

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

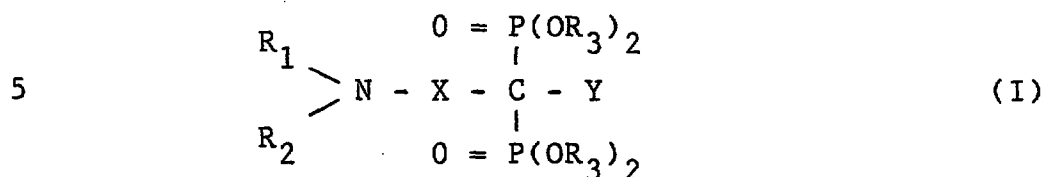
5 In US-A-3,733,270 is described the compound di-zinc 2-dibutylamino-1-hydroxyethane-1,1-diphosphonate which can find use for the prevention of boiler scale.

In DE-OS 18 13 659 are described diphosphonic acid derivatives of which 1-hydroxyethane-1,1-diphosphonic acid has achieved importance as agent for
10 the treatment of Paget's disease. In BE 896,453, EP-A-175,315, DE-A-24 05 254, DE-OS 25 34 391, as well as EP 96 931, are described aminoalkane-1,1-diphosphonic acids as good calcium complex formers which can also be used for the treatment of increased bone resorption.
15 In the case of therapeutically effective dosaging, such substances frequently show side effects. The task exists to find aminoalkane-diphosphonates which manifest their therapeutic action at the lowest possible dosaging. It has now been found that analogous
20 derivatives of these compounds, in which the nitrogen atom is completely alkylated, whereby one of the alkyl radicals possesses at least 4 C-atoms, fulfil this task and are suitable as good calcium complex formers for the wider treatment of calcium metabolism disturbances.
25 In particular, they can very well be used there where the build up and breakdown of the bone is disturbed, i.e. they are suitable for the treatment of diseases of the skeletal system, such as e.g. osteoporosis, Paget's disease, Bechterew's disease and the
30 like.

However, on the basis of these properties, they also find use for the therapy of bone metastases, urolithiasis and for the prevention of heterotopic ossifications. Due to their influencing of the calcium
35 metabolism, they also form a basis for the treatment of

rheumatoid arthritis, of osteoarthritis and of degenerative arthrosis.

Thus, the subject of the present invention are diphosphonates of the general formula I



in which R_1 signifies the methyl, n-propyl, isopropyl, 3-methylbutyl, pentyl, nonyl or cyclohexylmethyl radical, R_2 represents a butyl, isobutyl, 3-methylbutyl, pentyl, heptyl, nonyl, undecyl, dodecyl, tetradecyl, hexadecyl, octadecyl, cyclohexyl, cyclohexylmethyl or benzyl group, R_3 signifies hydrogen or a methyl, ethyl, isopropyl or isobutyl group, X represents a methylene, ethylene or propylene group and Y signifies hydrogen, amino or hydroxyl, as well as their pharmacologically acceptable salts.

For the substituent R_1 , there preferably comes into question the methyl, n-propyl, isopropyl, 3-methylbutyl, pentyl and nonyl radical.

Preferred for R_2 is a butyl, isobutyl, 3-methylbutyl, pentyl, heptyl, nonyl, undecyl, dodecyl, tetradecyl, hexadecyl, octadecyl, cyclohexyl, cyclohexylmethyl or benzyl group.

The radical R_3 preferably signifies hydrogen or the methyl, ethyl or isobutyl radical.

Asymmetrical carbon atoms occurring in R_1 , R_2 and X can possess the R-, S- or R,S-configuration.

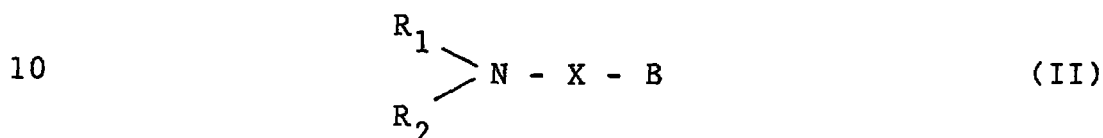
Preferred compounds of the present invention are compounds of the general formula I in which R_1 represents a methyl radical and R_2 a C_3 - C_5 radical, especially the compounds 1-hydroxy-3-(N-methyl-N-

pentylamino)-propane-1,1-diphosphonic acid and 1-hydroxy-3-(N-isobutyl-N-methylamino)-propane-1,1-diphosphonic acid.

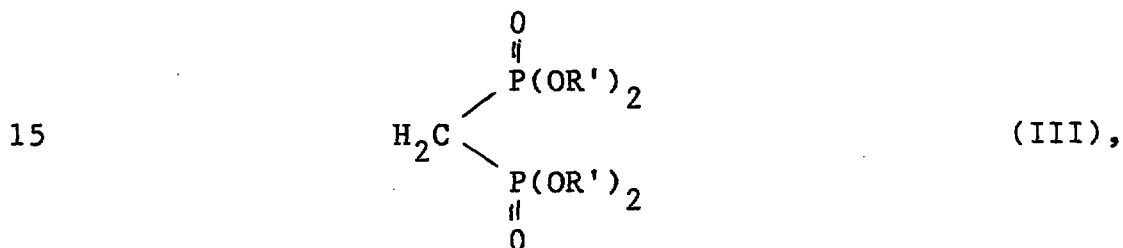
Compounds of the general formula I are prepared according to per se known processes.

