

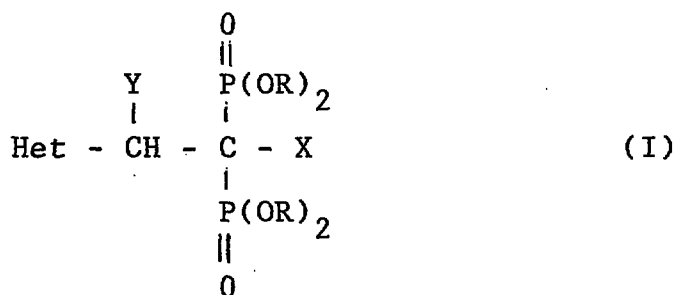
The present invention concerns new diphosphonic acid derivatives, processes for their preparation, as well as medicaments which contain these substances.

5 In DE-OS 32 03 307 and DE-OS 32 03 308 are described aryethanediphosphonates, e.g. thienyl-ethanediphosphonate and a pyrazole-ethane-diphosphonate, respectively, with outstanding anti-inflammatory action.

10 In DE-PS 18 13 659 are described diphosphonic acid derivatives of which 1-hydroxyethane-1,1-diphosphonic acid has achieved importance as agent for the treatment of Paget's disease. In EP-OS 186,903 are described, inter alia, pyridylalkyldiphosphonates and in DE-OS 34 28 524 are described heteroaromatic alkyl-diphosphonates in which the alkylene chain contains at
15 least 2 carbon atoms. It has now been found that analogous derivatives of these compounds in which only one carbon atom stands between the diphosphonate residue and the heterocyclic radical and the heterocycle is not pyrazole also show this action and, furthermore, as
20 good calcium complex formers, are suitable for the wider treatment of calcium metabolism disturbances. In particular, they can be very well used there where the bone formation and breakdown is disturbed, i.e. they are suitable for the treatment of diseases of the skeletal
25 system, such as e.g., osteoporosis, Bechterew's disease and the like.

However, on the basis of these properties, they also find use in the therapy of bone metastases, of urolithiasis and for the prevention of heterotopic
30 ossifications. Furthermore, due to their influencing of the calcium metabolism, they form a basis for the treatment of rheumatoid arthritis, of osteoarthritis and of degenerative arthrosis.

Consequently, the subject of the invention are
35 diphosphonates of the general formula I



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in which Het signifies an imidazole, imidazoline, isoxazole, oxazole, oxazoline, thiazole, thiazoline, triazole, oxadiazole or thiadiazole radical which can possibly be substituted one or more times by C₁-C₄-alkyl, C₁-C₄-alkoxy, phenyl, cyclohexyl, cyclohexyl-methyl, halogen or the amino group, Y hydrogen or C₁-C₄-alkyl, X hydrogen, hydroxyl group or amino possibly substituted by C₁-C₄-alkyl and R hydrogen or C₁-C₄-alkyl radical, as well as their pharmacologically acceptable salts.

15

Alkyl preferably means the methyl, ethyl or isobutyl radical.

Asymmetric carbon atoms can possess the R-, S- or R,S-configuration.

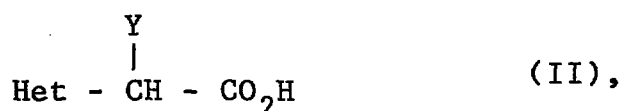
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Compounds of general formula I are prepared according to per se known processes.

For the case that X in the general formula I signifies OH, one preferably prepares the substances in that one

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a) reacts a carboxylic acid of the general formula II



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in which Het and Y have the above-given meanings, with a mixture of phosphorous acid or phosphoric acid and a phosphorus halide and subsequently saponifies to the free diphosphonic acid, or

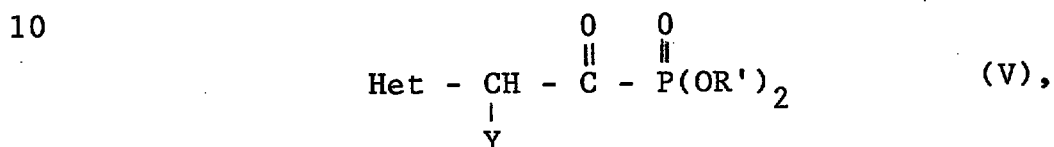
b) reacts a carboxylic acid chloride of the general formula III



