

COMMONWEALTH of AUSTRALIA
Patents Act 1952

616283

APPLICATION FOR A STANDARD PATENT

I/We

Boehringer Mannheim GmbH

of

Sandhofer Strasse 112-132, D-6800 Mannheim-Waldhof, Federal Republic of Germany

hereby apply for the grant of a Standard Patent for an invention entitled:

Diphosphonic acid derivatives, processes for the preparation thereof and pharmaceutical compositions containing them

which is described in the accompanying complete specification.

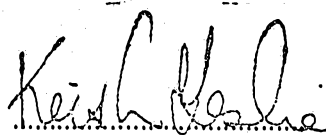
Details of basic application(s):-

<u>Number</u>	<u>Convention Country</u>	<u>Date</u>
P 38 22 650.2	Federal Republic of Germany	5 July 1988

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

DATED this FOURTH day of JULY 1989

To: THE COMMISSIONER OF PATENTS


a member of the firm of
DAVIES & COLLISON for
and on behalf of the
applicant(s)

Davies & Collison, Melbourne

M 010457 040789

DECLARATION IN SUPPORT OF CONVENTION OR
NON-CONVENTION APPLICATION FOR A PATENT

Insert title of invention.

Insert full name(s) and address(es) of declarant(s) being the applicant(s) or person(s) authorized to sign on behalf of an applicant company.

In support of the Application made for a patent for an invention
entitled: "DIPHOSPHONIC ACID DERIVATIVES, PROCESSES FOR
THE PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS
CONTAINING THEM"

Both of Martin Daum AND Herbert Fouquet
of Boehringer Mannheim GmbH
of Sandhofer Strasse 116,
6800 Mannheim 31,
Federal Republic of Germany.

Cross out whichever of paragraphs
81 or 1(b) does not apply

do solemnly and sincerely declare as follows :—

1. (a) XXXXXXXXXXXXXXXXXXXXXXXX

or (b) I am authorized by

Boehringer Mannheim GmbH

the applicant..... for the patent to make this declaration on ^{its}~~his~~ behalf.

2. (a) $\frac{d}{dx} \left(x^2 + 3x - 7 \right)$

or(b) 1. Elmar BOSIES
of Delpstr. 11
6940 Weinheim

AND 2. Harald ZILCH
of Alsenweg 2 A
6800 Mannheim 31

Both of Federal Republic of Germany

He is the actual inventor..... of the invention and the facts upon which the applicant..... is entitled to make the application are as follows :-

The applicant would, if a patent were granted on an application made by the said actual inventors, be entitled to have the patent assigned to it.

State manner in which applicant(s)
derive title from inventor(s)

Cross out paragraphs 3 and 4
for non-convention applications.
For convention applications,
insert basic country(s) followed
by date(s) and basic applicant(s).

3. The basic application,..... as defined by Section 141 of the Act ^{was} ~~wasn't~~ made
in Federal Republic of Germany on the 5 July 1988
by Boehringer Mannheim GmbH

in on the
by
in on the
by

4 The basic application..... referred to in paragraph 3 of this Declaration, ^{was} ~~were~~ the first application..... made in a Convention country in respect of the invention the subject of the application.

Insert place and date of signature.

Declared at Mannheim this 14th day of June, 1989

Signature of declarant(s) (no attestation required)

Note: Initial all alterations.

BOEHRINGER MANNHEIM GMBH
ppa. *au* ppa. *Herbert Fouquet*
Dr. Martin Daum Dr. Herbert Fouquet

DAVIES & COLLISON, MELBOURNE and CANBERRA.

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 (19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 616283

(54) Title
 DIPHOSPHONIC ACID DERIVATIVES, PROCESSES FOR THE PREPARATION THEREOF AND
 PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

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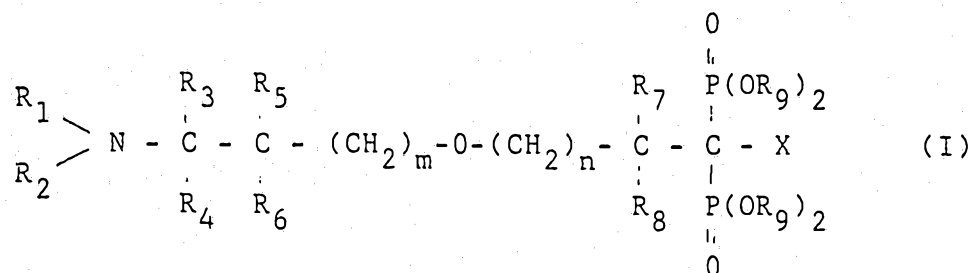
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(56) Prior Art Documents
 AU 82694/87 C07F 9/65 A61K 31/675
 AU 598569 76487/87 C07F 9/38 A61K 31/66 C07F 9/40
 AU 598279 75291/87 C07F 9/38 9/40 A61K 31/66

(57) Claim.

1. Compounds of the general formula:-



wherein R_1 and R_2 , independently of one another, are hydrogen atoms, straight-chained or branched, saturated or unsaturated alkyl chains containing up to 9 carbon atoms which can optionally be substituted by hydroxyl, C_1 - C_5 -alkoxy or C_1 - C_5 -alkylthio, a phenyl or C_5 - C_7 -cycloalkyl ring, whereby the phenyl ring can be optionally substituted by C_1 - C_5 -alkyl, C_1 - C_5 -alkoxy, hydroxyl or halogen, or are C_5 - C_7 -cycloalkyl or phenyl radicals, R_3 is a hydrogen atom, a straight-chained or branched

C₁-C₅-alkyl radical which can optionally be substituted by hydroxyl, C₁-C₅-alkoxy, C₁-C₅-alkylthio, mercapto, phenyl, 3-indolyl or 4-imidazolyl, or a phenyl radical optionally substituted by hydroxyl or C₁-C₅-alkoxy, R₄, R₆, R₈ and R₉, independently of one another, are hydrogen atoms or C₁-C₅-alkyl radicals, R₅ and R₇, independently of one another, are hydrogen atoms, C₁-C₅-alkyl radicals or phenyl radicals optionally substituted by hydroxyl or C₁-C₅-alkoxy, X is a hydrogen atom, a hydroxyl group or an -NR₁₀R₁₁ radical, whereby R₁₀ and R₁₁, independently of one another, are hydrogen atoms or C₁-C₅-alkyl radicals and m and n are 0 or 1, whereby R₁ and R₂, together with the nitrogen atom to which they are attached, can form a mono- or bicyclic ring system containing 4 to 9 carbon atoms which is partly or wholly hydrogenated and possibly substituted by hydroxyl, C₁-C₅-alkyl or C₁-C₅-alkoxy and/or, in the case of a monocyclic ring, can be interrupted by an oxygen, nitrogen or sulphur atom, R₁ and R₃, together with the carbon and nitrogen atoms to which they are attached, can form a five- or six-membered ring which can possibly be condensed with a further six-membered ring, R₁ and R₅, together with the carbon and nitrogen atoms to which they are attached, as well as the carbon atom lying therebetween, can form a five- or six-membered ring, R₃ and R₄, together with the carbon atom to which they are attached, can form a five- or six-membered ring, R₄ and R₆, together with the carbon

atoms to which they are attached, can form a five- or six-membered ring, R_5 and R_6 , together with the carbon atom to which they are attached, can form a five- or six-membered ring and R_7 and R_8 , together with the carbon atom to which they are attached, can form a five- or six-membered ring; as well as the pharmacologically acceptable salts thereof and the optical isomers thereof; with the proviso that R_1 and R_2 together with the nitrogen atom cannot form a piperidine or piperazine ring and R_1 and R_3 as well as R_1 and R_5 together with the nitrogen atom cannot form a piperidine ring.

7. A method for the treatment of calcium metabolism disturbances in a mammal in need thereof comprising administering to said mammal an effective amount of the compounds according to any one of claims 1, 2 or 5.

6 1 6 2 8 3

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

**NAME & ADDRESS
OF APPLICANT:**

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NAME(S) OF INVENTOR(S):

Elmar BOSIES
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DAVIES & COLLISON
Patent Attorneys
1 Little Collins Street, Melbourne, 3000.

COMPLETE SPECIFICATION FOR THE INVENTION ENTITLED:

Diphosphonic acid derivatives, processes for the preparation thereof and pharmaceutical compositions containing them

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

The present invention is concerned with new diphosphonic acid derivatives, processes for the preparation thereof and pharmaceutical compositions containing them.

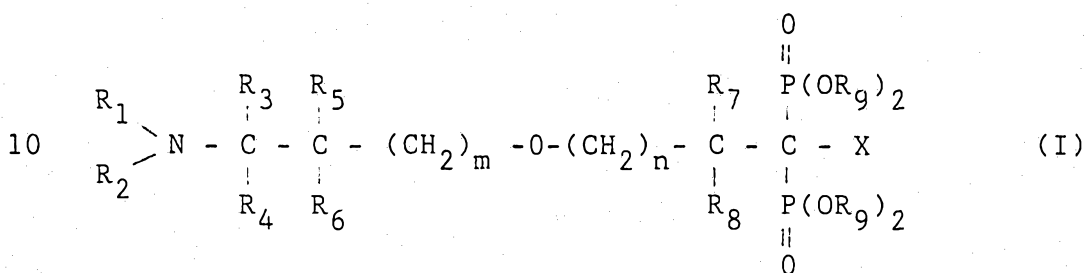
5 Federal Republic of Germany Patent Specification No. 18 13 659 describes diphosphonic acid derivatives of which 1-hydroxyethane-1,1-diphosphonic acid has achieved importance for the treatment of Paget's disease.

10 In Federal Republic of Germany Patent Specification No. 25 34 391 are described aminoalkane-1,1-diphosphonic acids which can be substituted on the nitrogen atom by C_1 - C_3 -alkyl radicals and which have an action on the calcium metabolism.

15 Surprisingly, we have now found that aminoalkane-1,1-diphosphonic acids in which the alkyl chain is interrupted by an oxygen atom display a distinctly more marked action on the calcium metabolism than the compounds hitherto known. Thus, these compounds are
20 especially suitable for a wide treatment of calcium metabolism disturbances. In particular, they can be used especially well in cases where the build up and breakdown of bone is disturbed, i.e. they are suitable for the treatment of diseases of the skeletal system,
25 for example osteoporosis, Paget's disease, Bechterew's disease and the like. On the basis of these properties, they can also be used for the therapy of bone

metastases, urolithiasis and for the prevention of heterotopic ossification. Furthermore, due to their influence on the calcium metabolism, they also provide a basis for the treatment of rheumatoid arthritis, of osteoarthritis and of degenerative arthrosis.

