

Description**TECHNICAL FIELD**

5 The present invention relates to processes for the preparation of aminomethylene phosphonoalkylphosphinate compounds.

BACKGROUND OF THE INVENTION

10 Methylene phosphonoalkylphosphinate compounds which are useful for treating abnormal calcium and phosphate metabolism are the subject of co-pending patent application of Frank H. Ebetino entitled "Methylene Phosphonoalkylphosphinates, Pharmaceutical Compositions, and Methods for Treating Abnormal Calcium and Phosphate Metabolism", EP-A-298553, filed on the same day as the present patent application.

15 Some of the highly preferred compounds disclosed in this copending patent application are substituted aminomethylene phosphonoalkylphosphinates.

Certain methylene phosphonoalkylphosphinate compounds are disclosed in the following references : Gilmore, W. F., & J. W. Huber, "Base-Catalyzed Condensation of Aldehydes with Ethyl Bis(diethylphosphonomethyl)phosphonate", *Journal of Organic Chemistry*, Volume 38, No. 7 (1973), pp. 1423-1424 ; Gilmore, W. F., & J. S. Park, "Base-Catalyzed Condensation of Bis(diethylphosphonomethyl)phosphinic Amides with Aldehydes", *Phosphorus and Sulfur*, Volume 29 (1987), pp. 287-292 ; Aboujaoude, E. E., N. Collignon & P. Savignac, "Synthesis of Beta-carbonyl Phosphinates", *Journal of Organometallic Chemistry*, Volume 264 (1984), pp. 9-17 ; Henning, H. G., & G. Petzold, "Methylene-bis-phosphonic Acid Ester and Methylene-bis-phosphinic Acid Ester", *Z. Chem.*, Volume 5, No. 11 (1965), pp. 419-420 ; Abramov, V. S., & V. I. Barabanov, "Reaction of Phosphinic Acids with Aldehydes and Ketones, XXVII." *Zhurnal Obshchei Khimii*, Volume 36, No. 10 (1966), pp. 1830-1834 ; Abramov, V. S., V. I. Barabanov & L. I. Long, "Reactions of Phosphinic Acids with Aldehydes and Ketones, XXXII." *Zhurnal Obshchei Khimii*, Volume 37, No. 3 (1967), pp. 714-718 ; Pudovik, A. N., I. V. Gur'yanova, L. V. Banderova & M. G. Limin, "Reaction of Partial Esters of Ethylphosphinic and Phosphorothioic Acids with Alpha-oxo Phosphonic Acid Esters and Diacetyl", *Zhurnal Obshchei Khimii*, Volume 37, No. 4 (1967), pp. 876-881 ; Pudovik, A. N., I. V. Gur'yanova & M. G. Zimin, "Reactions of Phosphorus Acid, Ethylphosphinic Acid, and Thiophosphorus Acid Esters with some Substituted Benzoyl Phosphates", *Zhurnal Obshchei Khimii*, Volume 37, No. 11 (1967), pp. 2580-2585 ; Pudovik, A. N., I. V. Gur'yanova, L. V. Banderova & G. V. Romanov, "Phosphonate-phosphate Rearrangement of Esters of Alpha-hydroxyalkylphosphonic Acids", *Zhurnal Obshchei Khimii*, Volume 38, No. 1 (1968), pp. 143-150 ; Pudovik, A. N., G. E. Yastrebova, V. I. Nikitina & Y. Y. Samitov, "Synthesis and Reactions of Esters of (Beta-cyanovinyl)phosphonic Acid", *Zhurnal Obshchei Khimii*, Volume 38, No. 2 (1968), pp. 292-299 ; Romanov, G. V., M. S. Yafarov, A. I. Konovalov, A. N. Pudovik, I. V. Konovalova & T. N. Yusupova, "Thermodynamic and Kinetic Characteristics of the Phosphonate-phosphate Rearrangement", *Zhurnal Obshchei Khimii*, Volume 43, No. 11 (1973), pp. 2378-2386 ; Novikova, Z. S., S. N. Mashoshina & I. F. Lutsenko, "Addition of Tetraethyl Pyrophosphite and Tetraethyl Isohypophosphate to Compounds with Activated Multiple Bonds", *Zhurnal Obshchei Khimii*, Volume 44, No. 2 (1974), pp. 276-281 ; Novikova, Z. S., A. A. Prishchenko & I. F. Lutsenko, "Synthesis of 1,3-Di(oxalkoxyphospho)cycloalkanes", *Zhurnal Obshchei Khimii*, Volume 47, No. 11 (1977), pp. 2636-2637 ; Novikova, Z. S., S. Y. Skorobogatova & I. F. Lutsenko, "Reaction of Tetraethyl Carbomethoxymethylene-1,1-diphosphonite with Alkyl Halides", *Zhurnal Obshchei Khimii*, Volume 48, No. 4 (1978), pp. 757-764. These references are hereby incorporated herein in their entirety. Processes for synthesizing certain phosphonoalkylphosphinate compounds are disclosed in the above references.