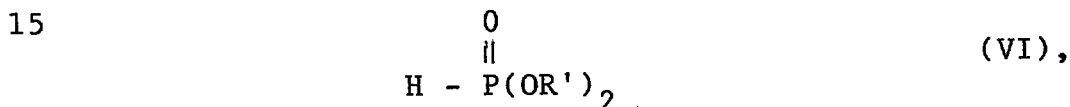
5 in which Het and Y have the above-given meanings, with a trialkyl phosphite of the general formula IV



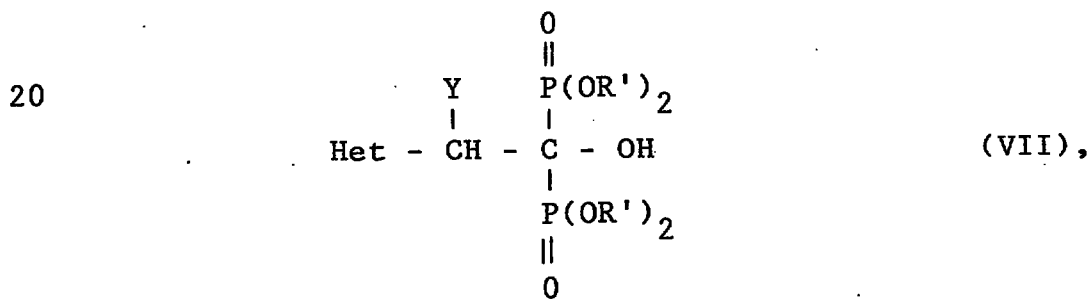
in which R' signifies lower alkyl, to give an acyl phosphonate of the general formula V



in which Het, Y and R' have the above-given meanings, subsequently allows to react with a dialkyl phosphite of the general formula VI



in which R' has the above-given meaning, to give a diphosphonate of the general formula VII



25 in which Het, Y and R' have the above-given meanings, and saponifies the resultant tetraesters to diesters or acids of the general formula I;

for the case that X in the general formula I signifies amino possibly substituted by alkyl groups,

30 c) reacts a carboxylic acid derivative of the general formula VIII



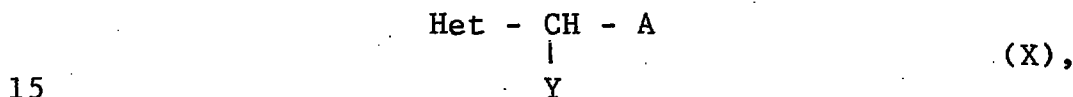
in which Het and Y have the above-given meanings and Z represents a nitrile, iminoether or an N,N-dialkyl-carboxamido group, with a phosphorus compound of the
5 general formula IX



in which T = halogen, OH or OR', whereby R' has the above-given meaning, and possibly subsequently
10 optionally saponifies;

or for the case that X in the general formula I signifies hydrogen,

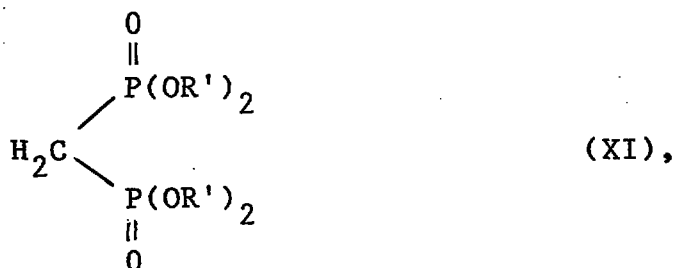
d) reacts a compound of the general formula X



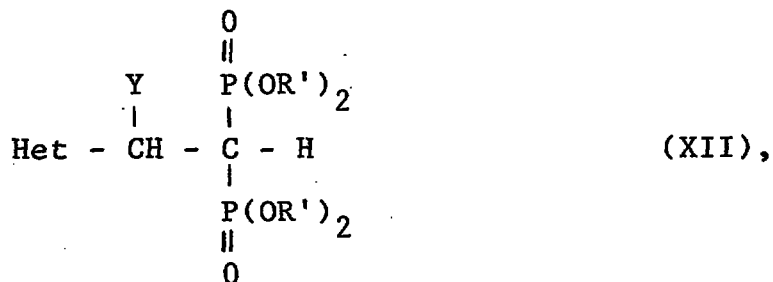
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in which Het and Y have the above-given meanings and A represents a reactive residue, such as e.g. halogen or a sulphonate, with a compound of the general
formula XI