Thus, according to the present invention, there are provided diphosphonates of the general formula:-



wherein R_1 and R_2 , independently of one another, are hydrogen atoms, straight-chained or branched, saturated or unsaturated alkyl radicals containing up to 9 carbon atoms which can optionally be substituted by hydroxyl, C_1 - C_5 -alkoxy or C_1 - C_5 -alkylthio, a phenyl or C_5 - C_7 -cycloalkyl ring, whereby the phenyl moiety can optionally be substituted by C_1 - C_5 -alkyl, C_1 - C_5 -alkoxy, hydroxyl or halogen, or are C_5 - C_7 -cycloalkyl or phenyl radicals, R_3 is a hydrogen atom, a straight-chained or branched C_1 - C_5 -alkyl radical, which is optionally substituted by hydroxyl, C_1 - C_5 -alkoxy, C_1 - C_5 -alkylthio, mercapto, phenyl, 3-indolyl or 4-imidazolyl, or a phenyl radical optionally substituted by hydroxyl or C_1 - C_5 -alkoxy, R_4 , R_6 , R_8 and R_9 , independently of one another, are hydrogen atoms or C_1 - C_5 -alkyl radicals,

R_5 and R_7 , independently of one another, are hydrogen atoms, C_1 - C_5 -alkyl radicals or phenyl radicals optionally substituted by hydroxyl or C_1 - C_5 -alkoxy, X is a hydrogen atom, a hydroxyl group or an $-NR_{10}R_{11}$ radical, where by R_{10} and R_{11} , independently of one another, are hydrogen atoms or C_1 - C_5 -alkyl radicals and m and n are 0 or 1, where by R_1 and R_2 , together with the nitrogen atom to which they are attached, can form a mono- or bicyclic ring system containing 4 to 9 carbon atoms which is partly or wholly hydrogenated and optionally substituted by hydroxyl, C_1 - C_5 -alkyl or C_1 - C_5 -alkoxy and/or, in the case of a monocyclic radical, can be interrupted by an oxygen, nitrogen or sulphur atom, R_1 and R_3 , together with the carbon and nitrogen atoms to which they are attached, can form a five- or six-membered ring which can optionally be condensed by a further six-membered ring, R_1 and R_5 , together with the carbon and nitrogen atoms to which they are attached, as well as the carbon atom lying therebetween, can form a five- or six-membered ring, R_3 and R_4 , together with the carbon atom to which they are attached, can form a five- or six-membered ring, R_4 and R_6 , together with the carbon atoms to which they are attached, can form a five- or six-membered ring, R_5 and R_6 , together with the carbon atom to which they are attached, can form a five- or six-membered ring and R_7 and R_8 , together with the carbon atom to which they are

attached, can form a five- or six-membered ring; as well as the pharmacologically acceptable salts thereof.

By C_1 - C_5 -alkyl radicals are preferably to be understood methyl, ethyl, isopropyl and isobutyl radicals.

C_1 - C_5 -alkoxy and alkylthio radicals are preferably methoxy and methylthio radicals, respectively.

The C_5 - C_7 -cycloalkyl radical is preferably a cyclohexyl radical.

Halogen is to be understood to be especially a chlorine or bromine atom.

The alkyl chains with up to 9 carbon atoms in the case of R_1 and R_2 are preferably methyl, ethyl, isopropyl, isobutyl, sec.-butyl, n-pentyl, n-nonyl, allyl or methallyl radicals.

By an alkyl radical substituted by an optionally substituted phenyl radical is to be understood especially a benzyl radical.

The $-NR_{10}R_{11}$ radical is preferably an amino, dimethylamino or diethylamino radical.

If R_1 and R_2 , together with the nitrogen atom to which they are attached, form a ring, then this is preferably understood to be a pyrrolidine, piperidine, di- or octahydroisoindoline or decahydroquinoline ring.

A ring interrupted by a heteroatom is preferably a piperazine, morpholine or thiamorpholine ring.

When R_1 and R_3 , together with the nitrogen atom

to which they are attached, form a ring, then this is to be understood to be, inter alia, a pyrrolidine, piperidine or octahydroindole ring substituted in the 2-position.

5 When R_1 and R_5 , together with the carbon and nitrogen atoms to which they are attached, as well as the carbon atom lying therebetween, form a ring, this ring is preferably a pyrrolidine or piperidine ring substituted in the 3-position.

10 When R_3 and R_4 or R_5 and R_6 or R_7 and R_8 , together with the carbon atom to which they are attached, form a ring, this is preferably a cyclopentyl ring.

15 If R_4 and R_6 , together with the carbon atoms to which they are attached, form a ring, then this is preferably a cyclohexyl or cyclopentyl ring.

X is preferably a hydrogen atom or a hydroxyl group.

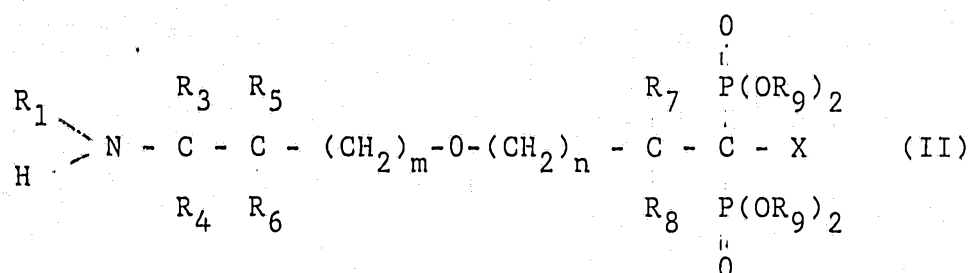
20 Preferred compounds of formula I are compounds wherein R_1 is hydrogen or methyl, R_2 is hydrogen or methyl, R_3 is hydrogen or C_1 - C_5 -alkyl, R_4 is hydrogen or methyl, R_5 is hydrogen or methyl, R_6 is hydrogen, R_7 is hydrogen, R_8 is hydrogen, R_9 is hydrogen, m is zero or 1, n is zero and X is a hydroxyl group

whereby R_1 and R_6 together with the nitrogen atom form a morpholine ring, R_1 and R_3 together with the carbon and nitrogen atoms to which they are attached form a pyrrolidine or piperidine ring, 5 R_1 and R_5 together with the carbon and nitrogen atoms to which they are attached form a piperidine ring, R_4 and R_6 together with the carbon atom to which they are attached form a cyclohexyl ring and R_5 and R_6 together with the carbon atom to which they are 10 attached form a spiro-cyclopentane ring.

Asymmetric carbon atoms can have the R- or S- configuration and the compounds can be present in the optically-active form or as a racemic mixture. They are also within the scope of the present invention.

15 Compounds of general formula I are prepared by known processes and preferably by

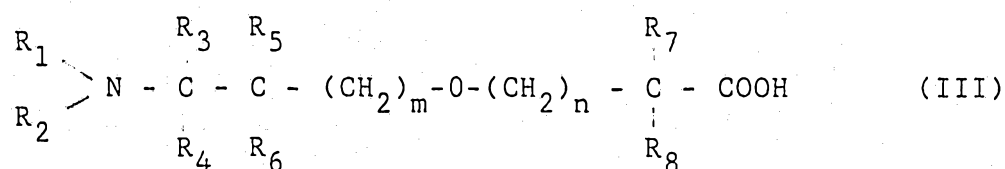
I. mono- or dialkylating a compound of the general formula:



5 in which R_1 , R_3 - R_9 , X , m and n have the above-given meanings, and optionally saponifying the resulting tetraester to give the corresponding diester or acid of general formula I; or

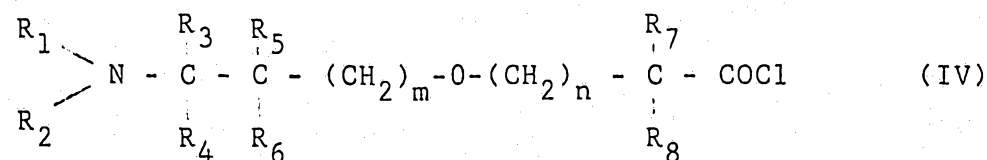
II. when X in general formula I is a hydroxyl group,

10 a) reacting a carboxylic acid of the general formula:



in which R_1 - R_8 , m and n have the above-given meanings,
 15 with a mixture of phosphorous acid or phosphoric acid and a phosphorus halide or phosphorus oxyhalide and subsequently saponifying to the free diphosphonic acid;
 or

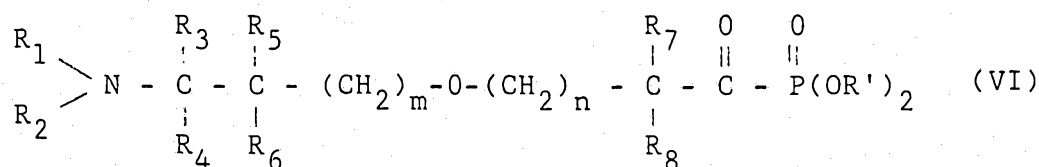
b) reacting a carboxylic acid chloride of the general
 20 formula:-



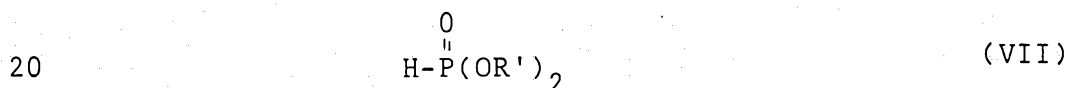
in which R_1-R_8 , m and n have the above-given meanings and in which R_1 can also be an acyl radical or, together with R_2 , can also be a phthaloyl radical as protective group, with a trialkyl phosphite of the
5 general formula:-



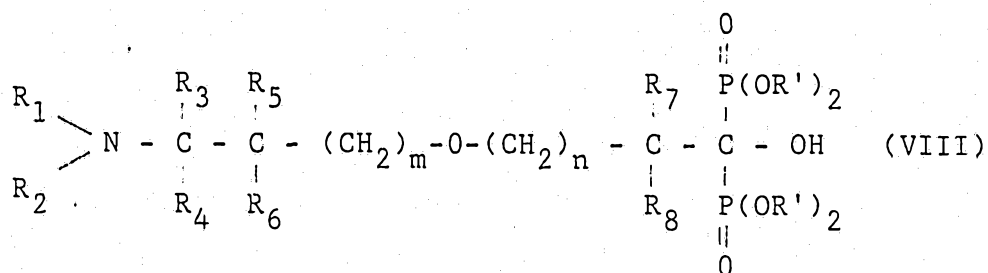
in which R' is an alkyl radical containing up to 4 carbon atoms and preferably a methyl, ethyl, isopropyl or isobutyl radical, to give an acyl phosphonate of the
10 general formula:-



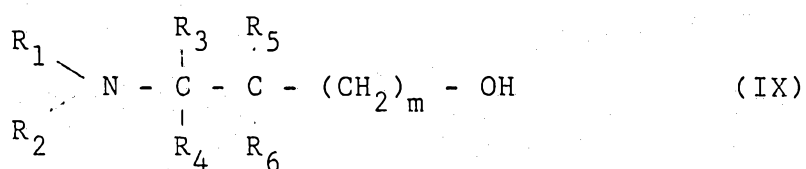
in which R_1-R_8 , m , n and R' have the above-given meanings and R_1 can also be an acyl radical or, together
15 with R_2 , can be a phthaloyl radical, subsequently reacting with a dialkyl phosphite of the general formula:-