Processes for the synthesis of alpha-aminophosphinates are disclosed in the following references : Maier, L., "Advances in the Chemistry of Aminophosphinic Acids", *Phosphorus and Sulfur*, Volume 14 (1983), pp. 295-322 ; and Oleksyszyn, J., M. Soraka & J. Rachon, "Phosphoranaloge von Aminosauern und Peptiden : Phosphon- und Phosphinanaloge von Cycloleucin", *Chimia*, Volume 32, Number 7 (July, 1978), pp. 253-255.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide novel processes for preparing certain aminomethylene phosphonoalkylphosphinate compounds.

55 It is a further object of this invention to provide such processes which result in aminomethylene phosphonoalkylphosphinate products having a minimal quantity of diphosphonate (bisphosphonate) impurities.

The present invention provides a process for making aminomethylene phosphonoalkylphosphinate compounds, said process comprising :

- (a) heating a substantially anhydrous mixture comprising an amine, an ester of an alkyl phosphite, and an ester of a phosphonate acetal ; and then
- (b) adding water to said mixture.

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DETAILED DESCRIPTION OF THE INVENTION

The process of the present invention uses as raw materials for making certain aminomethylene phosphonoalkylphosphinate compounds an amine, an ester of an alkyl phosphite, and an ester of a phosphonate acetal. The three raw materials are combined, preferably with a small amount of a suitable solvent, to form a substantially anhydrous mixture. The mixture is heated for a period of time, then preferably cooled, and then mixed with water and allowed to react.

The term "alkyl" as used herein unless otherwise specified, means chemically-stable carbon-containing chains which may be straight, branched, or cyclic ; and further which may be saturated, monounsaturated (e.g., one double bond ; one triple bond), or polyunsaturated (e.g., two double bonds ; two triple bonds ; three double bonds ; one double and one triple bond). Preferred alkyl have from 1 to about 20 carbon atoms, more preferred alkyl have from 1 to about 10 carbon atoms, and more preferred still alkyl have from 1 to about 6 carbon atoms. Still more preferred alkyl have from 1 to 4 carbon atoms, most preferred alkyl have 1 or 2 carbon atoms. "Cycloalkyls" as used herein, having from about 4 to about 10 carbon atoms are preferred ; more preferred are cycloalkyls having 5 or 6 carbon atoms. Also preferred are straight chain alkyl, saturated alkyl or monounsaturated alkyl. Most preferred are straight chain, saturated alkyl.

Alkyl is preferably unsubstituted but may be substituted. Preferred substituent groups for alkyl are as follows : fluoro ; cyano ; heterocycle ; aryl ; heteroaryl ; unsubstituted amino, and the amide thereof derived from a carboxylic acid of an alkyl, heterocycle, aryl or heteroaryl group ; amino substituted with one alkyl, heterocycle, aryl or heteroaryl group and the amide thereof derived from a carboxylic acid of an alkyl group ; hydroxy ; ether having an alkyl, heterocycle, aryl or heteroaryl group ; thiol ; thioether having an alkyl, heterocycle, aryl or heteroaryl group ; $-\text{SO}_3\text{H}$, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two alkyl groups ; $-\text{CO}_2\text{H}$, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two alkyl groups ; PO_3H_2 , the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two alkyl groups ; $-(\text{R}^6)\text{PO}_2\text{H}$ (where R^6 is hydrogen or unsubstituted lower alkyl), the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two alkyl groups ; carbamate, unsubstituted or substituted with one or two alkyl groups ; peptidyl ; and chemically-stable combinations thereof. More preferred alkyl substituents are halogen, especially fluoro ; trifluoromethyl ; ether having a lower alkyl group ; unsubstituted amino, and the amide thereof derived from a carboxylic acid of a lower alkyl group, amino substituted with one lower alkyl group and the amide thereof derived from carboxylic acid of a lower alkyl group ; peptidyl having from one to about six amino acid moieties ; and chemically-stable combinations thereof.