20



25 in which R' has the above-given meaning, to give a diphosphonate of the general formula XII



in which Het, Y and R' have the above-given meanings, and possibly saponifies the tetraesters obtained to diesters or acids of the general formula I.

5 The carboxylic acids of the general formula II used in process a) are reacted with 1 - 2, preferably 1.5 mole of phosphorous acid or phosphoric acid and 1 - 2, preferably 1.5 mole phosphorus trihalide at temperatures of 80 - 130°C, preferably 100 - 110°C. One can carry out the reaction in the presence of
10 diluents, such as halogenated hydrocarbons, especially chlorobenzene, tetrachloroethane, or also dioxan. The subsequent hydrolysis takes place by boiling with water but expediently with semi-concentrated hydrochloric acid or hydrobromic acid.

15 In the case of process b), one allows the acid chloride of the general formula III to come to reaction with the trialkyl phosphite of the general formula IV at temperatures between 0 and 60°C, preferably at 20 - 40°C. One can work without solvent or also in the
20 presence of inert solvents, such as diethyl ether, tetrahydrofuran, dioxan or also halogenated hydrocarbons, such as e.g. methylene chloride. The acyl phosphonate of the general formula V resulting as an intermediate can be isolated or further reacted
25 directly.

One carries out the subsequent reaction in the presence of a weak base, preferably of a sec. amine, such as e.g. dibutylamine, at a temperature of from 0 to 60°C, preferably at 10 - 30°C.

30 In the case of process c), one reacts the nitriles of the general formula VIII with phosphorous acid at temperatures of 110 - 180°C. The reaction can be carried out without or in the presence of aprotic solvents, such as e.g. diglycol dimethyl ether or
35 diglycol diethyl ether. However, one can also bring

the nitriles to reaction with a phosphorus trihalide, e.g. phosphorus tribromide or phosphorus trichloride, in an inert solvent, such as e.g. dioxan or tetrahydrofuran, possibly with the addition of water, at temperatures of 20 - 80°C. One allows imino ethers of the general formula VIII to react with dialkyl phosphites, preferably in the presence of equimolar amounts of sodium, in inert solvents, such as diethyl ether, dioxan or also benzene, whereby the reactions take place, as a rule, at the reflux temperature of the corresponding solvent. One can react acid amides of the general formula VIII in inert solvents, such as e.g. halogenated hydrocarbons or ethers, such as e.g. diethyl ether, with a mixture of phosphorus pentahalide/phosphorous acid or also of oxalyl chloride/trialkyl phosphite.

In the case of process d), one uses the methylenediphosphonic acid ester of the general formula XI in the form of its sodium or potassium salt. For this purpose, it is reacted with sodium, potassium or the corresponding hydride in an inert solvent, such as e.g. benzene, toluene or dimethylformamide, at a temperature of 0 to 40°C, preferably of 25°C. The alkali metal salt is brought to reaction, without isolation, with the corresponding halide or sulphonate. The temperature hereby lies at 20 - 110°C.

The tetraalkyl esters possibly obtained in the case of processes b), c) and d) can be saponified to diesters or to the free tetra acids. The saponification to diesters takes place, as a rule, in that one treats the tetraalkyl esters with an alkali metal halide, preferably sodium iodide, in a suitable solvent, such as e.g. acetone, at room temperature.

There hereby results the symmetrical diester/disodium salt which can possibly be converted by means of an acidic ion exchanger into the diester/diacid.

The saponification to free diphosphonic acids takes place, as a rule, by boiling with hydrochloric or hydrobromic acid. However, one can also carry out a cleavage with trimethylsilyl halide, preferably the bromide or iodide. On the other hand, the free diphosphonic acids can again be converted into the tetraalkyl esters by boiling with orthoformic acid alkyl esters. The free diphosphonic acids of the general formula I can be isolated as free acids or in the form of their mono- or dialkali metal or ammonium salts. As a rule, the alkali metal salts can be readily purified by reprecipitation from water/methanol or water/acetone.