I. For the case in which Y in the general formula I signifies hydrogen, one preferably prepares the substances in that one

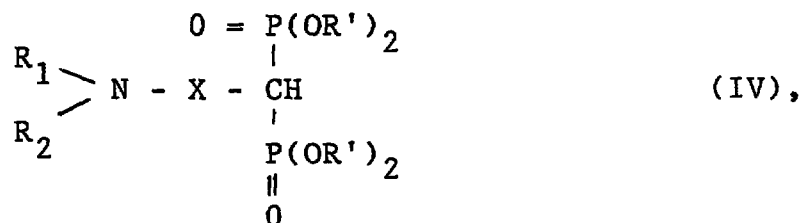
a) reacts a compound of the general formula II



in which R_1 , R_2 and X have the above-given meanings and B represents a reactive residue, such as e.g. halogen or a sulphonate, with a compound of the general formula III

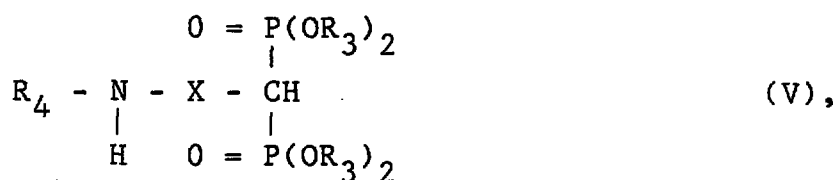


in which R' stands for alkyl radicals with 1 - 4 carbon atoms, preferably methyl, ethyl and isobutyl, to give a diphosphonate of the general formula IV



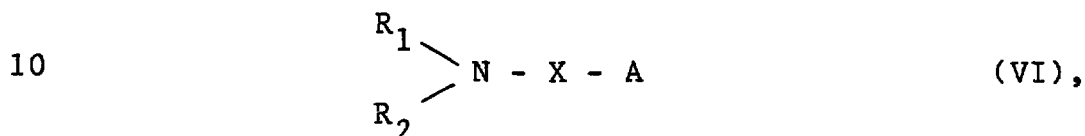
wherein R_1 , R_2 , X and R' have the above-given meaning, and possibly saponifies the resultant tetraester to diesters or acids of the general formula I; or

b) mono- or dialkylates a compound of the general formula V



in which R_3 and X have the above-given meaning and R_4 signifies hydrogen or R_2 , and possibly saponifies the resultant tetraesters to diesters or acids of the general formula I; or

II. for the case in which Y in the general formula I signifies amino possibly substituted by alkyl groups, reacts a carboxylic acid derivative of the general formula VI



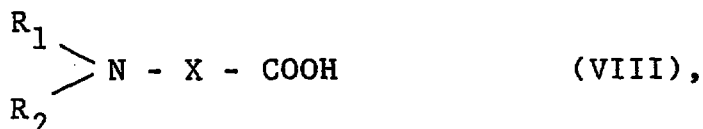
in which R_1 , R_2 and X have the above-given meaning and A represents a nitrile, imino ether or a carboxamide group possibly substituted on the nitrogen by lower alkyl radical, with a phosphorus compound of the general formula VII



wherein T signifies halogen, OH or OR' , whereby R' has the above-given meaning, and possibly subsequently saponifies to compounds of the general formula I; or

III. for the case in which Y in general formula I signifies OH ,

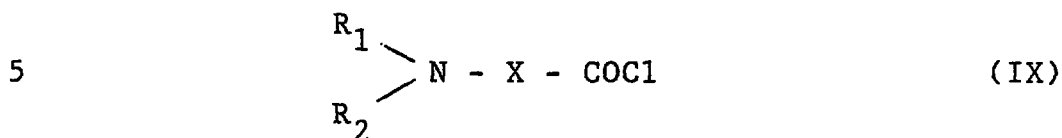
a) reacts a carboxylic acid of the general formula VIII



in which R_1 , R_2 and X 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 of the general formula I; or

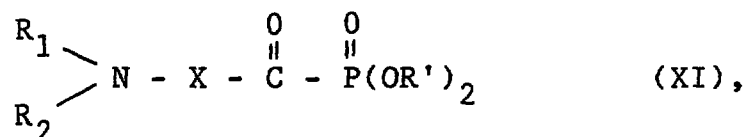
b) reacts a carboxylic acid chloride of the general formula IX



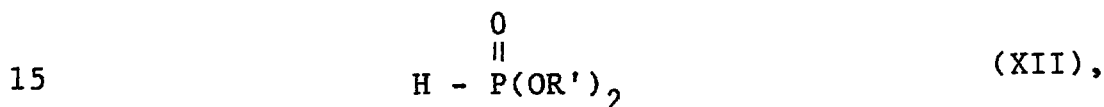
in which R_1 , R_2 and X have the above-given meanings, with a trialkyl phosphite of the general formula X



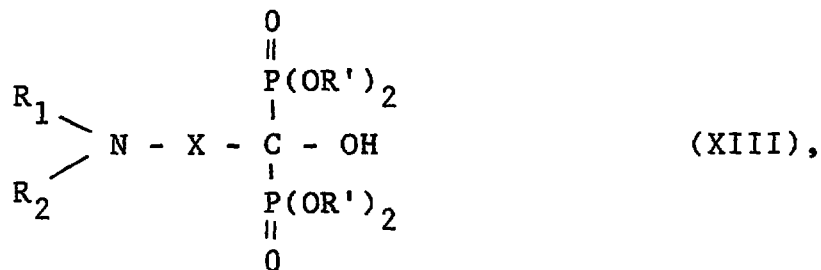
10 in which R' has the above-given meaning, to give an acyl phosphonate of the general formula XI



in which R_1 , R_2 , X and R' have the above-given meanings, subsequently allows to react with a dialkyl phosphite of the general formula XII