The term "lower alkyl", as used herein, unless otherwise specified, means unsubstituted alkyl having from 1 to about 6 carbon atoms which may be saturated or unsaturated. Preferred lower alkyl have from one to about 4 carbon atoms ; more preferred lower alkyl have one or two carbon atoms, Preferred lower alkyl are saturated. Most preferred lower alkyl are methyl and ethyl. For lower alkyl groups specified herein as substituted, preferred substituents are the same as for alkyl hereinabove.

The term "heterocycle", as used herein unless otherwise specified, means chemically-stable non-aromatic rings having from about 5 to about 20 atoms, comprising at least one heteroatom selected from nitrogen, sulfur, phosphorus and oxygen. Preferred are 5 and 6 membered ring heterocycles which comprise from about 1 to about 3 heteroatoms. More preferred are 5 and 6 membered ring heterocycles which comprise one or two heteroatoms (especially nitrogen heteroatoms). Most preferred are the 6 membered ring heterocycles comprising one nitrogen atom, especially piperidinyl and piperidinylidene heterocycles. Heterocycles may be unsubstituted or substituted. Preferred heterocycles are unsubstituted or substituted with alkyl ; halogen ; nitro ; cyano ; heterocycle ; aryl ; heteroaryl ; unsubstituted amino, and the amide thereof derived from a carboxylic acid of an alkyl, heterocycle, aryl or heteroaryl group ; amino substituted with one alkyl, heterocycle, aryl or heteroaryl group and the amide thereof derived from a carboxylic acid of an alkyl group ; hydroxy ; ether having an alkyl, heterocycle, aryl or heteroaryl group ; thiol ; thioether having an alkyl, heterocycle, aryl or heteroaryl group ; $-\text{SO}_3\text{H}$, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two alkyl groups ;

—CO₂H, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two alkyl groups ; PO₃H₂, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two alkyl groups ; —(R⁸)PO₂H (where R⁸ is hydrogen or unsubstituted lower alkyl), the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two alkyl groups ; aldehyde ; ketone having an alkyl group ; carbamate, unsubstituted or substituted with one or two alkyl groups ; peptidyl ; and chemically-stable combinations thereof. More preferred heterocycles are unsubstituted or substituted with lower alkyl ; fluoro ; trifluoromethyl ; ether having a lower alkyl group ; unsubstituted amino, and the amide thereof derived from a carboxylic acid of a lower alkyl group, amino substituted with one lower alkyl group and the amide thereof derived from carboxylic acid of a lower alkyl group ; peptidyl having from one to about six amino acid moieties ; and chemically-stable combinations thereof.

The term "aryl", as used herein unless otherwise specified, means chemically-stable aromatic rings having from about 6 to about 20 carbon atoms. Preferred aryl are phenyl or naphthyl ; most preferred is phenyl. Aryls may be unsubstituted or substituted. Preferred aryls are unsubstituted or substituted with alkyl ; fluoro ; cyano ; heterocycle ; aryl ; heteroaryl ; unsubstituted amino, and the amide thereof derived from a carboxylic acid of an alkyl, heterocycle, aryl or heteroaryl group ; amino substituted with one alkyl, heterocycle, aryl or heteroaryl group and the amide thereof derived from a carboxylic acid of an alkyl group ; hydroxy ; ether having an alkyl, heterocycle, aryl or heteroaryl group ; thiol ; thioether having an alkyl, heterocycle, aryl or heteroaryl group ; —SO₃H, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two alkyl groups ; —CO₂H, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two alkyl groups ; PO₃H₂, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two alkyl groups ; —(R⁸)PO₂H (where R⁸ is hydrogen or unsubstituted lower alkyl), the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two alkyl groups ; carbamate, unsubstituted or substituted with one or two alkyl groups ; peptidyl ; and chemically-stable combinations thereof. More preferred aryl are unsubstituted or substituted with lower alkyl ; fluoro ; trifluoromethyl ; ether having a lower alkyl group ; unsubstituted amino, and the amide thereof derived from a carboxylic acid of a lower alkyl group, amino substituted with one lower alkyl group and the amide thereof derived from carboxylic acid of a lower alkyl group ; peptidyl having from one to about six amino acid moieties ; and chemically-stable combinations thereof.