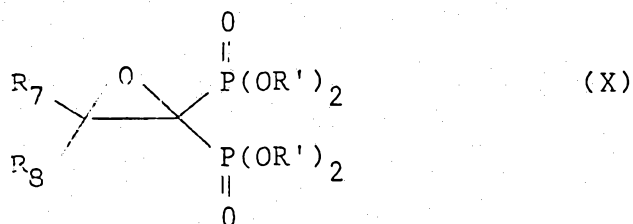
in which R' has the above-given meaning, to give a diphosphonate of the general formula:-



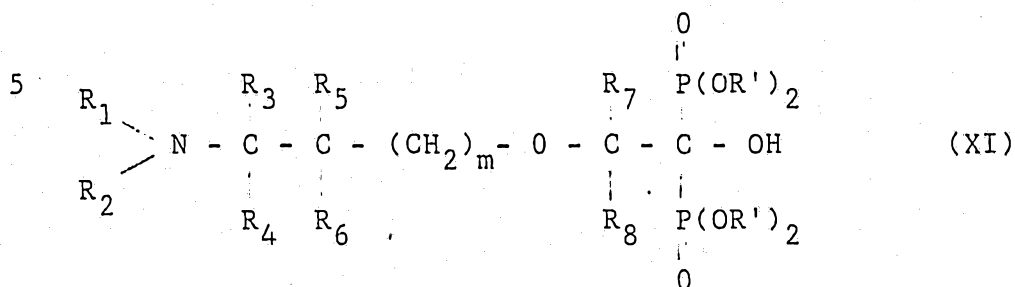
- 5 in which R_1-R_8 , m , n and R' have the above-given meanings and R_1 can also be an acyl radical or, together with R_2 , can form a phthaloyl radical, optionally removing the phthaloyl radical by hydrazinolysis and saponifying the resultant tetraester to the
- 10 corresponding diester or acid of general formula I, whereby, under these conditions, the acyl or phthaloyl radical used as protective group, is simultaneously split off; or
- 15 c) when n is 0, reacting a compound of the general formula:-



- 20 in which R_1-R_6 and m have the above-given meanings, with an epoxide of the general formula:-

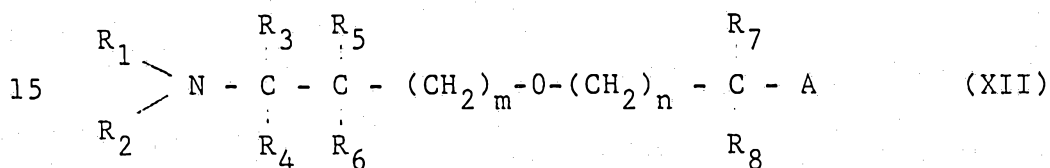


in which R_7 , R_8 and R' have the above-given meanings,
and, if desired, saponifying the resultant
diphosphonic acid derivative of the general formula:-



in which R_1 - R_8 , R' and m have the above-given meanings,
10 to the corresponding diester or acid; or

III. when X in general formula I is an $-NR_{10}R_{11}$
radical, reacting a carboxylic acid derivative of the
general formula:-



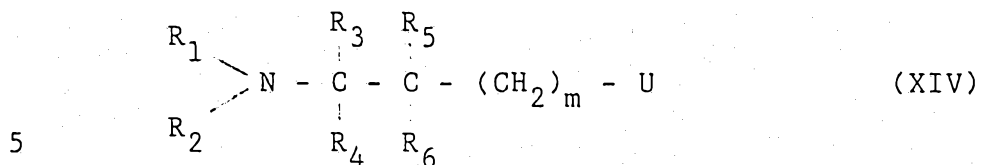
in which R_1 - R_8 , m and n have the above-given meanings
and A is a nitrile, imino ether or $-CONR_{10}R_{11}$ radical,
 R_{10} and R_{11} having the above-given meanings, with a
20 phosphorus compound of the general formula:-



in which T is a halogen atom, a hydroxyl group or an
OR' radical, R' having the above-given meaning, and
possibly saponifying; or

IV. when X in general formula I is a hydrogen atom

a) reacting a compound of the general formula:-



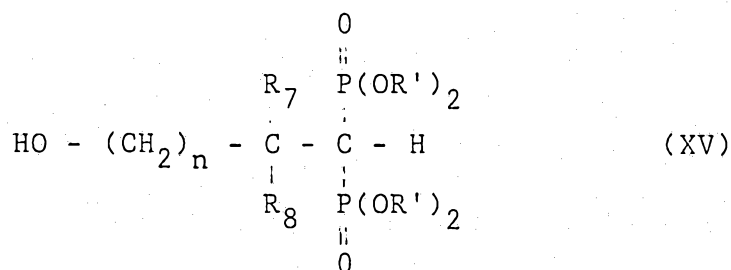
in which R_1 - R_6 and m have the above-given meanings and

R_1 can also be an acyl radical or, together with R_2 , a

phthaloyl radical and U is a reactive group, for

example a halogen atom or a sulphonate group, with a

diphosphonic acid derivative of the general formula;-



in which R_7 , R_8 , R' and n have the above-given meanings,

optionally removing the phthaloyl radical by hydrazino-

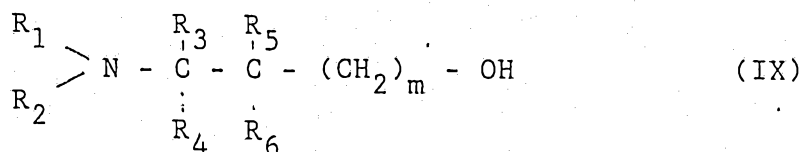
lysis and optionally saponifying the tetraester formed

to the corresponding diester or acid, whereby, under

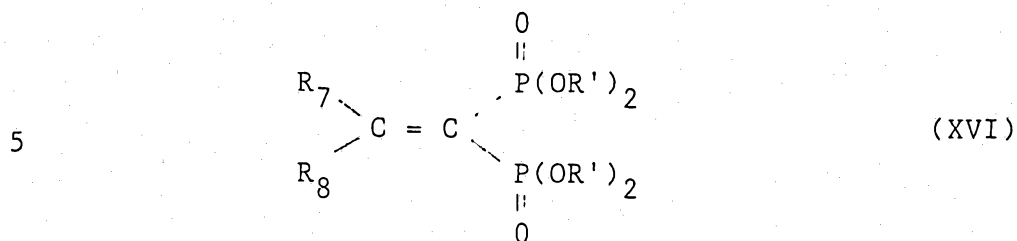
these conditions, the acyl or phthaloyl radical used

as protective group, is simultaneously split off; or

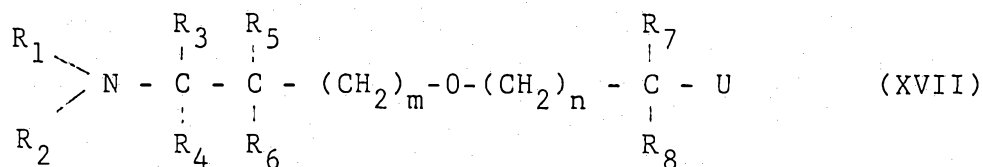
b) adding a compound of the general formula:-



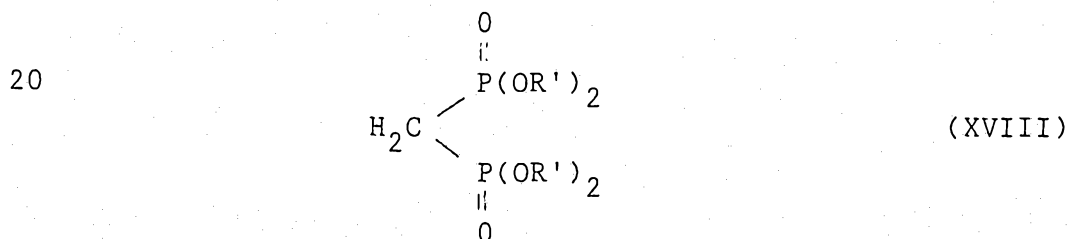
in which R_1-R_6 and m have the above-given meanings, to a compound of the general formula:-



in which R_7 , R_8 and R' have the above-given meanings, and optionally saponifying the tetraester obtained to the corresponding diester or acid; or
 c) reacting a compound of the general formula:-



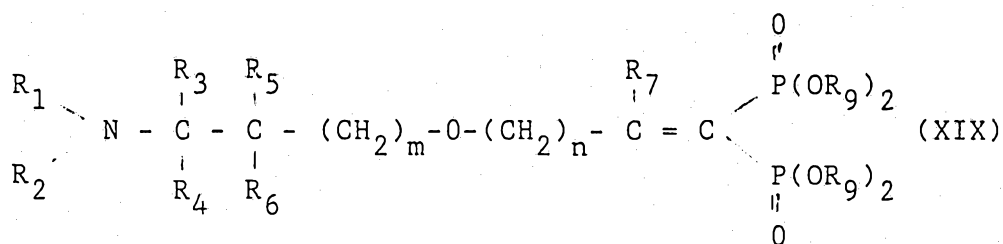
in which R_1-R_8 , U , m and n have the above-given meanings and R_1 can also be an acyl radical or, together with R_2 , can be a phthaloyl radical, with a diposphonic acid derivative of the general formula:-



in which R' has the above-given meaning, removing, if desired, the phthaloyl radical by hydrazinolysis and

optionally saponifying the resultant tetraester to the corresponding diester or acid, whereby, under these conditions, the acyl or phthaloyl radical used as protective group is simultaneously split off; or

5 d) when R_8 is a hydrogen atom, catalytically
hydrogenating a compound of the general formula:-



10

in which R_1 - R_7 , R_9 , $\underline{m}$ and $\underline{n}$ have the above-given meanings and R_1 can also be an acyl radical; and subsequently, if desired, saponifying the resultant tetraester to the corresponding diester or acid,

15 whereby acyl radicals possibly present can thereby also
be split off at the same time and, if desired,
converting a free acid obtained into a pharmacologically
acceptable salt.

In the case of the reductive alkylation (process I), a mixture of primary or secondary amines of general formula II and of a carbonyl compound or an acetal thereof is treated in the presence of a hydrogenation catalyst, for example palladium on charcoal or nickel, with hydrogen under atmospheric or elevated pressure or formic acid is used as reducing

agent. Furthermore, the alkylation of a secondary amine of general formula I can be carried out especially advantageously by the phase transfer process with dialkyl sulphates.

5 The carboxylic acids of general formula II used in process II a) are reacted with 1 - 2 and preferably with 1.5 mole of phosphorous acid or phosphoric acid and 1 to 2 and preferably 1.5 mole of phosphorus trihalide or phosphorus oxyhalide at a temperature of
10 from 80 to 130°C. and preferably of from 100 to 110°C. The reaction can also be carried out in the presence of a diluent, for example a halogenated hydrocarbon and especially chlorobenzene, tetrachloroethane or also sulfolane or dioxan. The subsequent hydrolysis takes
15 place by boiling with water but advantageously with semi-concentrated hydrochloric or hydrobromic acid. As phosphorus trihalides in the above process, there can be used, for example, phosphorus trichloride or phosphorus tribromide and, as phosphorus oxyhalide,
20 especially phosphorus oxychloride.