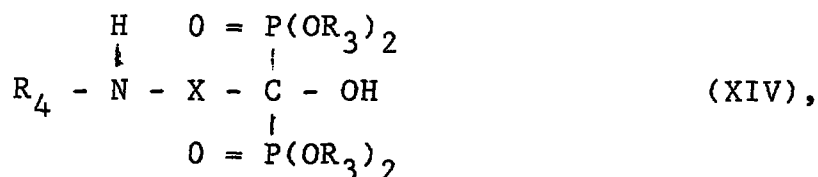


in which R' has the above-given meaning, to give a diphosphonate of the general formula XIII



20 in which R_1 , R_2 , X and R' have the above-given meanings, and possibly saponifies the resultant tetraesters to diesters or acids of the general formula I; or

c) mono- or dialkylates a compound of the general formula XIV



5 in which R_3 and X have the above-given meaning and R_4 signifies hydrogen or R_2 , and possibly saponifies the resultant tetraesters to diesters or acids of the general formula I;

and possibly converts the so prepared compounds into their pharmacologically acceptable salts.

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

20 In the case of the reductive alkylation (process I b)), one treats a mixture of primary or secondary amine of the general formula V and of a carbonyl compound or its acetal in the presence of a hydrogenation catalyst, such as palladium on charcoal or nickel, with
25 hydrogen under atmospheric or increased pressure or one adds formic acid as reducing agent. Subsequently, alkylations of a secondary amine of the general formula V can be carried out especially advantageously according to the phase transfer process with dialkyl
30 sulphates.

In the case of process II, one reacts the nitriles of the general formula VI 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 diglycol diethyl ether. However, one can also bring
5 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
10 general formula VI 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
15 solvent. One can react acid amides of the general formula VI 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.

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

In the case of process III b), one allows the acid chloride of the general formula IX to come to reaction with the trialkyl phosphite of the general formula X at temperatures between 0 and 60°C., preferably at 20 -
35 40°C. One can work without solvent or also in the

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 XI formed as intermediate product can be isolated or further reacted 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 0 - 60°C., preferably at 10 - 30°C.

10 As phosphorus trihalides in the above-mentioned processes, there come into question, for example, phosphorus trichloride or phosphorus tribromide.

 In the case of process III c), the description given under I b applies analogously.

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

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

25 The saponification to the free diphosphonic acids takes place, as a rule, by boiling with hydrochloric or hydrobromic acid. However, one can also carry out a cleavage with a trimethylsilyl halide, preferably the bromide or iodide. On the other hand, the free
30 diphosphonic acids can be converted again 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 salts. As a
35 rule, the alkali metal salts can be well purified by

reprecipitation from water/methanol or from water/
acetone.

As pharmacologically acceptable salts, there are,
above all, used alkali metal or ammonium salts which
5 one prepares in the usual way, e.g. by titration of
the compounds with inorganic or organic bases, such as
e.g. sodium or potassium hydrogen carbonate, aqueous
sodium hydroxide solutions, aqueous potassium hydroxide
solution, aqueous ammonia or amines, such as e.g.
10 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
15 administration, for example tablets, capsules, dragees,
syrups, solutions, suspensions etc. As injection
medium, water is preferably used which contains the
additives usual in the case of injection solutions,
such as stabilising agents, solubilising agents and
20 buffers. Such additives are e.g. tartrate and citrate
buffers, ethanol, complex formers (such as ethylene-
diamine-tetraacetic acid and its non-toxic salts),
high molecular polymers (such as liquid polyethylene
oxide) for viscosity regulation. Liquid carrier
25 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
molecular fatty acids (such as stearic acid), gelatine,
30 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, contain
flavouring and sweetening agents.

35 The dosage can depend upon various factors, such
as mode of administration, species, age and/or

individual condition. The dosages to be administered daily lie at about 1 - 1000 mg./humans, preferably 10 - 200 mg./human and can be given divided up one or more times.

5 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 meanings given in the claims, the following diphosphonates, as well as their methyl and ethyl esters:

- 10 1-amino-3-(N-methyl-N-nonylamino)-propane-1,1-diphosphonic acid
3-(N-methyl-N-nonylamino)-propane-1,1-diphosphonic acid
3-(N-methyl-N-octadecylamino)-propane-1-hydroxy-1,1-diphosphonic acid
15 3-(N-methyl-N-tetradecylamino)-propane-1-hydroxy-1,1-diphosphonic acid
3-(N-heptyl-N-methylamino)-propane-1-hydroxy-1,1-diphosphonic acid
4-(N-dodecyl-N-methylamino)-butane-1-hydroxy-1,1-diphosphonic acid
20 3-(N-dodecyl-N-isopropylamino)-propane-1-hydroxy-1,1-diphosphonic acid
1-(hydroxy-3-(N-cyclohexylmethyl)-N-propylamino)-propane-1,1-diphosphonic acid
25 2-(N-methyl-N-isobutylamino)-ethane-1,1-diphosphonic acid
2-(N-methyl-N-pentylamino)-ethane-1,1-diphosphonic acid.