If desired, the compounds of the general formula I can subsequently be converted from one into another. They can e.g. be alkylated or, when X in the general formula I signifies an unsubstituted amino group, can be converted by diazotisation into the compounds of the general formula I with $X = OH$. By hydrogenolytic splitting off of an N-benzyl group, there can be prepared e.g. the corresponding unsubstituted compounds of the general formula I.

As pharmacologically acceptable salts, there are used, in particular, alkali metal or ammonium salts which one prepares in the usual way, e.g. by neutralisation of the compounds with inorganic or organic bases, such as e.g. sodium or potassium hydrogen carbonate, aqueous sodium hydroxide solution, aqueous potassium hydroxide solution, aqueous ammonia or amines, such as e.g. trimethyl- or triethylamine.

The new substances of the formula I according to the invention and their salts can be administered enterally or parenterally in liquid or solid form. There hereby come into question all usual forms of administration, for example tablets, capsules, dragees,

5 syrups, solutions, suspensions etc. As injection medium, it is preferred to use water which contains the additives usual in the case of injection solutions, such as stabilising agents, solubilising agents and buffers.

10 Such additives are e.g. tartrate and citrate buffers, ethanol, complex formers (such as ethylenediamine-tetraacetic acid and its non-toxic salts), high molecular polymers (such as liquid polyethylene oxide) for viscosity regulation. Liquid carrier materials for injection solutions must be sterile and are preferably filled into ampoules. Solid carrier materials are e.g. starch, lactose, mannitol, methyl cellulose, talc, highly dispersed silicic acids, high
15 molecular fatty acids (such as stearic acid), gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats, solid high molecular polymers (such as polyethylene glycols); compositions suitable for oral administration can, if desired,
20 contain flavouring and sweetening agents.

The dosage can depend upon various factors, such as mode of administration, species, age and/or individual state. The dosages to be administered daily lie at about 1 - 1000 mg/human, preferably 10 - 200 mg/
25 human and can be taken once or divided several times.

Preferred in the sense of the present invention are, apart from the compounds mentioned in the Examples and the compounds derivable by combination of all of the meanings given in the claims, the following
30 diphosphonic acids, as well as their sodium salts, methyl and ethyl esters.

1-hydroxy-2-(3-methyl-1,2,4-thiadiazol-5-yl)-ethane-1,1-diphosphonic acid
1-hydroxy-2-(3-phenyl-1,2,4-thiadiazol-5-yl)-ethane-
35 1,1-diphosphonic acid

- 1-hydroxy-2-(3-cyclohexylmethyl-1,2,4-thiadiazol-5-yl)-ethane-1,1-phosphonic acid
- 1-hydroxy-2-(3-methylisoxazol-5-yl)-ethane-1,1-diphosphonic acid
- 5 1-hydroxy-2-(3-phenylisoxazol-5-yl)-ethane-1,1-diphosphonic acid
- 1-hydroxy-2-(3-methyl-1,2,5-oxadiazol-4-yl)-ethane-1,1-diphosphonic acid
- 1-hydroxy-2-(2-methyl-1,3,4-oxadiazol-5-yl)-ethane-1,1-diphosphonic acid
- 10 1-hydroxy-2-(3-phenyl-1,2,4-oxadiazol-5-yl)-ethane-1,1-diphosphonic acid
- 1-hydroxy-2-(1,2,3-thiadiazol-4-yl)-ethane-1,1-diphosphonic acid
- 15 1-hydroxy-2-(1,2,5-thiadiazol-4-yl)-ethane-1,1-diphosphonic acid
- 1-hydroxy-2-(4-oxazolin-2-yl)-ethane-1,1-diphosphonic acid
- 1-hydroxy-2-(5-methoxyoxazol-4-yl)-ethane-1,1-diphosphonic acid
- 20 1-hydroxy-2-(5-ethoxyoxazol-4-yl)-ethane-1,1-diphosphonic acid
- 1-hydroxy-2-(2-aminooxazol-4-yl)-ethane-1,1-diphosphonic acid
- 25 1-hydroxy-2-(2,5-dimethyloxazol-4-yl)-ethane-1,1-diphosphonic acid
- 1-hydroxy-2-(5-ethoxy-2-methyloxazol-4-yl)-ethane-1,1-diphosphonic acid
- 1-hydroxy-2-(2-methyl-1,3,4-oxadiazol-5-yl)-ethane-1,1-diphosphonic acid
- 30 1-hydroxy-2-(3-phenyl-1,2,4-oxadiazol-5-yl)-ethane-1,1-diphosphonic acid
- 1-hydroxy-2-(1,2,3-thiadiazol-5-yl)-ethane-1,1-diphosphonic acid
- 35 1-hydroxy-2-(4-methyl-1,2,3-thiadiazol-5-yl)-ethane-1,1-diphosphonic acid