 In the case of process II b), the acid chloride of general formula IV is reacted with the trialkyl phosphite of general formula V at a temperature of from 0 to 60°C. and preferably of from 20 to 40°C. It is
25 possible to work without a solvent or also in the presence of an inert solvent, for example diethyl ether, tetrahydrofuran, dioxan or a halogenated hydrocarbon,

for example methylene chloride. The acyl phosphonate of general formula VI obtained as intermediate can be isolated or further reacted directly. The subsequent reaction is carried out in the presence of a weak
5 base, preferably of a secondary amine, for example dibutylamine, at a temperature of from 0 to 60°C. and preferably of from 10 to 30°C. When R_1 and R_2 together form a phthaloyl radical as protective group, this is split off by hydrazinolysis or acid hydrolysis. In the
10 case of hydrazinolysis, hydrazine is used in acetic acid or also in ethanol at a temperature of from 20 to 80°C. The acidic hydrolysis can be carried out very well by boiling with semi-concentrated hydrochloric acid. In this manner, an acyl radical, preferably an
15 acetyl radical, used as protective group, is also split off.

In the case of process II c), the alcohols of general formula IX are, as a rule, used in the form of their alkali metal salts and preferably as their
20 sodium salts. As solvent, it is preferred to use toluene, dioxan, tetrahydrofuran or also dimethylformamide. The reaction is carried out at a temperature of from 20 to 80°C.

In the case of process III, the nitriles of
25 general formula XII are reacted with phosphorous acid at a temperature of from 110 to 180°C. The reaction can be carried out with a solvent or in the presence

of an aprotic solvent, for example diethylene glycol dimethyl ether or diethylene glycol diethyl ether. However, the nitriles can also be reacted with a phosphorus trihalide, for example phosphorus tribromide or phosphorus trichloride, in an inert solvent, for example dioxan or tetrahydrofuran, optionally with the addition of water, at a temperature of from 20 to 80°C. Imino ethers of general formula XII can be reacted with dialkyl phosphites, preferably in the presence of equimolar amounts of sodium, in an inert solvent, for example diethyl ether, dioxan or also benzene, the reaction taking place, as a rule, at the reflux temperature of the solvent employed. Acid amides of general formula XII can be reacted in an inert solvent, for example a halogenated hydrocarbon or an ether, such as diethyl ether, with a mixture of phosphorus pentahalide/phosphorous acid or also of oxalyl chloride/trialkyl phosphite.

In the case of process IV a), the diphosphonic acid derivative of general formula XV is used in the form of a sodium or potassium salt. For this purpose, it is reacted with sodium, potassium or the corresponding hydride in an inert solvent, for example benzene, toluene or dimethylformamide, at a temperature of from 0 to 40°C. and preferably of about 25°C. The alkali metal salt is reacted, without isolation, with the appropriate halide or sulphonate, the temperature

thereby used being from 20 to 110°C.

If R_1 and R_2 together form a phthaloyl radical as protective group or R_1 is an acyl radical and preferably an acetyl radical, these radicals are split
5 off in the manner described in process II b).

In the case of process IV b), the alcohols of general formula IX are used in the form of their alkali metal salts and preferably of their sodium salts. For this purpose, they are reacted with sodium or sodium
10 hydride in an inert solvent, for example benzene, toluene, dioxan or dimethylformamide, at a temperature of from 0 to 60°C. and preferably of about 25°C. As a rule, the alkali metal salt is reacted, without isolation, with the appropriate diphosphonate of
15 general formula XVI, the temperature used being from 20 to 80°C.

In the case of process IV c), the methylene-diphosphonic acid esters of general formula XVIII are used in the form of their sodium or potassium salts.
20 For this purpose, they are reacted with sodium, potassium or the corresponding hydride in an inert solvent, for example benzene, toluene or dimethylformamide, at a temperature of from 0 to 40°C. and preferably of about 25°C. The alkali metal salt is
25 reacted, without isolation, with the appropriate halide or sulphonate, the temperature used being from 20 to 110°C.

The hydrogenation in the case of process IV d) is carried out in the presence of a noble metal catalyst, for example palladium on charcoal or platinum, in an alcohol, for example methanol or ethanol, as
5 solvent or also in water. However, nickel can also be used in an alkaline medium. The splitting off of the N-acyl radical can be carried out under alkaline conditions but preferably under acidic conditions, for example with 6N hydrochloric acid.

10 Optically-active compounds of general formula I are usually prepared by using optically-active starting materials.

The aminooxaalkanecarboxylic acids used in process II a) are usually prepared in the following
15 manner: The appropriate aminoalkanol is reacted with, for example, a haloacetic acid ester, to give an aminooxaalkanecarboxylic acid ester which, depending upon the chain length and the substitution on the nitrogen atom, can be cyclised to give an oxalactam. The
20 resultant carboxylic acid ester is saponified in the usual manner under acidic or alkaline conditions. In the case of ring formation, the lactam ring is opened by boiling with barium hydroxide solution and the barium salt of the aminooxaalkanecarboxylic acid is
25 converted into the free acid with sulphuric acid.

The aminoalkanols used in the case of this process, as well as in the case of processes II c) and

IV b), are, as a rule, known from the literature or can easily be prepared from the appropriate amino acids or the esters thereof by reduction with, for example lithium aluminium hydride.

5 The aminooxaalkanecarboxylic acid nitriles or amides used in the case of process III can be synthesised from the appropriate aminoalkanols by reaction with haloacetic acid nitriles or haloacetic acid amides. From the nitriles thus obtained can be
10 obtained the corresponding imino ethers by conventional processes, for example by reaction with a lower alcohol in the presence of gaseous hydrogen chloride.

 By the reaction of an aminoalkanol with a phosphorus halide, for example phosphorus trichloride
15 or phosphorus tribromide, or with an aliphatic or aromatic sulphochloride, for example methanesulphochloride or benzenesulphochloride, there is obtained a compound of general formula XIV used in the case of process IV a).

20 The compounds of general formula XIX used in the case of process IV b) can be prepared, for example, by the elimination of an H-Y group, wherein Y is, for example, a halogen atom, preferably a bromine or chlorine atom, or an acyloxy radical, especially an
25 acetoxo or propionyloxy radical. The elimination can take place by the use of bases, for example tertiary amines and especially triethylamine, pyridine or

diazabicycloundecane, in an inert solvent, for example an alcohol or ether, such as dioxan or tetrahydrofuran. In the case of the splitting off of acetic or propionic acid, there is preferably used the tetra-
5 sodium or tetrapotassium salt of the corresponding diposphonic acid, the splitting off being carried out by heating to a temperature of from 180 to 300°C. and preferably of from 180 to 240°C. The free acid can be liberated from the tetraalkali metal salt, for example
10 by treatment with an acidic ion exchanger, such as Amberlite IR 120, H⁺ form.

The above-mentioned starting compounds can be used as racemates or as enantiomers, the optically-active compounds usually being obtained from the
15 corresponding optically-active amino acids.

The tetraalkyl esters possibly obtained in the case of the above-mentioned processes can be saponified to the diesters or to the free tetraacids. The saponification to diesters takes place, as a rule, by
20 treating the tetraalkyl esters with an alkali metal halide, preferably with sodium iodide, in an appropriate solvent, for example acetone, at ambient temperature. There is thereby formed the symmetrical diester/disodium salt which can possibly be converted into the
25 diester/diacid by means of an acidic ion exchanger. The saponification to the free diposphonic acids takes place, as a rule, by boiling with semi-concentrated

hydrochloric or hydrobromic acid. However, a splitting off can also be carried out with a trimethylsilyl halide and preferably with the bromide or iodide. On the other hand, the free diphosphonic acids can again
5 be converted into the tetraalkyl esters by boiling with orthoformic acid alkyl esters. The free diphosphonic acids of general formula I can be isolated as free acids or in the form of their mono- or dialkali metal salts. As a rule, the alkali metal salts can be
10 purified by reprecipitation from water/methanol or water/acetone.

As pharmacologically acceptable salts, there are especially used the alkali metal and ammonium salts which are prepared in the usual manner, for example by
15 titration of the compounds with inorganic or organic bases, for example sodium or potassium hydrogen carbonate, aqueous sodium hydroxide solution, aqueous potassium hydroxide solution, aqueous ammonia solution or amines, for example trimethylamine or triethylamine.

20 The new compounds of general formula I according to the present invention and the salts thereof can be administered enterally or parenterally in liquid or solid form. For this purpose, there can be used all conventional forms of administration, for example
25 tablets, capsules, dragees, syrups, solutions, suspensions and the like. As injection medium, it is preferred to use water which contains the additives

usual in the case of injection solutions, for example stabilising agents, solubilising agents and buffers.

Additives of this kind include, for example, tartrate and citrate buffers, ethanol, complex formers (such

5 as ethylenediamine-tetraacetic acid and the non-toxic salts thereof) and high molecular weight polymers (such as liquid polyethylene oxide) for viscosity regulation. Liquid carrier materials for injection solutions must be sterile and are preferably filled into ampoules.

10 Solid carrier materials include, for example, starch, lactose, mannitol, methylcellulose, talc, highly dispersed silicic acid, high molecular weight fatty acids (such as stearic acid), gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable
15 fats and solid high molecular weight polymers (such as polyethylene glycols). Compositions suitable for oral administration can, if desired, contain flavouring and sweetening agents.

The dosage used can depend upon various factors,
20 for example mode of administration, species, age and/or the individual state of health. The doses to be administered daily are from about 0.1 to 100 mg./human and preferably 1 to 20 mg./human and can be administered divided up one or more times.

25 Preferred in the sense of the present invention are, apart from the compounds described in the following Examples and compounds which can be derived by the

combination of all of the definitions given in the claims, the following diphosphonates, as well as the sodium salts and the methyl, ethyl and isopropyl esters thereof:

- 5 5-N,N-dimethylamino-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 5-N-methyl-N-propylamino-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 5-N-methyl-N-nonylamino-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 10 5-N-benzylamino-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 5-N-isobutyl-N-methylamino-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 15 5-N-methallyl-N-methylamino-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 5-N-(2-methoxyethyl)-N-methylamino-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 5-N-(2-hydroxyethyl)-N-methylamino-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 20 5-N-(2-methylthioethyl)-N-methylamino-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 5-N-(4-methylbenzyl)-amino-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 25 5-N-(2-chlorobenzyl)-amino-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 5-N-cyclohexyl-N-methylamino-3-oxapentane-1-hydroxy-1,1-diphosphonic acid

- 5-amino-7-methyl-3-oxaoctane-1-hydroxy-1,1-diphosphonic acid
- 5-amino-6-phenyl-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
- 5 5-amino-6-(3-indolyl)-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
- 5-amino-6-(4-imidazolyl)-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
- 5-amino-6-hydroxy-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
- 10 5-amino-7-methylthio-3-oxaheptane-1-hydroxy-1,1-diphosphonic acid
- 5-N-methyl-N-propylamino-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
- 15 5-N-methyl-N-pentylamino-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
- 5-N-allyl-N-methylamino-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
- 5-amino-6-(4-hydroxyphenyl)-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
- 20 5-amino-4,4-dimethyl-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 5-amino-4-phenyl-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 25 5-amino-2-methyl-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 5-amino-2,2-dimethyl-3-oxapentane-1-hydroxy-1,1-diphosphonic acid