The following Examples show some of the process variants which can be used for the synthesis of the
30 compounds according to the invention. However, they are not to represent a limitation of the subject matter of the invention. The structures of these compounds is verified by H- and P-NMR spectroscopy, the purity by means of P-NMR spectroscopy, thin layer electrophoresis
35 (cellulose, oxalate buffer of pH = 4.0) and by means of

C, H, N, P, Na analyses. For the characterisation of the individual substances, there are given the M_{rel} values (= relative mobilities) referred to pyrophosphate ($M_{rel} = 1.0$).

5 Example 1.

1-Hydroxy-3-(N,N-dipentylamino)-propane-1,1-diphosphonic acid.

13.3 g. 3-N,N-Dipentylaminopropionic acid are kept for 20 hours at 100°C. with 7.1 g. phosphorous acid and 10 14.8 ml. phosphorus trichloride in 67 ml. chlorobenzene. One then decants off from the solvent and stirs the residue under reflux with 180 ml. 6N hydrochloric acid for 8 hours. One filters off from some insolubles, concentrates the filtrate and applies it to an Amberlite 15 column IR 120, H^+ form. The elution with water is monitored electrophoretically. The desired fractions are combined, evaporated, stirred up with acetone and the crystals obtained isolated.

One thus obtains 12.9 g. of crude product. After 20 recrystallising twice from water, one obtains 4.7 g. = 22% of analytically pure product as hemihydrate. M.p. 114°C. sinters, 189 - 191°C. decomp. ($M_{rel} = 0.24$).

The starting material is obtained as follows: Dipentylamine is reacted with acrylic acid methyl ester 25 in toluene in the mole ratio of 1:3. One obtains 28% of the oily dipentylaminopropionic ester which is saponified with 1N aqueous sodium hydroxide solution and gives 56% of the desired acid; m.p. 47 - 49°C.

Example 2.

30 1-Hydroxy-3-(N-methyl-N-nonylamino)-propane-1,1-diphosphonic acid.

In a manner analogous to that described in Example 1, from 3-N-methyl-N-nonylaminopropionic acid one obtains the corresponding diphosphonate with 10% 35 yield, m.p. 159°C. sinters, 178 - 184°C. ($M_{rel} = 0.22$).

The starting material is obtained as follows:
Nonylamine is reacted with benzaldehyde in 96% yield
to give the oily Schiff base. The hydrogenation with
palladium-charcoal catalyst gives N-benzyl-N-nonylamine
5 as oil with 94% yield. From this, one obtains with
formaldehyde and formic acid, 98% of the oily N-benzyl-
N-methyl-N-nonylamine. The hydrogenolytic splitting
off of the benzyl radical with palladium-charcoal
catalyst gives quantitatively the sec. amine as oil
10 which, as described in Example 1, is reacted with methyl
acrylate and saponified. Yield of ester 81% of oil,
of acid 95% of pasty substance.

Example 3.

3-(N-Cyclohexyl-N-methylamino)-1-hydroxy-propane-1,1-
15 diphosphonic acid.

15 g. 3-N-Cyclohexyl-N-methylaminopropionic acid,
prepared from N-cyclohexyl-N-methylamine (commercial
preparation) and methyl acrylate in toluene (76% yield
of ester, m.p. 131 - 134°C.; 92% yield of acid, m.p.
20 101 - 105°C.) are heated to 80°C. with 13.3 g.
phosphorous acid. The melt is mixed with 14.1 ml.
phosphorus trichloride and kept at the same temperature
for 16 hours. One then adds 240 ml. of water thereto
and stirs for one day at 100°C. One filters, concent-
25 rates in a vacuum and pours the oil into 1 l. of
acetone, whereby crystallisation commences. One
dissolves in water and purifies by ion exchanger
chromatography, as described in Example 1. Yield
4.5 g. = 16.9%, of monohydrate. M.p. 142°C. sinters,
30 182°C., decomp. ($M_{rel} = 0.3$).

Example 4.

1 g. 3-N-Cyclohexylaminopropane-1-hydroxy-1,1-
diphosphonic acid are suspended in 30 ml. methylene
chloride, 2.5 ml. conc. aqueous solution of sodium
35 hydroxide added thereto and, with cooling, mixed with

1 g. tetrabutylammonium hydrogen sulphate and 0.3 ml. dimethyl sulphate. One stirs vigorously for several hours at room temperature. After usual working up, one allows the identity of the product obtained with that prepared according to Example 3 to be demonstrated by mass spectroscopy after silylation.

The diphosphonic acid used is obtained as follows:

Cyclohexylamine is reacted with acrylic acid in pyridine. Yield of 3-N-cyclohexylaminopropionic acid 70%, m.p. 170 - 171°C. The reaction with phosphorous acid and phosphorus trichloride gives 31% of the diphosphonic acid of the m.p. 164°C., decomp.

Example 5.

3-(N-Cyclohexylmethyl-N-methylamino)-propane-1,1-hydroxy-1,1-diphosphonic acid.

3-(N-Cyclohexylmethyl-N-methylamino)-propionic acid (prepared from N-benzyl-N-methylamine by hydrogenation with platinum catalyst, 70% yield, b.p. 60°C./16, reaction with methyl acrylate in toluene, 37% yield of 3-(N-cyclohexylmethyl-N-methylamino)-propionic acid methyl ester, saponification with 1N aqueous sodium hydroxide solution to the acid, m.p. 98 - 102°C., 63% yield). The reaction with phosphorous acid/phosphorus trichloride analogous to Example 3 gives 34% of the diphosphonic acid, m.p. 180 - 194°C. decomp. ($M_{rel} = 0.31$).

