound of formula I wherein  $R_2$  is amino, and, if desired, converting a resultant compound into another compound of formula I and/or a resultant free compound into a salt or a resultant salt into the free compound or into another salt.

29. The use of a compound according to any one of claims 1 to 22 for the manufacture of a medicament suitable for the treatment of diseases associated with impaired calcium metabolism.