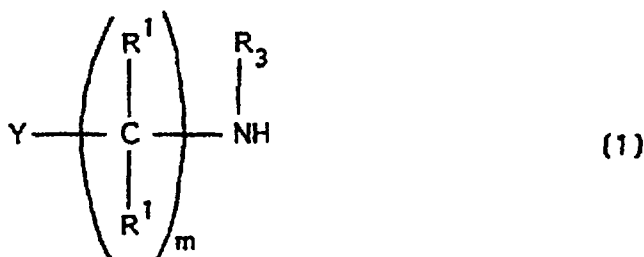
The term "heteroaryl", as used herein unless otherwise specified, means chemically-stable aromatic rings having from about 5 to about 20 atoms, comprising at least one heteroatom selected from nitrogen, sulfur, phosphorus and oxygen. Preferred are 5 and 6 membered ring heteroaryls which comprise from about 1 to about 3 heteroatoms. More preferred are 5 and 6 membered ring heteroaryls which comprise one or two heteroatoms (especially nitrogen heteroatoms). Most preferred heteroaryl is pyridinyl. Heteroaryls may be unsubstituted or substituted. Preferred heteroaryls are unsubstituted or substituted with alkyl ; fluoro ; cyano ; heterocycle ; aryl ; heteroaryl ; unsubstituted amino, and the amide thereof derived from a carboxylic acid of an alkyl, heterocycle, aryl or heteroaryl group ; amino substituted with one alkyl, heterocycle, aryl or heteroaryl group and the amide thereof derived from a carboxylic acid of an alkyl group ; hydroxy ; ether having an alkyl, heterocycle, aryl or heteroaryl group ; thiol ; thioether having an alkyl, heterocycle, aryl or heteroaryl group ; —SO₃H, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two alkyl groups ; —CO₂H, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two alkyl groups ; PO₃H₂, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two alkyl groups ; —(R⁸)PO₂H (where R⁸ is hydrogen or unsubstituted lower alkyl), the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two alkyl groups ; carbamate, unsubstituted or substituted with one or two alkyl groups ; peptidyl ; and combinations thereof. More preferred heteroaryls are unsubstituted or substituted with lower alkyl ; fluoro ; trifluoromethyl ; ether having a lower alkyl group ; unsubstituted amino, and the amide thereof derived from a carboxylic acid of a lower alkyl group, amino substituted with one lower alkyl group and the amide thereof derived from carboxylic acid of a lower alkyl group ; peptidyl having from one to about six amino acid moieties ; and chemically-stable combinations thereof.

The term "substituent group" as used herein means hydrogen or an alkyl, heterocycle, aryl or heteroaryl

group, unless otherwise specified.

The term "chemically-stable, as used herein, refers to compounds which are sufficiently stable under normal storage and use conditions such that they can provide their intended uses. Compounds having combinations of substituents and/or moieties which would result in chemically-unstable compounds are not included in the compounds made by the processes of the present invention. Such chemically-unstable compounds are readily identified by a skilled chemist.

As used herein, an "amine" is a compound having the following chemical structure :



In structure (1) hereinabove, m is an integer from 0 to about 10 ; preferably m is from 0 to about 5 ; more preferably m is 0 or 1 ; and most preferably m is 0 ; and R³ is hydrogen or lower alkyl.