- 5-amino-2-phenyl-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 5-(1-pyrrolidinyl)-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 5 5-(1-piperidinyl)-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 5-(3-hydroxy-1-pyrrolidinyl)-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 5-(3,4-dimethoxy-1-pyrrolidinyl)-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 10 5-(2,3-dihydroisoindolin-1-yl)-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 5-(octahydroisoindolin-1-yl)-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 15 5-(decahydroquinolin-1-yl)-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 5-(1-piperazinyl)-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 5-(4-methyl-1-piperazinyl)-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 20 5-(4-thiamorpholinyl)-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 5-(4-hydroxy-1-piperidinyl)-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
- 25 S-4-(2-pyrrolidinyl)-3-oxabutane-1-hydroxy-1,1-diphosphonic acid
- 4-(2-piperidinyl)-3-oxabutane-1-hydroxy-1,1-diphosphonic acid

- 4-(1-methyl-2-piperidinyl)-3-oxabutane-1-hydroxy-
1,1-diphosphonic acid
- 5-(1-methyl-2-piperidinyl)-3-oxapentane-1-hydroxy-
1,1-diphosphonic acid
- 5 4-(octahydroindolin-2-yl)-3-oxabutane-1-hydroxy-1,1-
diphosphonic acid
- 4-(1-ethyl-2-pyrrolidinyl)-3-oxabutane-1-hydroxy-1,1-
diphosphonic acid
- 3-(3-pyrrolidinyl)-3-oxapropane-1-hydroxy-1,1-
10 diphosphonic acid
- 5-amino-5,5-butylene-3-oxapentane-1-hydroxy-1,1-
diphosphonic acid
- 5-N,N-dimethylamino-5,5-pentylene-3-oxapentane-1-
hydroxy-1,1-diphosphonic acid
- 15 4-(2-aminocyclohexyl)-3-oxabutane-1-hydroxy-1,1-
diphosphonic acid
- 3-(2-aminocyclopentyl)-3-oxapropane-1-hydroxy-1,1-
diphosphonic acid
- 4-(2-aminocyclopentyl)-3-oxabutane-1-hydroxy-1,1-
20 diphosphonic acid
- 4-(2-N,N-dimethylaminocyclohexyl)-3-oxabutane-1-
hydroxy-1,1-diphosphonic acid
- 5-amino-4,4-butylene-3-oxapentane-1-hydroxy-1,1-
diphosphonic acid
- 25 6-amino-2,2-butylene-3-oxahexane-1-hydroxy-1,1-
diphosphonic acid
- 5-N,N-dimethylamino-2,2-pentylene-3-oxapentane-1-
hydroxy-1,1-diphosphonic acid

- 1,5-diamino-3-oxapentane-1,1-diphosphonic acid
5-amino-1-N,N-diethylamino-3-oxahexane-1,1-diphosphonic acid
5-amino-3-oxahexane-1,1-diphosphonic acid
5 R-5-amino-3-oxahexane-1,1-diphosphonic acid
S-5-amino-3-oxahexane-1,1-diphosphonic acid
5-N,N-dimethylamino-3-oxapentane-1,1-diphosphonic acid
R-5-amino-7-methyl-3-oxaoctane-1-hydroxy-1,1-diphosphonic acid
10 R-5-amino-6-phenyl-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
S-5-amino-6-phenyl-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
R-5-amino-6-(3-indolyl)-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
15 S-5-amino-6-(3-indolyl)-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
R-5-amino-6-(4-imidazolyl)-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
20 S-5-amino-6-(4-imidazolyl)-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
R-5-amino-1,6-dihydroxy-3-oxahexane-1,1-diphosphonic acid
S-5-amino-1,6-dihydroxy-3-oxahexane-1,1-diphosphonic acid
25 R-5-amino-7-methylthio-3-oxaheptane-1-hydroxy-1,1-diphosphonic acid

- S-5-amino-7-methylthio-3-oxaheptane-1-hydroxy-1,1-diphosphonic acid
- R-5-N-methyl-N-propylamino-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
- 5 S-5-N-methyl-N-propylamino-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
- R-5-N-methyl-N-pentylamino-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
- S-5-N-methyl-N-pentylamino-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
- 10 S-5-N-methyl-N-pentylamino-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
- R-5-N-allyl-N-methylamino-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
- S-5-N-allyl-N-methylamino-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
- 15 R-5-amino-5-6-(4-hydroxyphenyl)-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
- S-5-amino-6-(4-hydroxyphenyl)-3-oxahexane-1-hydroxy-1,1-diphosphonic acid
- R-5-amino-4-phenyl-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 20 S-5-amino-4-phenyl-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- R-5-amino-2-methyl-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
- 25 S-5-amino-2-methyl-3-oxaheptane-1-hydroxy-1,1-diphosphonic acid
- R-5-amino-2-phenyl-3-oxapentane-1-hydroxy-1,1-diphosphonic acid

S-5-amino-2-phenyl-3-oxapentane-1-hydroxy-1,1-diphosphonic acid

5-amino-2-methyl-3-oxahexane-1-hydroxy-1,1-diphosphonic acid

5 6-amino-3-oxaheptane-1-hydroxy-1,1-diphosphonic acid

6-amino-5-methyl-3-oxahexane-1-hydroxy-1,1-diphosphonic acid

6-amino-4-methyl-3-oxahexane-1-hydroxy-1,1-diphosphonic acid.

10 The following Examples show some of the process variants which can be used for the synthesis of the compounds according to the present invention. However, they are not to represent a limitation of the subject matter of the present invention. As a rule, the compounds are obtained as high melting point solid products (mono- or disodium salts), the structures of which have been verified by H, P and possibly by ^{13}C NMR spectroscopy. The purity of the substances was determined by means of C, H, N, P, S and Na analyses, as well as by
15 thin layer electrophoresis (cellulose, oxalate buffer of pH 4.0). For the characterisation of the individual compounds, there are given the M_{rel} values (relative mobility), referred to pyrophosphate ($M_{\text{rel}} = 1$).

Example 1.

25 R,S-5-Amino-3-oxahexane-1-hydroxy-1,1-diphosphonic acid.

0.67 g. (5 mmol) R,S-5-amino-3-oxahexanoic acid are melted at 100°C . with 0.82 g. (10 mmol) phosphorous

acid. The oil bath used is removed, 1 ml. (11 mmol) phosphorus trichloride is added dropwise thereto and heating continued for a further 24 hours at an external temperature of 100°C. After cooling, the reaction mixture is mixed with 10 ml. water, boiled under reflux for 45 minutes and filtered off with suction. The filtrate is concentrated to one half, the solution is adjusted to pH 5 with 10N aqueous sodium hydroxide solution, mixed with 20 ml. methanol and the solution is cooled in an ice-bath. The precipitate obtained is filtered off with suction, washed with methanol and dried. The residue is dissolved in a little water and purified over an ion exchanger column (35 g. Amberlite-IT 120; H⁺ form). There is obtained 0.49 g. (34% of theory) of the desired compound which contains 0.5 mole of water of crystallisation; m.p. 240 - 260°C.; $M_{rel} = 0.40$.

The R,S-5-amino-3-oxahexanoic acid used as starting material is prepared in the following way: R,S-5-methylmorpholin-3-one (m.p. 62 - 64°C.) is boiled with barium hydroxide and the free acid produced from the barium salt with sulphuric acid at pH 5; m.p. 190 - 193°C.

In an analogous manner, by reacting phosphorous acid and phosphorus trichloride with the following starting material, there is obtained:

a) from R,S-5-N,N-dimethylamino-3-oxahexanoic acid

(m.p. 108 - 110°C.) (prepared by the reductive methylation of R,S-5-amino-3-oxahexanoic acid by means of formic acid/formaldehyde), R,S-5-N,N-dimethylamino-3-oxahexane-1-hydroxy-1,1-diphosphonic acid as the free acid with 1 mole of water of crystallisation in a yield of 36% of theory; m.p. about 270°C.; $M_{rel} = 0.40$.

Example 2.

Analogously to Example 1, there are obtained, by the use of:

- 10 a) 5-amino-3-oxapentanoic acid (m.p. 188 - 190°C.),
5-amino-3-oxapentane-1-hydroxy-1,1-diphosphonic acid
with 1 mole water of crystallisation; yield 31% of theory; m.p. 255 - 260°C.; $M_{rel} : 0.30$.
- 15 b) 6-(N-acetylamino)-3-oxahexanoic acid (oil), 6-amino-3-oxahexane-1-hydroxy-1,1-diphosphonic acid with
1 mole water of crystallisation; yield 23% of theory;
m.p. 125 - 130°C.; $M_{rel} : 0.30$.
- 20 c) 5-N-methylamino-3-oxapentanoic acid (m.p. 242 - 245°C.),
5-N-methylamino-3-oxapentane-1-hydroxy-1,1-
diphosphonic acid with 1 mole water of crystallisation; yield 28% of theory; m.p. 155 - 160°C.;
 $M_{rel} : 0.35$.
- 25 d) 6-N,N-dimethylamino-3-oxahexanoic acid hydrochloride
(oil), 6-N,N-dimethylamino-3-oxahexane-1-hydroxy-
1,1-diphosphonic acid with 1 mole water of
crystallisation; yield 22% of theory; m.p. 115 -
120°C.; $M_{rel} : 0.30$.

- e) R-5-amino-3-oxahexanoic acid (m.p. 182 - 185°C.;
[α]_D²⁰: -30.5°, c = 1.5 in water), R-5-amino-3-oxahexane-1-hydroxy-1,1-diphosphonic acid with
1 mole water of crystallisation; yield 30% of
theory; m.p. 118 - 123°C.; [α]_D²⁰: -22.6°, c =
0.8 in water; M_{rel}: 0.30.
- f) S-5-amino-3-oxahexanoic acid (m.p. 180 - 182°C.;
[α]_D²⁰: -28.5°, c = 1.4 in water), S-5-amino-3-oxahexane-1-hydroxy-1,1-diphosphonic acid with
1 mole water of crystallisation; yield 34% of
theory; m.p. 115 - 120°C.; [α]_D²⁰: +21.2°, c = 0.8
in water; M_{rel}: 0.30.
- g) 5-amino-6-methyl-3-oxaheptanoic acid (oil), 5-amino-6-methyl-3-oxaheptane-1-hydroxy-1,1-diphosphonic acid with 1 mole water of crystallisation; yield
22% of theory; m.p. 135 - 140°C.; M_{rel}: 0.35.
- h) S-5-amino-6-methyl-3-oxaheptanoic acid (m.p. 140 -
145°C.; [α]_D²⁰: +23.9°, c = 1 in water), S-5-amino-6-methyl-3-oxaheptane-1-hydroxy-1,1-diphosphonic acid with 1 mole water of crystallisation; yield
27% of theory; m.p. 245 - 250°C.; [α]_D²⁰: +19.3°,
c = 1.0 in water; M_{rel}: 0.30.
- i) R-5-amino-6-methyl-3-oxaheptanoic acid (m.p. 143 -
147°C.; [α]_D²⁰: -24.3°, c = 1.1 in water), R-5-amino-6-methyl-3-oxaheptane-1-hydroxy-1,1-diphosphonic acid with 1 mole water of crystallisation; yield 26% of
theory; m.p. 245 - 250°C.; [α]_D²⁰: -18.9°, c = 1.0
in water; M_{rel}: 0.30.