Example 6.

1-Hydroxy-3-(N-nonyl-N-propylamino)-propane-1,1-diphosphonic acid.

In a manner analogous to that described in Example 3, from 3-N-nonyl-N-propylaminopropionic acid one obtains the corresponding diphosphonic acid of the m.p. 100 - 105°C. with 50% yield ($M_{rel} = 0.23$).

The starting material is obtained as follows:
2 mole nonylamine are reacted quantitatively with
1 mole propionyl chloride to give the acid amide which
is reduced with lithium aluminium hydride to give the
5 secondary amine with 71% yield (b.p. 113 - 117°C./16).
1 mole N-nonyl-N-propylamine are reacted with 3 mole
methyl acrylate in toluene and gives 81% of an oil
which is saponified with 1N aqueous sodium hydroxide
solution and gives 14% of the desired acid of the m.p.
10 45 - 47°C.

Example 7.

500 mg. of the diphosphonic acid prepared accord-
ing to Example 1 are suspended in 5 ml. water, dissolved
with 2.68 ml. 1N aqueous sodium hydroxide solution,
15 concentrated somewhat and brought to crystallisation
by pouring into acetone. One thus obtains 440 mg. =
78% of the disodium salt in the form of the monohydrate
of 1-hydroxy-3-(N,N-dipentylamino)-propane-1,1-
diphosphonic acid. The melting point lies above 300°C.

20 Example 8.

1-Hydroxy-3-(N-nonyl-N-pentylamino)-propane-1,1-
diphosphonic acid.

2 mole nonylamine are reacted with 1 mole valeroyl
chloride in ether, the suspension is filtered off with
25 suction, the filtrate is evaporated and N-nonyl-valeric
acid amide of the m.p. 29 - 31°C. is thus obtained
quantitatively. The reduction with 1.65 mole lithium
aluminium hydride in ether gives 78% of a colourless
oil (b.p. 142 - 146°C./16 Torr.). The addition of this
30 N-nonyl-N-pentylamine to methyl acrylate (96% yield,
oil) and subsequent saponification with 1N aqueous
sodium hydroxide solution gives 64% of a pasty
substance: 3-(N-nonyl-N-pentylamino)-propionic acid
which is reacted analogously to Example 3 to give the
35 diphosphonic acid. Yield 87%, m.p. 168 - 176°C.
($M_{rel} = 0.14$).

Example 9.

In a manner analogous to that described in Example 2, there are prepared:

		yield	m.p.
5	<u>A. Intermediate products:</u>		
	N-benzylidenepentylamine	94%	oil
	N-benzyl-N-pentylamine	74%	paste
	N-benzyl-N-methyl-N-pentylamine	95%	oil
	N-methyl-N-pentylamine	49%	oil
10	3-(N-methyl-N-pentylamino)-propionic acid methyl ester	93%	oil
	3-(N-methyl-N-pentylamino)-propionic acid	34%	deliquescent crystals
	<u>End product:</u>		
15	<u>1-hydroxy-3-(N-methyl-N-pentylamino)-propane-1,1-diphosphonic acid</u>	12%	84°C. decomp.
	$M_{rel} = 0.44$		
	<u>B. Intermediate products:</u>		
	N-benzylideneisobutylamine	96%	oil
20	N-benzyl-N-isobutylamine	71%	oil
	N-benzyl-N-isobutyl-N-methylamine	93%	oil
	N-isobutyl-N-methylamine	96%	oil
	3-(N-isobutyl-N-methylamino)-propionic acid methyl ester	90%	oil
25	3-(N-isobutyl-N-methylamino)-propionic acid	57%	oil
	<u>End product:</u>		
	<u>1-hydroxy-3-(N-isobutyl-N-methylamino)-propane-1,1-diphosphonic acid</u>	39%	140°C. decomp.
30	$M_{rel} = 0.40$ (monohydrate)		
	<u>C. Intermediate products:</u>		
	N-benzylidenehexadecylamine	85%	oil
	N-benzyl-N-hexadecylamine	76%	wax
	N-benzyl-N-hexadecyl-N-methylamine	93%	oil
35	N-hexadecyl-N-methylamine	98%	wax

	yield	m.p.
3-(N-hexadecyl-N-methylamino)-propionic acid methyl ester	100%	wax
3-(N-hexadecyl-N-methylamino)-propionic acid	37%	58-60°C.

5 End product:

<u>3-(N-hexadecyl-N-methylamino)-propane-1-hydroxy-1,1-diphosphonic acid</u>	72%	198/254°C. decomp.
$M_{rel} = 0.1$		

10 The oily intermediate products are further reacted without distillation. The purification of the end products takes place by ion exchange chromatography.

Example 10.

3-N,N-Dinonylaminopropane-1-hydroxy-1,1-diphosphonic acid.

15 In a manner analogous to that described in Example 3, from 3-N,N-dinonylaminopropionic acid one obtains the corresponding diphosphonic acid as hemi-hydrate with 49% yield of the m.p. 83°C. sinters, 161 - 171°C. melts with gas evolution ($M_{rel} = 0.16$).