In structure (1) hereinabove, each R¹ is independently selected from the group consisting of hydrogen, fluoro, lower alkyl, unsubstituted amino or the amide thereof derived from a carboxylic acid of a lower alkyl group, amino substituted with one lower alkyl group or the amide thereof derived from a carboxylic acid of a lower alkyl group, hydroxy, —CO₂H or the pharmaceutically-acceptable salts thereof or the ester thereof derived from an alcohol of a lower alkyl group or the unsubstituted amide thereof or the amide thereof substituted with one or two lower alkyl groups, ether having a lower alkyl group, —PO₃H₂ or the pharmaceutically-acceptable salts thereof, and nitro, or two R¹'s on the same carbon atom are =O or =NR⁹ (where R⁹ is unsubstituted lower alkyl or may be hydrogen when there is another nitrogen atom attached to the same carbon atom as the =NR⁹ moiety), or two R¹'s on adjacent carbon atoms may be replaced by an additional bond between the carbon atoms. (For the sake of chemical stability of the compounds of the present invention, R¹ cannot be such that there is a halogen and an oxygen or sulfur or nitrogen singly bonded to the same carbon atom or such that two of an oxygen or sulfur or nitrogen are singly bonded to the same carbon atom). Each R¹ moiety is preferably independently selected from hydrogen, methyl, ethyl, hydroxy, unsubstituted amino, or two R¹'s on the same carbon atom are =O or =NR⁹ (where R⁹ is unsubstituted lower alkyl or may be hydrogen when there is another nitrogen atom attached to the same carbon atom as the =NR⁹ moiety), or two R¹'s on adjacent carbon atoms are replaced by an additional bond between the carbon atoms. Most preferred is all R¹ groups being hydrogen.

In structure (1) hereinabove, Y is a substituent of alkyl as defined hereinbefore. Y is preferably Y¹, Y² or Z as hereinafter defined.

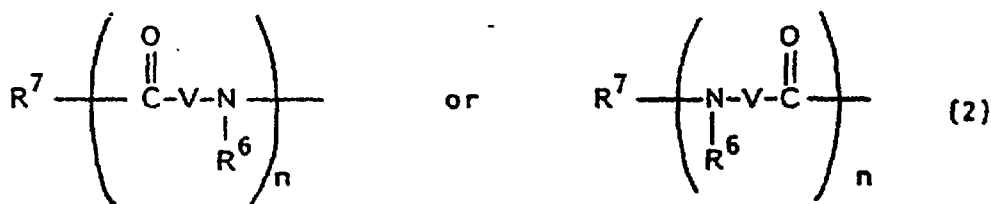
When Y is Y¹, m is more preferably from 1 to about 5. The Y¹ moiety is preferably selected from hydrogen, fluoro, unsubstituted amino or the amide thereof derived from a carboxylic acid of a lower alkyl group, amino substituted with one lower alkyl group or the amide thereof derived from a carboxylic acid of a lower alkyl group, hydroxy, —CO₂H or the pharmaceutically-acceptable salts thereof or the ester thereof derived from an alcohol of a lower alkyl group or the unsubstituted amide thereof or the amide thereof substituted with one or two lower alkyl groups. Preferred Y¹ is hydrogen, fluoro, unsubstituted amino or the amide thereof derived from a carboxylic acid of a lower alkyl group, amino substituted with one lower alkyl group, and hydroxy. Most preferred Y¹ is hydrogen, hydroxy, amino substituted with one methyl group, and especially unsubstituted amino.

When Y is Z, m is preferably from 0 to about 2 ; especially preferred is m being 0 or 1 ; most preferred is m = 0. The Z moiety is selected from the group consisting of unsubstituted or substituted cycloalkyl, heterocycle, aryl and heteroaryl ; with preferred Z being selected from five-membered ring heterocycles and heteroaryls having one heteroatom, five-membered ring heterocycles and heteroaryls having two heteroatoms, unsubstituted or substituted phenyl, six-membered ring heterocycles and heteroaryls having one heteroatom, and six-membered ring heterocycles and heteroaryls having two heteroatoms ; and preferably all the heteroatoms in the ring are nitrogen. More preferred Z is phenyl, pyrrolidinyl, pyrrolyl, pyridinyl, piperidinyl, piperidinylidene, pyridazinyl, pyrimidinyl, pyrazinyl, and morpholinyl. Most preferred Z is pyrimidinyl, and especially piperidinyl and pyridinyl.