- 1-hydroxy-2-(5-methylimidazol-4-yl)-ethane-1,1-diphosphonic acid
2-(2-methylthiazol-4-yl)-ethane-1,1-diphosphonic acid
2-(2-methylthiazol-4-yl)-propane-1,1-diphosphonic acid
5 1-hydroxy-2-(2-methylthiazol-5-yl)-ethane-1,1-diphosphonic acid
2-(2-methylthiazol-5-yl)-propane-1,1-diphosphonic acid
1-hydroxy-2-(1,2,3-triazol-4-yl)-ethane-1,1-diphosphonic acid
10 1-hydroxy-2-(1,2,4-triazol-3-yl)-ethane-1,1-diphosphonic acid
1-hydroxy-2-(2-aminoimidazol-4-yl)-ethane-1,1-diphosphonic acid
2-(2-methylthiazol-5-yl)-ethane-1,1-diphosphonic acid
15 1-hydroxy-2-(imidazol-4-yl)-propane-1,1-diphosphonic acid
1-amino-2-(imidazol-4-yl)-ethane-1,1-diphosphonic acid
1-dimethylamino-2-(imidazol-4-yl)-ethane-1,1-diphosphonic acid
20 1-hydroxy-2-(2-cyclohexylmethyl-1,3,4-oxadiazol-5-yl)-ethane-1,1-diphosphonic acid
1-hydroxy-2-(2-cyclohexyl-1,3,4-oxadiazol-5-yl)-ethane-1,1-diphosphonic acid
1-hydroxy-2-(2-aminothiazol-5-yl)-ethane-1,1-diphosphonic acid
25 1-hydroxy-2-(2-chlorothiazol-5-yl)-ethane-1,1-diphosphonic acid
1-hydroxy-2-(2-chlorooxazol-4-yl)-ethane-1,1-diphosphonic acid
30 1-hydroxy-2-(imidazol-2-yl)-ethane-1,1-diphosphonic acid
1-hydroxy-2-(1,2,4-triazol-1-yl)-ethane-1,1-diphosphonic acid.

The following Examples show some of the process variants which can be used for the synthesis of the
35 compounds according to the invention. However, they

are not to represent a limitation of the subject of the invention. As a rule, the compounds are obtained as high melting (m.p. $> 300^{\circ}\text{C}$) solid products (mono- or disodium salts), the structures of which have been
5 verified by H-, P- and possibly by ^{13}C - NMR spectroscopy. The purity of the compounds was determined by means of C, H, N, P, S, Na analyses, as well as by thin layer electrophoresis (cellulose, oxalate buffer of pH = 4.0). For the characterisation of the individual
10 compounds, there are given the M_{rel} values (= relative mobilities), referred to pyrophosphate ($M_{\text{rel}} = 1$).

Example 1.