- j) S-5-amino-7-methyl-3-oxaoctanoic acid; m.p. 148 - 150°C.; $[\alpha]_D^{20}$: +17.7°, c = 1.2 in water),
S-5-amino-7-methyl-3-oxaoctane-1-hydroxy-1,1-
diphosphonic acid with 1 mole water of crystallis-
5 ation; yield 31% of theory; m.p. 250 - 255°C.;
 $[\alpha]_D^{20}$: +14.8°, c = 1.2 in water; M_{rel} : 0.30.
- k) 5-amino-5-methyl-3-oxahexanoic acid (m.p. 243 -
245°C., 5-amino-5-methyl-3-oxahexane-1-hydroxy-1,1-
diphosphonic acid with 1 mole water of crystallis-
10 ation; yield 27% of theory; m.p. 155 - 160°C.;
 M_{rel} : 0.40.
- l) 5-amino-4-methyl-3-oxapentanoic acid (m.p. 213 -
215°C.), 5-amino-4-methyl-3-oxapentane-1-hydroxy-
1,1-diphosphonic acid with 1 mole water of
15 crystallisation; yield 33% of theory; m.p. 145 -
150°C.; M_{rel} : 0.30.
- m) 5-(4-morpholinyl)-3-oxapentanoic acid hydrochloride
(oil), 1-hydroxy-5-(4-morpholinyl)-3-oxapentane-1,1-
diphosphonic acid with 1 mole water of crystallis-
20 ation; yield 28% of theory; m.p. 135 - 140°C.;
 M_{rel} : 0.35.
- n) 3-(N-acetyl-3-piperidinyl)-3-oxapropionic acid (oil),
1-hydroxy-(3-piperidinyl)-3-oxapropane-1,1-
diphosphonic acid with 1 mole water of crystallis-
25 ation; yield 15% of theory; m.p. 185 - 190°C.;
 M_{rel} : 0.30.

- o) 3-(2-aminocyclohexyl)-3-oxapropionic acid (m.p. 218 - 220°C.), 3-(2-aminocyclohexyl)-3-oxapropane-1-hydroxy-1,1-diphosphonic acid with 1 mole water of crystallisation; yield 19% of theory; m.p. 215 - 220°C.; M_{rel} : 0.25.
- 5 p) 5-amino-4,4-pentylene-3-oxapentanoic acid (m.p. 203 - 205°C.), 5-amino-4,4-pentylene-3-oxapentane-1-hydroxy-1,1-diphosphonic acid with 1 mole water of crystallisation; yield 29% of theory; m.p. 235 - 240°C.; M_{rel} : 0.30.
- 10 q) S-4-(2-pyrrolidinyl)-3-oxabutyric acid (m.p. 152 - 155°C.; $[\alpha]_D^{20}$: +20.3°, $c = 1.3$ in water, S-1-hydroxy-4-(2-pyrrolidinyl)-3-oxabutane-1,1-diphosphonic acid with 1 mole water of crystallisation; yield 26% of theory; m.p. 120 - 125°C., $[\alpha]_D^{20}$: +18.0°, $c = 0.9$ in water; M_{rel} : 0.30.
- 15 r) R-5-amino-4-methyl-3-oxapentanoic acid (m.p. 210 - 212°C.; $[\alpha]_D^{20}$: -97.0°, $c = 1$ in water), R-5-amino-4-methyl-3-oxapentane-1-hydroxy-1,1-diphosphonic acid with 1 mole water of crystallisation; yield 23% of theory; m.p. 140 - 145°C.; $[\alpha]_D^{20}$: -22.5°, $c = 1$ in water; M_{rel} : 0.30.
- 20 s) S-5-amino-4-methyl-3-oxapentanoic acid (m.p. 212 - 214°C.; $[\alpha]_D^{20}$: +97.8°, $c = 1$ in water), S-5-amino-4-methyl-3-oxapentane-1-hydroxy-1,1-diphosphonic acid with 1 mole water of crystallisation; yield 15% of theory; m.p. 145 - 150°C.; $[\alpha]_D^{20}$: +22.9°, $c = 1$ in water, M_{rel} : 0.30.
- 25

- t) 4-(2-piperidiny1)-3-oxabutyric acid (m.p. 158 -
160°C.), 1-hydroxy-4-(2-piperidiny1)-3-oxabutane-
1,1-diphosphonic acid with 1 mole water of
crystallisation; yield 24% of theory; m.p. 175 -
5 180°C.; M_{rel} : 0.30.

The 5-amino-3-oxapentanoic acid used in Example
2 a) is prepared in the following way:

Ethanolamine is reacted in the presence of sodium
hydride with ethyl chloroacetate to give morpholin-3-one
10 (m.p. 100 - 102°C.) and the desired acid obtained there-
from by heating with barium hydroxide and subsequent
treatment with sulphuric acid.

The intermediate products set out in the following
Table are prepared and reacted in an analogous manner:

Example No.	Morpholinone	m.p. °C.	$[\alpha]_D^{20}$ in methanol
2 c	N-methylmorpholin-3-one	oil	-
2 e	R-5-methylmorpholin-3-one	60-62	-3.7°
5 2 f	S-5-methylmorpholin-3-one	59-61	+3.1°
2 g	5-isopropylmorpholin-3-one	86-88	-
2 h	S-5-isopropylmorpholin-3-one	86-88	+3.9°
2 i	R-5-isobutylmorpholin-3-one	87-89	-4.3°
2 j	S-5-isobutylmorpholin-3-one	70-72	-4.0°
10 2 k	5,5-dimethylmorpholin-3-one	133-35	-
2 l	6-methylmorpholin-3-one	96-98	-
2 o	2-oxa-5-azabicyclo[4.4.0]-decan-4-one	174-76	-
15 2 p	1-oxa-4-azabicyclospiro-[5.5]undecan-3-one	93-95	-
2 q	S-3-oxa-6-azabicyclo[4.3.0]-nonan-5-one	64-66	-
2 r	R-6-methylmorpholin-3-one	96-98	-134.1°
2 s	S-6-methylmorpholin-3-one	95-97	+131.1°
20 2 t	3-oxa-6-azabicyclo[4.4.0]-decan-5-one	oil	-

In the case of Examples 2 b) and 2 n), the starting aminoalcohols are first acetylated on the nitrogen atom, subsequently reacted in the presence of sodium

hydride with ethyl bromoacetate to give the corresponding ethyl alkoxyacetate and then saponified with an aqueous solution of sodium hydroxide. All the intermediates are obtained in the form of an oil.

5 In the case of Examples 2 d) and 2 m), the tert.-aminoalcohols are reacted in the presence of sodium hydride with ethyl bromoacetate (2 m)) or with the sodium salt of chloroacetic acid (2 d)), in the latter case esterified with ethanol-sulphuric acid to
10 the corresponding ethyl ester and in both cases subsequently saponified with 2N hydrochloric acid. Here, too, all the intermediates are obtained in the form of an oil.

Example 3.

15 5-Amino-3-oxapentane-1,1-diphosphonic acid.

1.73 g. (6 mmol) Methanediphosphonic acid tetraethyl ester is added dropwise to 144 mg. (6 mmol) sodium hydride in 5 ml. anhydrous toluene. After completion of the evolution of hydrogen, stirring is
20 continued for 30 minutes and then 1.7 g. (6 mmol) N-(2-bromoethoxyethyl)-phthalimide (m.p. 83 - 85°C.) is added dropwise thereto. The reaction mixture is stirred for 24 hours at ambient temperature, then mixed with water, the aqueous phase is adjusted to pH 5 with
25 2N hydrochloric acid and the organic phase is separated off, dried and evaporated. The residue is purified over 250 g. silica gel (elution agent: methylene

chloride/methanol 4/1 v/v) to give 0.35 g. (12% of theory) 5-phthalimido-3-oxapentane-1,1-diphosphonic acid tetraethyl ester in the form of an oily substance.

The ester is subsequently boiled under reflux for 12

5 hours with 10 ml. 6N hydrochloric acid and, after

cooling, the precipitated phthalic acid is filtered

off with suction. The residue is taken up in water,

the solution is adjusted with 2N aqueous sodium

hydroxide solution to pH 5 and mixed, while cooling

10 with ice, with a large excess of methanol. The

precipitate obtained is filtered off with suction and

dried. There is obtained 0.125 g. (7.2% of theory)

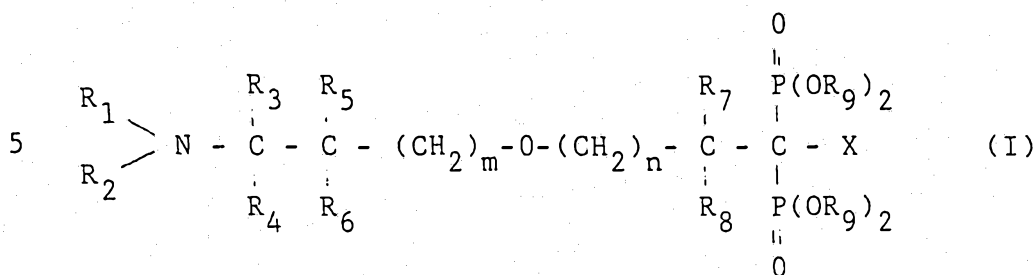
of the desired compound in the form of the monosodium

salt containing 1 mole water of crystallisation;

15 m.p. > 300°C.; $M_{rel} = 0.30$.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Compounds of the general formula:-



wherein R_1 and R_2 , independently of one another, are hydrogen atoms, straight-chained or branched, saturated or unsaturated alkyl chains containing up to 9 carbon atoms which can optionally be substituted by hydroxyl, C_1 - C_5 -alkoxy or C_1 - C_5 -alkylthio, a phenyl or C_5 - C_7 -cycloalkyl ring, whereby the phenyl ring can be optionally substituted by C_1 - C_5 -alkyl, C_1 - C_5 -alkoxy, hydroxyl or halogen, or are C_5 - C_7 -cycloalkyl or phenyl radicals, R_3 is a hydrogen atom, a straight-chained or branched C_1 - C_5 -alkyl radical which can optionally be substituted by hydroxyl, C_1 - C_5 -alkoxy, C_1 - C_5 -alkylthio, mercapto, phenyl, 3-indolyl or 4-imidazolyl, or a phenyl radical optionally substituted by hydroxyl or C_1 - C_5 -alkoxy, R_4 , R_6 , R_8 and R_9 , independently of one another, are hydrogen atoms or C_1 - C_5 -alkyl radicals, R_5 and R_7 , independently of one another, are hydrogen atoms, C_1 - C_5 -alkyl radicals or phenyl radicals optionally substituted by hydroxyl or C_1 - C_5 -alkoxy, X is a hydrogen atom, a hydroxyl group or an $-\text{NR}_{10}\text{R}_{11}$ radical, whereby

R_{10} and R_{11} , independently of one another, are hydrogen atoms or C_1 - C_5 -alkyl radicals and m and n are 0 or 1, whereby R_1 and R_2 , together with the nitrogen atom to which they are attached, can form a mono- or bicyclic ring system containing 4 to 9 carbon atoms which is partly or wholly hydrogenated and possibly substituted by hydroxyl, C_1 - C_5 -alkyl or C_1 - C_5 -alkoxy and/or, in the case of a monocyclic ring, can be interrupted by an oxygen, nitrogen or sulphur atom, R_1 and R_3 , together with the carbon and nitrogen atoms to which they are attached, can form a five- or six-membered ring which can possibly be condensed with a further six-membered ring, R_1 and R_5 , together with the carbon and nitrogen atoms to which they are attached, as well as the carbon atom lying therebetween, can form a five- or six-membered ring, R_3 and R_4 , together with the carbon atom to which they are attached, can form a five- or six-membered ring, R_4 and R_6 , together with the carbon atoms to which they are attached, can form a five- or six-membered ring, R_5 and R_6 , together with the carbon atom to which they are attached, can form a five- or six-membered ring and R_7 and R_8 , together with the carbon atom to which they are attached, can form a five- or six-membered ring; as well as the pharmaco- logically acceptable salts thereof and the optical isomers thereof; with the proviso that R_1 and R_2 together with the nitrogen atom cannot form a piperidine or piperazine ring and R_1 and R_3 as well as R_1 and R_5 together with the nitrogen atom cannot form a piperidine ring.