20 The reaction sequence for the preparation of the starting material is analogous to that described in Example 6:

pelargonic acid N-nonylamide; yield 100%, m.p. 52-55°C.
N,N-dinonylamide; yield 79%, m.p. 37-39°C.

25 3-N,N-dinonylaminopropionic acid methyl ester; yield 71%,
oil

3-N,N-dinonylaminopropionic acid; yield 18%,
deliquescent crystals.

Example 11.

30 1-Hydroxy-4-(N,N-di-3-methylbutylamino)-butane-1,1-diphosphonic acid.

35 4 g. 4-Amino-1-hydroxybutane-1,1-diphosphonic acid are dissolved in 64 ml. 1N aqueous sodium hydroxide solution, mixed with 3.8 ml. isovaleraldehyde and, after the addition of 2.5 g. of palladium-charcoal 10%,

hydrogenated at 5 bar. The course of the reaction is monitored electrophoretically until the starting material has disappeared. One filters, after acidification with Amberlite R 120 H⁺ form, evaporates until crystallisation commences and thus isolates 1.3 g. of crystals = 20% of the m.p. 225 - 227°C. decomp. ($M_{rel} = 0.39$). 1-Hydroxy-4-(N-3-methylbutylamino)-butane-1,1-diphosphonic acid remaining in the mother liquor, formed as an intermediate, can be used again for the reductive alkylation.

Example 12.

3-(N-Benzyl-N-methylamino)-propane-1-hydroxy-1,1-diphosphonic acid.

Analogously to Example 3, from 3-N-benzyl-N-methylaminopropionic acid one obtains the desired diphosphonic acid as monohydrate with 36% yield with the decomposition point 117°C. ($M_{rel} = 0.37$).

The starting material is obtained as follows: N-Benzyl-N-methylamine is reacted with methyl acrylate analogously to Example 1 and the oily ester obtained with 76% is, without distillation, saponified with 1N aqueous sodium hydroxide solution. One thus obtains, with 67% yield, the oily acid which is used without further purification.

Example 13.

3-(N-Dodecyl-N-methylamino)-propane-1-hydroxy-1,1-diphosphonic acid.

Analogously to Example 3, from 3-N-dodecyl-N-methylaminopropionic acid one obtains the desired compound with 28% yield. Decomposition point 200 - 216°C. ($M_{rel} = 0.1$).

The starting material is obtained as follows: The oily Schiff base from dodecylamine and benzaldehyde (81% yield) is hydrogenated with Pd catalyst: 74% of

oily N-benzyl compound. The reductive alkylation with formalin-formic acid gives 82% of the also oily tertiary amine. The catalytic removal of the benzyl radical by hydrogenolysis is quantitative. The oily
 5 sec. amine is reacted directly with methyl acrylate (50% of pasty substance) and saponified without purification. The desired acid is obtained with 39% as viscous mass and used directly.

Example 14.

10 3-(N-Benzyl-N-propylamino)-propane-1-hydroxy-1,1-diphosphonic acid.

Analogously to Example 3, from 3-(N-benzyl-N-propylamino)-propionic acid one obtains with 35% the desired compound. M.p. 112 - 115°C., decomp. ($M_{rel} =$
 15 0.33).

The starting material is obtained as follows: The oily Schiff base from propylamine and benzaldehyde (86% yield) is hydrogenated in the presence of Pd catalyst and gives N-benzyl-N-propylamine with 81%
 20 yield. The oily sec. amine is now reacted with methyl acrylate: 69% of oily ester and therefrom, by alkaline saponification, is obtained the also oily acid with 88% yield.

Example 15.

25 In a manner analogous to that described in Example 2 are prepared:

	yield	m.p.
<u>A. Intermediate products:</u>		
N-benzylidene-2-butylamine	89%	oil
N-benzyl-2-butylamine	92%	oil
30 N-benzyl-N-2-butyl-N-methylamine	85%	oil
N-2-butyl-N-methylamine, HCl	98%	40-46°C.
3-(N-2-butyl-N-methylamino)-propionic acid methyl ester	88%	oil
3-(N-2-butyl-N-methylamino)-propionic acid	95%	oil

End product:

<u>3-(N-2-butyl-N-methylamino)-propane-1-hydroxy-1,1-diphosphonic acid</u>	39%	95-105°C.
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$M_{rel} = 0.42$

5	<u>B. Intermediate products:</u>	yield	m.p.
	3-N-butylaminopropionic acid methyl ester, b.p. ₂₀ : 95-100°C.	75%	oil
	3-(N-butyl-N-methylamino)-propionic acid methyl ester	-	oil
10	3-(N-butyl-N-methylamino)-propionic acid	78%	oil
	(yield referred to first intermediate product)		

End product:

15	<u>3-(N-butyl-N-methylamino)-propane-1-hydroxy-1,1-diphosphonic acid</u>	65%	116-121°C.
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$M_{rel} = 0.39$

C. Intermediate product:

	4-(N-methyl-N-nonylamino)-butyric acid	47%	oil
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20	<u>End product:</u>		
	<u>1-hydroxy-4-(N-methyl-N-nonylamino)-butane-1,1-diphosphonic acid disodium salt dihydrate</u>	11%	>300°C.