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

15 One adds 3 g phosphorous acid to 3.5 g imidazol-4-ylacetic acid hydrochloride (m.p. $198 - 200^{\circ}\text{C}$) in 40 ml chlorobenzene, stirs for 10 min. at 110°C , cools and slowly adds 9 g phosphorus trichloride thereto. One heats for 16 h. to 110°C , cools, decants the
20 chlorobenzene from an orange-coloured syrup and mixes the residue with 50 ml 6N hydrochloric acid. The suspension is heated under reflux for 5 h., after cooling, mixed with charcoal and filtered off with suction. The filtrate is evaporated, dried and boiled
25 up with acetone for 2 h. One dissolves the residue (4.3 g) in 40 ml of water, brings the solution with 2N aqueous sodium hydroxide solution to a pH = 5, mixes with 50 ml methanol and filters off with suction the precipitate obtained. One obtains 1.2 g $\hat{=}$ 16.9% of
30 theory, with an m.p. $> 290^{\circ}\text{C}$. The compound is obtained as monosodium salt containing 2 moles of water of crystallisation ($M_{\text{rel}} = 0.37$).

Example 2.

In a manner analogous to that described in
35 Example 1, one obtains, by the reaction of phosphorous

acid and phosphorus trichloride with

- a) 2-methylthiazol-4-ylacetic acid (m.p. 119 - 121°C; prepared by saponification of the corresponding ethyl ester (b.p.₁₃ 127°C) which was prepared according to J. Chem. Soc., 1946, 91 from γ -bromoacetoacetic acid ester by reaction with thioacetamide, 1-hydroxy-2-(2-methylthiazol-4-yl)-ethane-1,1-diphosphonic acid which was isolated as disodium salt with 1 mole of water of crystallisation in a yield of 57% of theory; m.p. > 300°C; $M_{rel} = 0.55$.
- b) 4-imidazolin-2-ylacetic acid (m.p. 108 - 110°C; prepared by saponification of the ethyl ester (m.p. 102 - 105°C), which was prepared by reaction of ethylenediamine with the imino ether of cyanoacetic acid ethyl ester), 1-hydroxy-2-(4-imidazolin-2-yl)-ethane-1,1-diphosphonic acid which was isolated as free acid with 1 mole of water of crystallisation in a yield of 14% of theory; m.p. about 250°C and decomp.; $M_{rel} = 0.45$.
- c) 2-amino-4-thiazolin-4-ylacetic acid (m.p. 218 - 221°C; prepared by saponification of the ethyl ester (oily substance) which was prepared by reaction of thiourea with γ -bromoacetoacetic acid ethyl ester), 2-(2-amino-4-thiazolin-4-yl)-ethane-1-hydroxy-1,1-diphosphonic acid which was isolated as free acid with 2 moles of water of crystallisation in a yield of 59% of theory; m.p. 190 - 195°C and decomp.; $M_{rel} = 0.40$.

Example 3.

2-(1,2,5-thiadiazol-4-yl)-ethane-1,1-diphosphonic acid tetraethyl ester.

One adds dropwise a solution of 1.62 g methane-diphosphonic acid tetraethyl ester in 10 ml absolute toluene to 0.2 g sodium hydride (69%) in 10 ml absolute toluene. After ending of the hydrogen evolution, one adds thereto 1 g 4-bromomethyl-1,2,5-thiadiazole in

10 ml absolute toluene and allows to stir for 12 h. at room temperature. One adds a little water thereto, separates off the organic phase, dries and evaporates. The residue is purified over a silica gel column
5 (100 g; elution agent: methylene chloride/methanol 98:2 v/v). One thus obtains 1.18 g = 55% of a colourless oil.

Example 4.

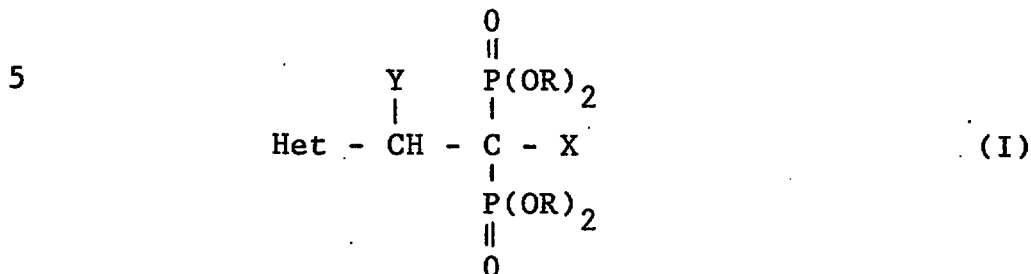
2-(1,2,5-Thiadiazol-4-yl)-ethane-1,1-diphosphonic acid.