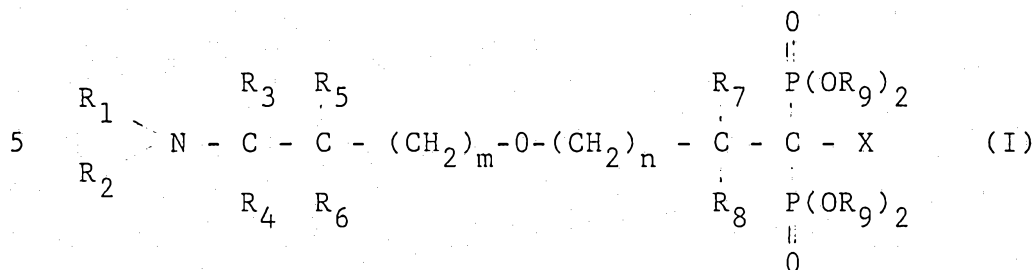
2. Compounds according to claim 1

wherein R_1 is hydrogen or methyl, R_2 is hydrogen or methyl, R_3 is hydrogen or C_1 - C_5 -alkyl, R_4 is hydrogen or methyl, R_5 is hydrogen or methyl, R_6 is hydrogen, R_7 is hydrogen, R_8 is hydrogen, R_9 is hydrogen, m is zero or 1, n is zero and X is a hydroxyl group whereby R_1 and R_6 together with the nitrogen atom form a morpholine ring, R_1 and R_3 together with the carbon and nitrogen atoms to which they are attached form a pyrrolidine ring, R_4 and R_6 together with the carbon atom to which they are attached form a cyclohexyl ring and R_5 and R_6 together with the carbon atom to which they are attached form a spiro-cyclopentane ring.

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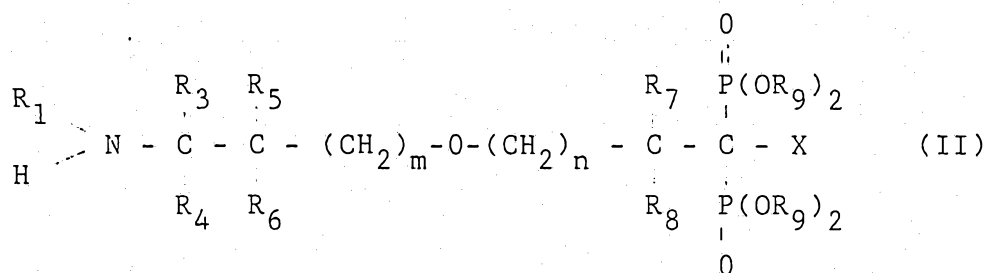
3. Process for the preparation of compounds of the general formula:-



wherein R_1 and R_2 , independently of one another, are hydrogen atoms, straight-chained or branched, saturated or unsaturated alkyl chains containing up to 9 carbon atoms which can optionally be substituted by hydroxyl, C_1 - C_5 -alkoxy or C_1 - C_5 -alkylthio, a phenyl or C_5 - C_7 -cycloalkyl ring, whereby the phenyl ring can be optionally substituted by C_1 - C_5 -alkyl, C_1 - C_5 -alkoxy, hydroxyl or halogen, or are C_5 - C_7 -cycloalkyl or phenyl radicals, R_3 is a hydrogen atom, a straight-chained or branched C_1 - C_5 -alkyl radical which can optionally be substituted by hydroxyl, C_1 - C_5 -alkoxy, C_1 - C_5 -alkylthio, mercapto, phenyl, 3-indolyl or 4-imidazolyl, or a phenyl radical optionally substituted by hydroxyl or C_1 - C_5 -alkoxy, R_4 , R_6 , R_8 and R_9 , independently of one another, are hydrogen atoms or C_1 - C_5 -alkyl radicals, R_5 and R_7 , independently of one another, are hydrogen atoms, C_1 - C_5 -alkyl radicals or phenyl radicals optionally substituted by hydroxyl or C_1 - C_5 -alkoxy, X is a hydrogen atom, a hydroxyl group or an $-NR_{10}R_{11}$ radical, whereby

R_{10} and R_{11} , independently of one another, are hydrogen atoms or C_1 - C_5 -alkyl radicals and m and n are 0 or 1, whereby R_1 and R_2 , together with the nitrogen atom to which they are attached, can form a mono- or bicyclic ring system containing 4 to 9 carbon atoms which is partly or wholly hydrogenated and possibly substituted by hydroxyl, C_1 - C_5 -alkyl or C_1 - C_5 -alkoxy and/or, in the case of a monocyclic ring, can be interrupted by an oxygen, nitrogen or sulphur atom, R_1 and R_3 , together with the carbon and nitrogen atoms to which they are attached, can form a five- or six-membered ring which can possibly be condensed with a further six-membered ring, R_1 and R_5 , together with the carbon and nitrogen atoms to which they are attached, as well as the carbon atom lying therebetween, can form a five- or six-membered ring, R_3 and R_4 , together with the carbon atom to which they are attached, can form a five- or six-membered ring, R_4 and R_6 , together with the carbon atoms to which they are attached, can form a five- or six-membered ring, R_5 and R_6 , together with the carbon atom to which they are attached, can form a five- or six-membered ring and R_7 and R_8 , together with the carbon atom to which they are attached, can form a five- or six-membered ring; as well as the pharmacologically acceptable salts thereof and the optical isomers thereof, wherein

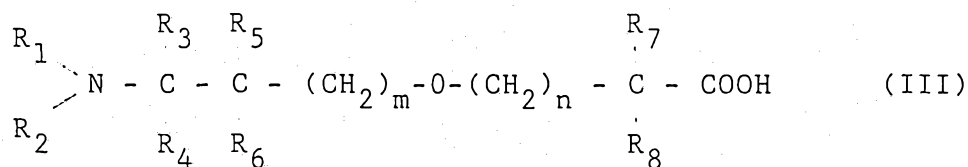
I. a compound of the general formula:-



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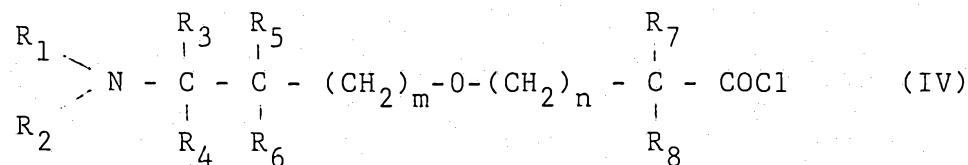
in which R_1 , R_3 - R_9 , X , m and n have the above-given meanings, is mono- or dialkylated and the tetraester obtained optionally saponified to the corresponding diester or acid of general formula I; or

- 10 II. when X in general formula I is a hydroxyl group
a) a carboxylic acid of the general formula:-



- 15 in which R_1 - R_8 , m and n have the above-given meanings,
is reacted with a mixture of phosphorous acid or
phosphoric acid and a phosphorus halide or phosphorus
oxyhalide and subsequently saponified to give the free
diphosphonic acid; or

- 20 b) a carboxylic acid chloride of the general formula:-

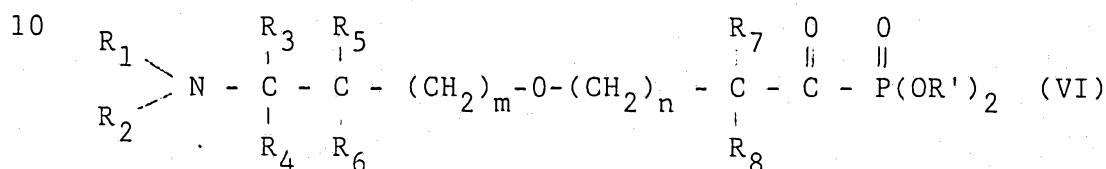


in which R_1-R_8 , m and n have the above-given meanings and R_1 can also be an acyl radical or, together with R_2 can represent a phthaloyl radical as protective group, is reacted with a trialkyl phosphite of the

5 general formula:-



in which R' is an alkyl radical containing up to 4 carbon atoms, to give an acyl phosphonate of the general formula:-

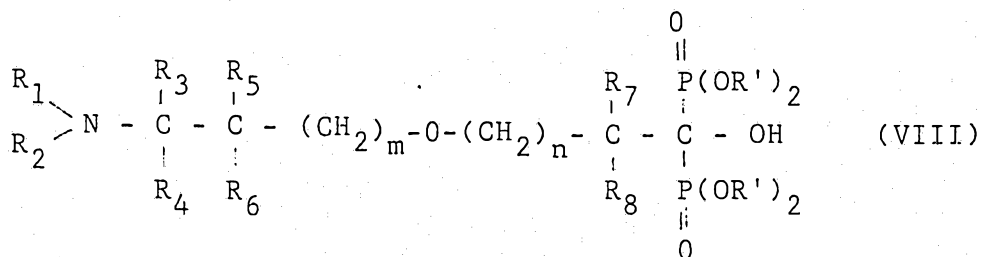


in which R_1-R_8 , m , n and R' have the above-given meanings and R_1 can also be an acyl radical or,

15 together with R_2 , can represent a phthaloyl radical, subsequently reacted with a dialkyl phosphite of the general formula:-



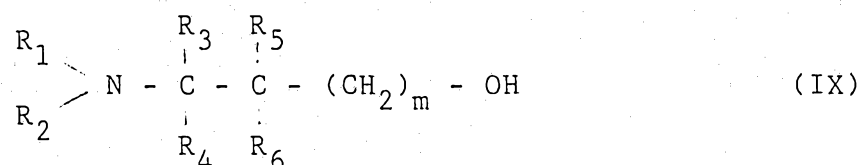
in which R' has the above-given meaning, to give a diphosphonate of the general formula:-



in which R_1 - R_8 , $\underline{m}$, $\underline{n}$ and R' have the above-given meanings, and R_1 can also be an acyl radical or, together with R_2 , can represent a phthaloyl radical, and the phthaloyl radical is optionally removed by