$M_{rel} = 0.25$

25	<u>D. Intermediate products:</u>		
	3-N-undecylaminopropionic acid	62%	76-80°C.
	3-N-methyl-N-undecylaminopropionic acid	59%	wax

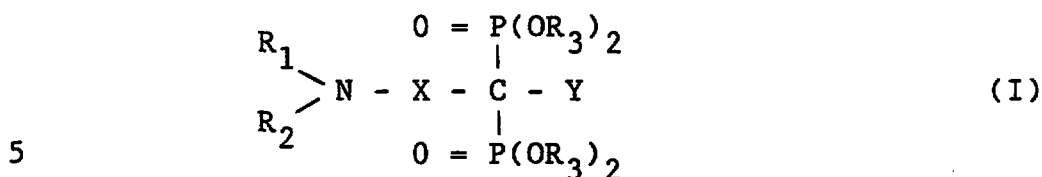
End product:

30	<u>1-hydroxy-3-(N-methyl-N-undecylamino)-propane-1,1-diphosphonic acid dipotassium salt dihydrate</u>	23%	238°C. foaming up
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35 The oily intermediate products are further reacted directly without distillation. The structure is verified spectroscopically. The purification of the end products takes place by ion exchanger chromatography.

Patent Claims

1. Diphosphonates of the general formula I

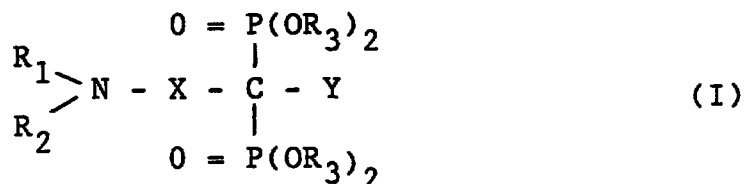


in which R_1 signifies a methyl, n-propyl, isopropyl, 3-methylbutyl, pentyl, nonyl or cyclohexylmethyl radical, R_2 represents a butyl, isobutyl, 3-methylbutyl, pentyl, heptyl, nonyl, undecyl, dodecyl, tetradecyl, hexadecyl, octadecyl, cyclohexyl, cyclohexylmethyl or benzyl group, R_3 signifies hydrogen or a methyl, ethyl, isopropyl or isobutyl group, X represents a methylene, ethylene and propylene group and Y signifies hydrogen, amino or hydroxyl, as well as their pharmacologically acceptable salts.

2. Diphosphonates of the general formula I according to claim 1, in which R_1 signifies a methyl or n-propyl group, R_2 represents an isobutyl, pentyl, nonyl or benzyl group, R_3 signifies hydrogen, X signifies an ethylene group and Y a hydroxyl group, as well as their pharmacologically acceptable salts.

3. 1-Hydroxy-3-(N-methyl-N-pentylamino)-propane-1,1-diphosphonic acid or 1-hydroxy-3-(N-isobutyl-N-methylamino)-propane-1,1-diphosphonic acid.

4. Process for the preparation of diphosphonates of the general formula I



in which R_1 signifies a methyl, n-propyl, isopropyl, 3-methylbutyl, pentyl, nonyl or cyclohexylmethyl radical, R_2 represents a butyl, isobutyl, 3-methylbutyl,



pentyl, heptyl, nonyl, undecyl, dodecyl, tetradecyl, hexadecyl, octadecyl, cyclohexyl, cyclohexylmethyl or benzyl group, R_3 signifies hydrogen or a methyl, ethyl, isopropyl or isobutyl group, X represents a methylene, ethylene and propylene group and Y signifies hydrogen, amino or hydroxyl, as well as of their pharmacologically acceptable salts, characterised in that one

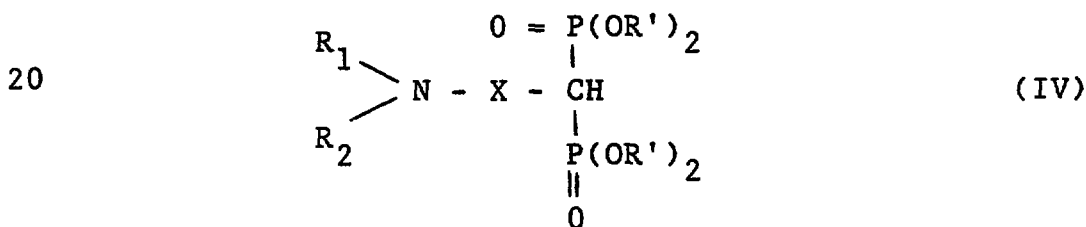
- I. for the case that Y in general formula I signifies hydrogen,
 10 a) reacts a compound of the general formula II



- in which R_1 , R_2 and X have the above-given meanings and B represents a reactive residue, such as e.g. halogen or a sulphonate, with a compound of the general
 15 formula III



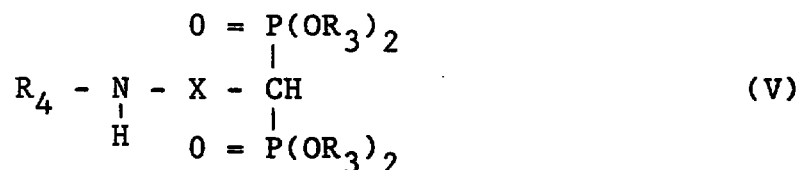
in which R' stands for alkyl radicals with 1 - 4 carbon atoms, preferably methyl, ethyl and isobutyl, to give a diphosphonate of the general formula IV



in which R_1 , R_2 , X and R' have the above-given meaning, and possibly saponifies the resulting tetraesters to diesters or acids of general formula I, or



b) a compound of the general formula V



5 in which R_3 and X have the above-given meaning and R_4 signifies hydrogen or R_2 , and possibly saponifies the resulting tetraesters to diesters or acids of general formula I, or