10 1.18 g of the 2-(1,2,5-thiadiazol-4-yl)-ethane-1,1-diphosphonic acid tetraethyl ester described in Example 3 are mixed with 3.3 ml trimethylbromosilane under nitrogen. One leaves the reaction mixture to stand for 24 hours at room temperature, evaporates the
15 solution, mixes the residue with water, adjusts the solution with NaOH to a pH = 5 and mixes it with methanol. The separated precipitate is filtered off with suction. One thus obtains 0.56 g = 53% of the
20 desired diphosphonic acid as disodium salt with 1 mole of water of crystallisation; m.p. > 300°C; $M_{rel} = 0.9$.



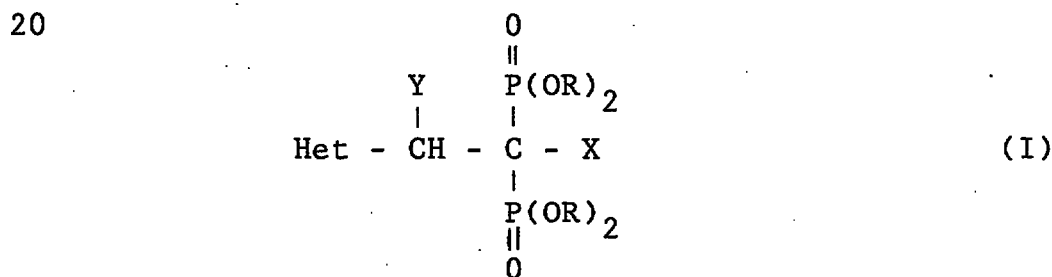
Patent Claims

1. New alkyldiphosphonic acid derivatives of the general formula I



in which Het signifies an imidazole, imidazoline, isoxazole, oxazole, oxazoline, thiazole, thiazoline, triazole, oxadiazole or thiadiazole radical which can possibly be substituted one or more times by C₁-C₄-alkyl, C₁-C₄-alkoxy, phenyl, cyclohexyl, cyclohexylmethyl, halogen or the amino group, Y hydrogen or C₁-C₄-alkyl, X hydrogen, hydroxyl or amino possibly substituted by C₁-C₄-alkyl and R hydrogen or C₁-C₄-alkyl, as well as their pharmacologically acceptable salts.

2. Process for the preparation of new alkyldiphosphonic acid derivatives of the general formula I



in which Het, Y, X, R possess the meanings given in claim 1, characterised in that one

a) reacts a carboxylic acid of the general formula II



in which Het and Y have the above-given meanings, with a mixture of phosphorous acid or phosphoric acid and a phosphorus halide and subsequently saponifies to the free diphosphonic acid; or



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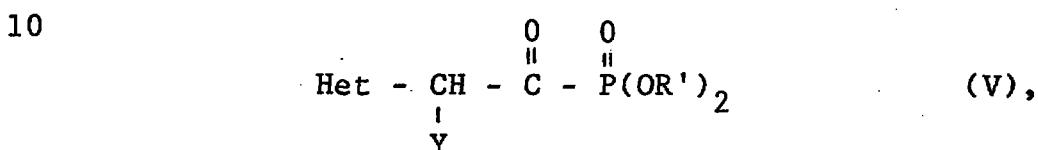
b) reacts a carboxylic acid chloride of the general formula III



5 in which Het and Y have the above-given meanings, with a trialkyl phosphite of the general formula IV



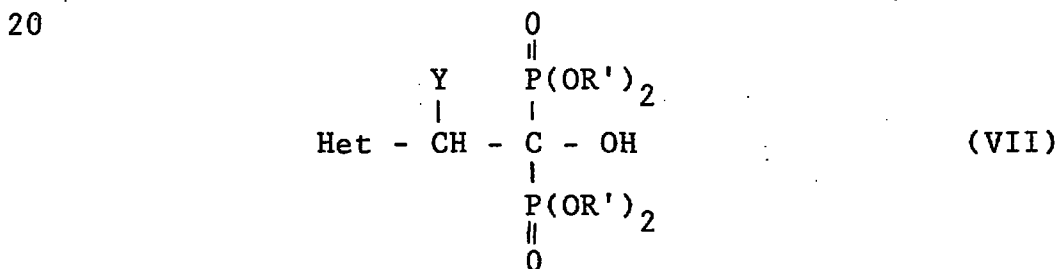
in which R' signifies lower alkyl, to an acyl phosphonate of the general formula V