The Z moiety may be unsubstituted or substituted. Preferred is the Z moiety being unsubstituted or substituted on the carbon atoms of the ring with one or more substituents selected from the group consisting of

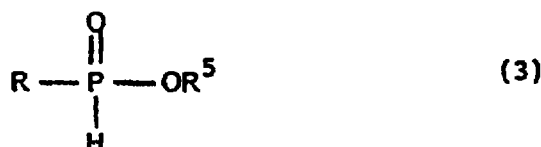
lower alkyl ; unsubstituted amino, and the amide thereof derived from a carboxylic acid of a lower alkyl group; amino substituted with one lower alkyl group, and the amide thereof derived from a carboxylic acid of a lower alkyl group ; hydroxy ; ether having a lower alkyl group ; $-\text{CO}_2\text{H}$, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of a lower alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one lower alkyl group ; and chemically-stable combinations thereof. Preferred is the Z moiety being unsubstituted or substituted on the carbon atoms of the ring with one or more substituents selected from the group consisting of fluoro, lower alkyl, unsubstituted amino and the acetyl amide thereof, amino substituted with one methyl group and the acetyl amide thereof, hydroxy, methyl ether, ethyl ether, $-\text{CO}_2\text{H}$ and the pharmaceutically-acceptable salts thereof, $-\text{CO}_2\text{CH}_3$, $-\text{CO}_2\text{C}_2\text{H}_5$, $-\text{CONH}_2$, $-\text{CONHCH}_3$, and $-\text{CON}(\text{CH}_3)_2$. More preferred is the Z moiety being unsubstituted, or mono-, di-, or tri-substituted independently with the preceding substituents. Most preferred is the Z moiety being unsubstituted, or mono-substituted with a substituent selected from the group consisting of methyl, ethyl, fluoro, trifluoromethyl, hydroxy, (N-methyl)amino, methyl ether, $-\text{CO}_2\text{H}$ and the pharmaceutically-acceptable salts thereof, $-\text{CO}_2\text{CH}_3$, $-\text{CONH}_2$, and especially unsubstituted amino.

When Y is Y^2 , m is preferably 0 to about 2, more preferably 0 or 1, most preferably 0. Y^2 is peptidyl having the following chemical structure :



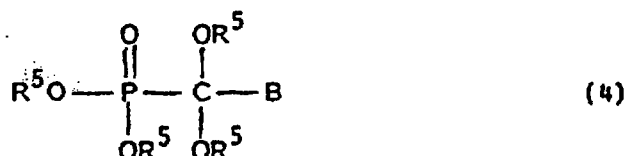
In structure (2) hereinabove, n is an integer from 1 to about 100, preferably from 1 to about 6 ; each R^6 and R^7 is independently hydrogen or lower alkyl, preferably each R^6 and R^7 are hydrogen ; each V is independently unsubstituted or substituted lower alkyl, or independently each R^6 and V together with the included nitrogen atom to which they are bound, form a 5- or 6-membered ring which is unsubstituted or substituted, preferably each V or rings in which they are incorporated are moieties found in naturally-occurring amino acid moieties, i.e. lysine, leucine, isoleucine, valine, phenylalanine, arginine, histidine, methionine, alanine, aspartic acid, threonine, proline, glycine, serine, tyrosine, tryptophan, glutamine and cysteine.

As used herein, an "ester of an alkyl phosphite" is a compound having the following chemical structure :



In structure (3) hereinabove, R^5 is alkyl, preferably lower alkyl. R is a moiety selected from the group consisting of hydrogen, and alkyl, other than alkyl having unsaturation between the carbon adjacent the phosphorus and an adjacent carbon or nitrogen atom. Preferred R is unsubstituted alkyl, especially lower alkyl. Preferred substituents on the R alkyl, when substituted, include fluoro, unsubstituted and substituted phenyl, unsubstituted and substituted pyridinyl, unsubstituted amino, amino substituted with one lower alkyl group, hydroxy, carboxy, and combinations thereof. More preferred substituents are fluoro, phenyl, unsubstituted amino, and hydroxy ; and most preferred are fluoro (especially when present as trifluoromethyl) and phenyl. Particularly preferred R moieties are selected from unsubstituted, straight-chain, saturated lower alkyl groups. Also preferred R moieties are selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and tert-butyl. More preferred still R moieties are selected from methyl, ethyl, n-propyl, and n-butyl. Most preferred R moiety is methyl.