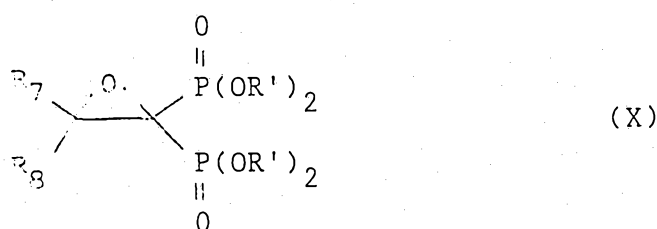
5 hydrazinolysis and the resultant tetraester is saponified to the corresponding diester or acid of general formula I, whereby, under these conditions, the acyl or phthaloyl radical used is simultaneously split off; or

10 c) when $\underline{n}$ is 0, a compound of the general formula:-

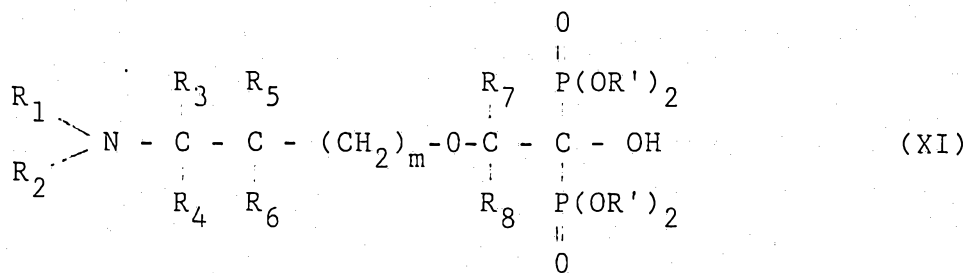


in which R_1 - R_6 and $\underline{m}$ have the above-given meanings,

15 is reacted with an epoxide of the general formula:-



20 in which R_7 , R_8 and R' have the above-given meanings, and the resultant diphosphonic acid derivative of the general formula:-

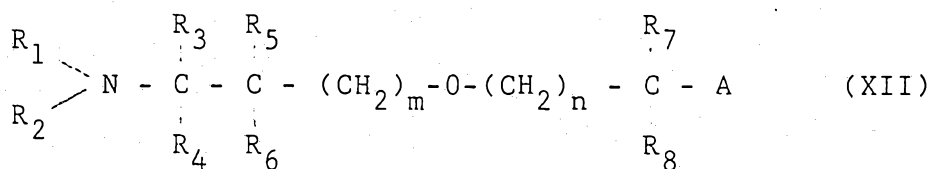


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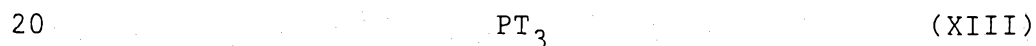
wherein R_1 - R_8 , R' and m have the above-given meanings, is, if desired, saponified to the corresponding diester or acid; or

III. when X in general formula I is an $-NR_{10}R_{11}$

10 radical, a carboxylic acid derivative of the general formula:-



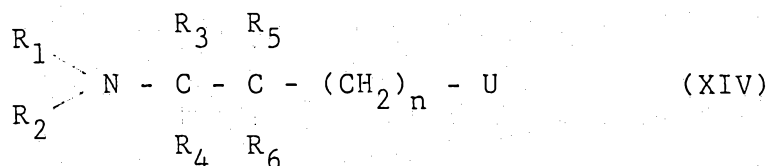
15 in which R_1 - R_8 , m and n have the above-given meanings and A is a nitrile, imino ether or a $-CONR_{10}R_{11}$ radical, R_{10} and R_{11} having the above-given meanings, is reacted with a phosphorus compound of the general formula:-



in which T is a halogen atom, a hydroxyl group or OR' , R' having the above-given meaning, and optionally subsequently saponified; or

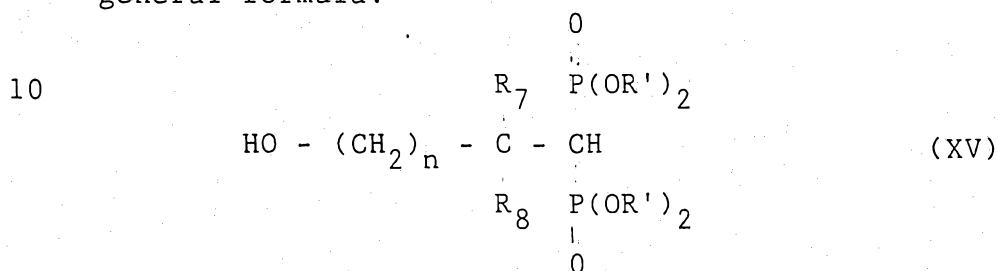
IV. when X in general formula I is a hydrogen atom,

25 a) a compound of the general formula:-



in which R_1 - R_6 and n have the above-given meanings and

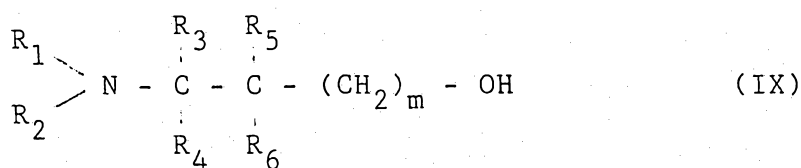
- 5 R_1 can also be an acyl radical or, together with R_2 ,
can be a phthaloyl radical and U is a reactive group,
is reacted with a diphosphonic acid derivative of the
general formula:-



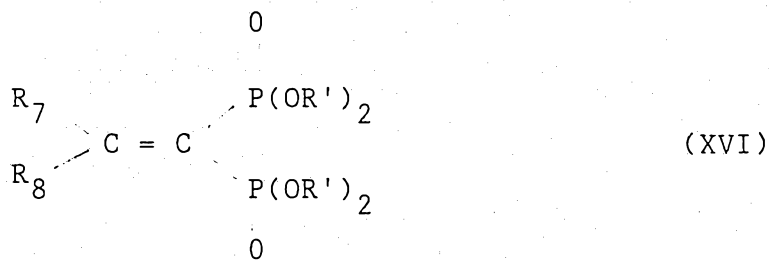
in which R_7 , R_8 , R' and n have the above-given meanings,

- 15 and the phthaloyl radical is, if desired, removed by
hydrazinolysis and the tetraester formed is optionally
saponified to the corresponding diester or acid,
whereby, under these conditions, the acyl or phthaloyl
radical used as protective group, is split off
20 simultaneously; or

b) a compound of the general formula:-



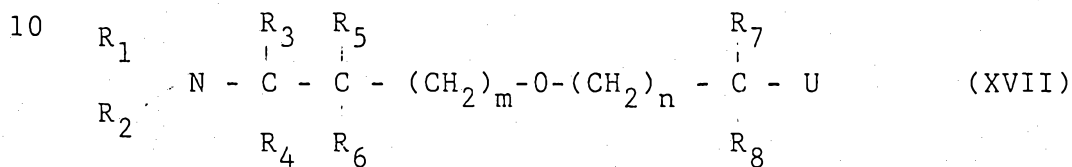
in which R_1 - R_6 and m have the above-given meanings, is
added to a compound of the general formula:-



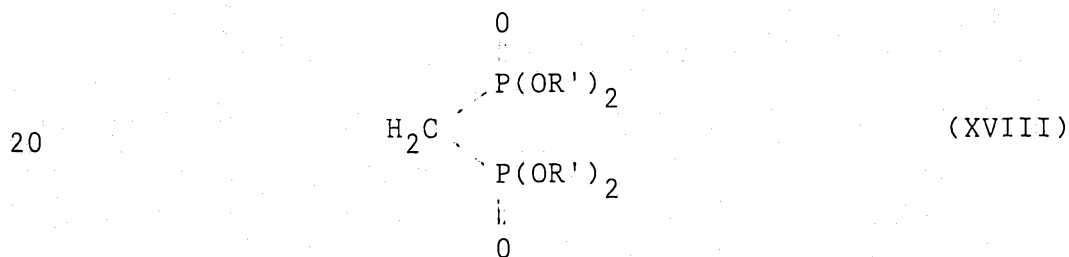
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in which R_7 , R_8 and R' have the above-given meanings, and the resultant tetraester is optionally saponified to the corresponding diester or acid; or

c) a compound of the general formula:-



in which R_1 - R_8 , U , m and n have the above-given meanings and R_1 can also be an acyl radical or, together with R_2 , can be a phthaloyl radical, is reacted with a diphosphonic acid derivative of the general formula:-

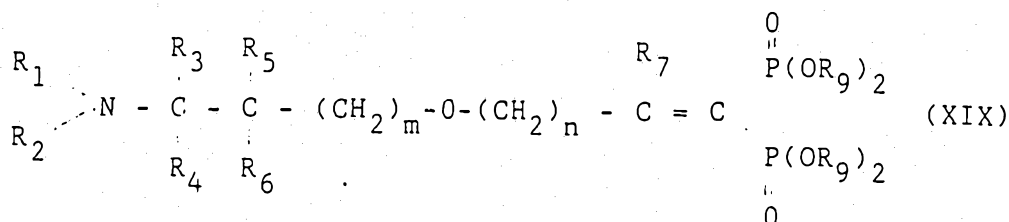


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in which R' has the above-given meaning, the phthaloyl radical is, if desired, removed by hydrazinolysis and the resultant tetraester is, if desired, saponified to the corresponding diester or acid, whereby, under

25

these conditions, the acyl or phthaloyl radical used as protective group is simultaneously split off; or
d) when R_8 is a hydrogen atom, a compound of the general formula:-



in which R_1 - R_7 , R_9 , m and n have the above-given meanings, whereby R_1 can also be an acyl radical, is catalytically hydrogenated, and subsequently, the resultant tetraester is optionally saponified to the corresponding diester or acid, whereby acyl radicals possibly present can thereby also be split off at the same time and the free acid is, if desired, converted into a pharmacologically acceptable salt; with the proviso that R_1 and R_2 together with the nitrogen atom cannot form a piperidine or piperazine ring and R_1 and R_3 as well as R_1 and R_5 together with the nitrogen atom cannot form a piperidine ring.

4. Process according to claim 3 for the preparation of compounds according to claim 1, substantially as hereinbefore described and exemplified.

5. Compounds according to claim 1, whenever prepared by the process according to claim 3 or 4.

6. Pharmaceutical compositions containing at least one compound according to any of claims 1, 2 and 5, in addition to conventional carrier and adjuvant materials.



7. A method for the treatment of calcium metabolism disturbances in a mammal in need thereof comprising administering to said mammal an effective amount of the compounds according to any one of claims 1, 2 or 5.

8. The method according to claim 7 wherein the mammal is a human.

DATED this 14th day of June, 1991
BOEHRINGER MANNHEIM GmbH
by DAVIES & COLLISON
Patent Attorneys for the applicant(s)