10 II. for the case that Y in general formula I signifies amino which is possibly substituted by alkyl groups, reacts a carboxylic acid derivative of the general formula VI



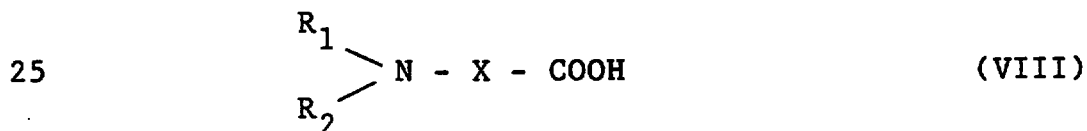
15 in which R_1 , R_2 and X have the above-given meaning and A represents a nitrile, imino ether or a carboxamido group possibly substituted on the nitrogen by lower alkyl, with a phosphorus compound of the general formula VII



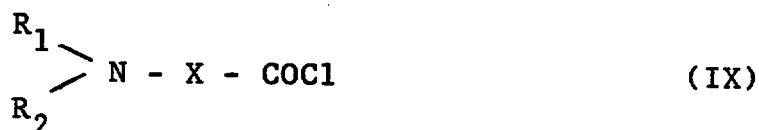
20 in which T = halogen, OH or OR' , whereby R' has the above-given meaning, and possibly subsequently saponifies to compounds of general formula I, or

III. for the case that Y in general formula I signifies OH

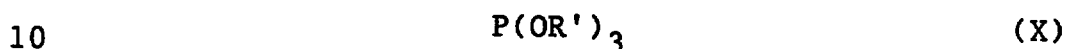
a) reacts a carboxylic acid of the general formula VIII



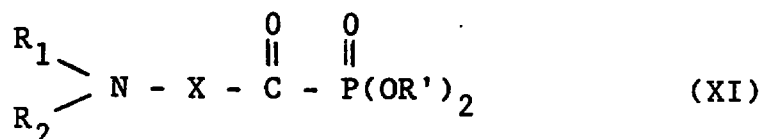
- in which R_1 , R_2 and X have the above-given meanings, with a mixture of phosphorous acid or phosphoric acid and a phosphorus halide and subsequently saponifies to the free diphosphonic acid of general formula I, or
- 5 b) reacts a carboxylic acid chloride of the general formula IX



in which R_1 , R_2 and X have the above-given meanings, with a trialkyl phosphite of the general formula X



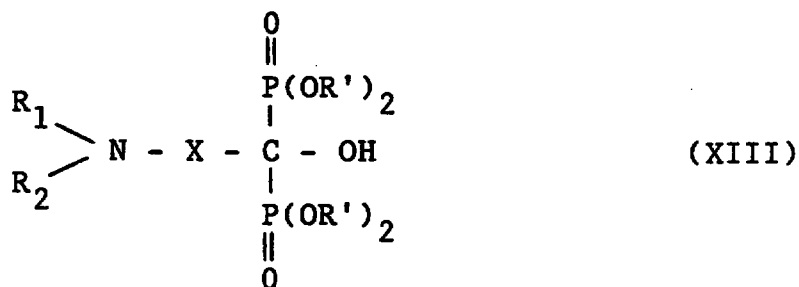
in which R' has the above-given meaning, to give an acyl phosphonate of the general formula XI



- in which R_1 , R_2 , X and R' have the above-given meanings, subsequently allows to react with a dialkyl phosphite of the general formula XII
- 15



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

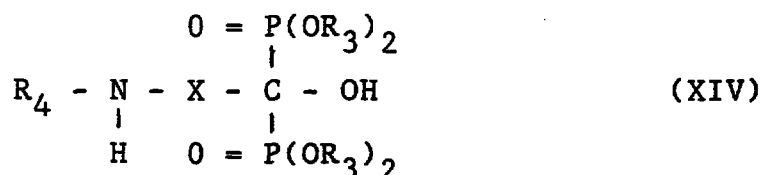


in which R_1 , R_2 , X and R' have the above-given meanings, and possibly saponifies the resulting tetraesters to



diesters or acids of general formula I, or

c) a compound of the general formula XIV



- 5 in which R_3 and X have the above-given meaning and R_4 signifies hydrogen or R_2 , and possibly saponifies the resulting tetraesters to diesters or acids of general formula I,
- and possibly converts the so prepared compounds into
- 10 their pharmacologically acceptable salts.
5. Process for the preparation of diphosphonates of general formula I according to claim 4, in which R_1 signifies a methyl or n-propyl group, R_2 represents an isobutyl, pentyl, nonyl or benzyl group, R_3 signifies
- 15 hydrogen, X signifies an ethylene group and Y a hydroxyl group, as well as of their pharmacologically acceptable salts.
6. Process according to claim 4 for the preparation of 1-hydroxy-3-(N-methyl-N-pentylamino)-propane-1,1-
- 20 diphosphonic acid or of 1-hydroxy-3-(N-isobutyl-N-methylamino)-propane-1,1-diphosphonic acid.
7. Medicaments containing at least one compound according to claim 1, 2 or 3, as well as usual pharmacological carrier and/or adjuvant materials.
- 25 8. Use of compounds according to claim 1, 2 or 3 for the preparation of medicaments.
9. Use of compounds according to claim 1, 2 or 3 for the preparation of medicaments for the treatment of calcium metabolism diseases.