As used herein, an "ester of a phosphonate acetal" is a compound having the chemical structure :

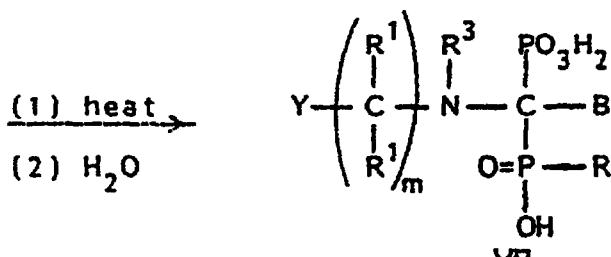
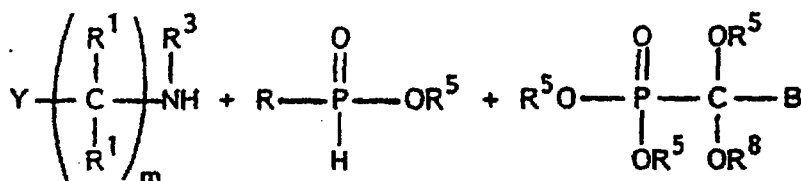


wherein R^5 is alkyl, preferably lower alkyl.

In structure (4) hereinabove, B is a moiety selected from the group consisting of hydrogen ; fluoro ; unsubstituted and substituted lower alkyl ; unsubstituted and substituted cycloalkyl having from about 3 to about 7 atoms in the ring ; unsubstituted and substituted heterocycle having from about 3 to about 7 atoms in the ring ; unsubstituted and substituted phenyl ; $-\text{CO}_2\text{H}$, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of a lower alkyl group, the unsubstituted amide thereof, and the amide thereof substituted with one or two lower alkyl groups. Preferred B is selected from the group consisting of hydrogen, fluoro, unsubstituted and substituted lower alkyl, unsubstituted and substituted phenyl, unsubstituted and substituted benzyl, and $-\text{CO}_2\text{H}$ and the pharmaceutically-acceptable salts thereof and the ester thereof derived from an alcohol of a lower alkyl group and the unsubstituted amide thereof or the amide thereof substituted with one or two lower alkyl groups. More preferred B is selected from hydrogen, methyl, ethyl, $-\text{CO}_2\text{H}$ and the pharmaceutically-acceptable salts thereof, $-\text{CO}_2\text{CH}_3$, and $-\text{CONH}_2$. Most preferred B is hydrogen.

The ester of a phosphonate acetal can be synthesized from trialkyl orthoformate and dialkyl chlorophosphite, as exemplified in Dietsche, W., "Darstellung von C-phosphorylierten Formaldehydacetalen", Liebigs Ann. Chem., Vol. 712 (1968), pp. 21-27, which is incorporated herein by reference.

The process of the present invention is depicted schematically as follows :



wherein m, Y, R, R^1 , R^3 and R^5 are as described hereinbefore.

To prepare the aminomethylene phosphonoalkylphosphinates according to the process of the present invention, the amine, ester of an alkyl phosphite, and ester of a phosphonate acetal are combined in a reaction vessel. (If necessary to prevent unwanted reactions of substituents on the raw materials, suitable protecting groups may be placed on such substituents for later removal.) A small amount of solvent is preferably included in this reaction mixture ; preferred solvents are alcohols having from 1 to about 6 carbon atoms ; more preferred are methanol, ethanol, n-propanol and isopropanol ; most preferred is ethanol. The reaction mixture is heated to a temperature which is determined for each combination of reactants ; overheating causes side reactions to be accelerated, and product of unacceptable purity results. Progress of the reaction is preferably followed by determining consumption of the amine by liquid chromatography or other suitable means. The alcohol is allowed to distill off the reaction mixture. Equimolar amounts of the three reactants are preferably included in the reaction mixture.

When the reactants have been consumed in the reaction, the resulting mixture is preferably cooled and an excess of water (preferably hot water) is added to the reaction mixture. The water is added with care since

this can result in an exotherm. The reaction mixture is preferably heated for a period sufficient to insure complete conversion to the phosphonophosphinic acid, preferably about one hour. The solid product is then filtered from the reaction mixture, washed with hot water, and dried.

Further product can generally be obtained by stripping the filtrate to one-quarter to one-third of its volume, cooling it to room temperature, and allowing it to stand. The resulting crystals are filtered, washed with water and dried.

The following nonlimiting examples are provided to exemplify the processes of the present invention.