15 in which Het, Y and R' have the above-given meanings, subsequently allows to react with a dialkyl phosphite of the general formula VI



in which R' has the above-given meaning, to a diphosphonate of the general formula VII



25 in which Het, Y and R' have the above-given meanings, and possibly saponifies the resultant tetraesters to diesters or acids of the general formula I;

or, for the case that X in general formula I signifies amino possibly substituted by alkyl groups,

30 c) reacts a carboxylic acid derivative of the general formula VIII



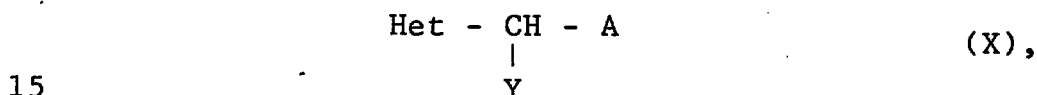
in which Het and Y have the above-given meanings and Z represents a nitrile, imino ether or an N,N-dialkyl-carboxamido group, with a phosphorus compound of the
5 general formula IX



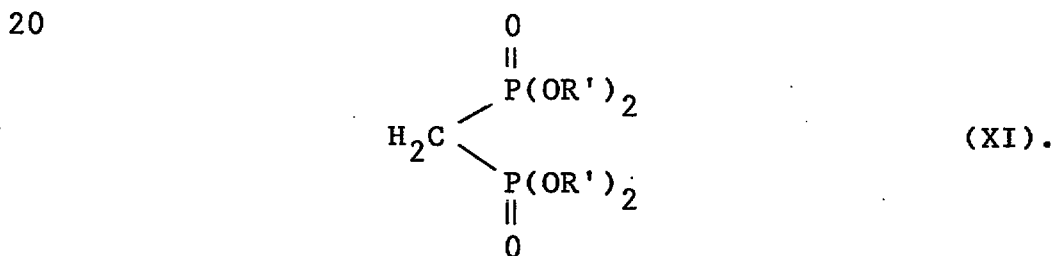
in which T = halogen, OH or OR', whereby R' has the above-given meaning, and possibly subsequently
10 saponifies;

or, for the case that X in general formula I signifies hydrogen,

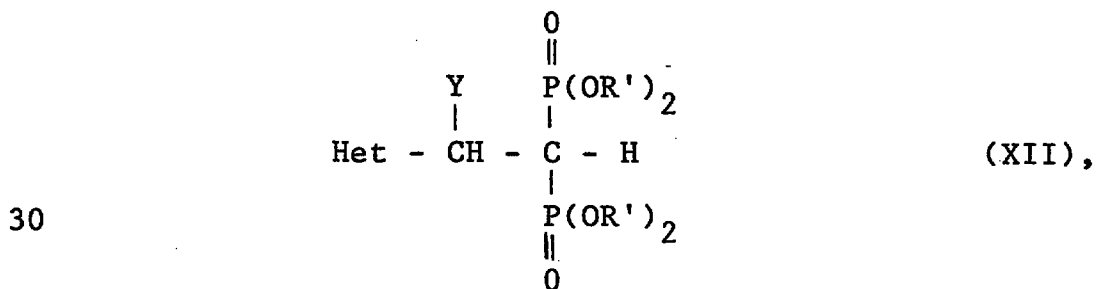
d) reacts a compound of the general formula X



in which Het and Y have the above-given meanings and A represents a reactive residue, such as e.g. halogen or a sulphonate, with a compound of the general
15 formula XI



25 in which R' has the above-given meaning, to a diphosphonate of the general formula XII





in which Het, Y and R' have the above-given meanings, and possibly saponifies the resultant tetraesters to diesters or acids of general formula I.

3. Medicaments containing a compound according to claim 1, as well as usual pharmacologically acceptable carrier or adjuvant materials.
4. Use of compounds according to claim 1 for the preparation of medicaments for the treatment of calcium metabolism disturbances.