Example 1

Synthesis of N-(2'-(3'-methyl)-pyridinyl)-Aminomethane Phosphonomethylphosphinic Acid

To a flask containing triethyl orthoformate (23.6 gm ; 0.16 moles) equipped with a magnetic stirrer, condensor, and nitrogen atmosphere, is added diethyl chlorophosphite (25 gm ; 0.16 moles) over 15-30 minutes; an extremely exothermic reaction occurs. The reaction solution is then heated at 135°C for 3 hours. The resulting solution is distilled using a Kugelrohr distillation apparatus at 80°C (0.01 mm Hg) to yield 32 gm of diethoxymethylphosphonic acid diethyl ester (³¹P NMR 13.2 ppm).

This ester (15 gm, 62.5 mmoles) is combined with ethyl hydrogen methylphosphinate (9.6 gm ; 62.5 mmoles ; See Dougherty, K.E., W. A. Eychaner & J. I. Stevens, *Applied Spectroscopy*, Volume 22, No. 2 (1968), p. 95, which is incorporated herein by reference in its entirety) and 2-amino-3-methylpyridine (6.75 gm ; 62.5 mmoles) in a flask equipped with a short path distillation head, magnetic stirrer, and a nitrogen atmosphere. The flask is placed in an oil bath and the temperature is slowly brought to 150°C. The reaction mixture is kept at this temperature until no further ethanol is distilled off (approximately 30 minutes), and then the mixture is heated at 170-175°C for 4 to 5 hours. After this time, the bath temperature is cooled to 110°C, 75 ml of water is added, and this reaction mixture is allowed to reflux for one hour. The resulting white precipitate is collected, rinsed with hot water (2 x 10 ml), and dried to yield 5.7 gm of N-(2'-(3'-methyl)-pyridinyl)-aminomethane phosphonomethylphosphinic acid.

The monosodium salt is prepared by the addition of one equivalent of 6N NaOH to bring a 10% aqueous solution to a pH of 4.0. ¹H NMR (D₂O ; 1 equivalent NaOH) : 7.69 (1H, d, J = 7.2 Hz) ; 7.65 (1H, d, J = 6.3 Hz) ; 6.8 (1H, dd) ; 4.0 (1H, dd, J = 20.1 Hz, J = 15.6 Hz) ; 2.23 (3H, s) ; 1.42 ppm (3H, d, J = 14.4 Hz). ³¹P NMR : 35.11 (d, J = 15 Hz) ; 11.54 ppm (d, J = 15 Hz). Anal. calc'd. for C₈H₁₄N₂O₅P₂ : C = 34.30 ; H = 5.04 ; N = 10.00. Found : C = 34.54 ; H = 5.30 ; N = 9.79.

Example 2

Synthesis of N-(2'-(3'-methyl)-piperidinylidene)-Aminomethane Phosphonomethylphosphinic Acid, Monosodium Salt

To a 10% solution of N-(2'-(3'-methyl)-pyridinyl)-aminomethane phosphonomethylphosphinic acid is added 6 N NaOH until the pH is adjusted to 4.0. The resulting solution is diluted to 820 ml water and hydrogenated for 48 hours at 50 psi at room temperature with 12 gm of 10% Pd/C in a Parr hydrogenation apparatus. The solution is then filtered and evaporated to dryness to yield 43 gm of N-(2'-(3'-methyl)-piperidinylidene)-aminomethane phosphonomethylphosphinic acid, monosodium salt. The following spectral data are reported on the 1 : 1 mixture of diastereoisomers. ³¹P NMR (2.5% in D₂O) : 33.37 (d, J = 13 Hz) 32.93 (d, J = 13 Hz), 9.99 (d, J = 13 Hz), 9.66 (d, J = 13 Hz). ¹H NMR (1% in D₂O) : 3.88 (1H, dd, J = 15.6, 19.9) ; 3.45 (2H, m) ; 2.92 (1H, m) ; 1.96 (2H, m) ; 1.82 (1H, m) ; 1.66 (1H, m) ; 1.46 (1.5H, d, J = 14.5) ; 1.44 (1.5H, d, J = 13.9) ; 1.40 (1.5H, d, J = 6.9) ; 1.39 ppm (1.5H, d, J = 6.8). ¹³C NMR (10% in D₂O) : 169.6, 55.7 (2 overlapping dd's), 44.0, 33.3, 27.7, 20.6, 19.5, 17.7 (d, J = 98). Anal. calc'd for C₈H₁₇N₂O₅P₂Na H₂O : C = 29.63 ; H = 5.91 ; N = 8.64. Found : C = 30.06 ; H = 6.31 ; N = 8.77.

Example 3

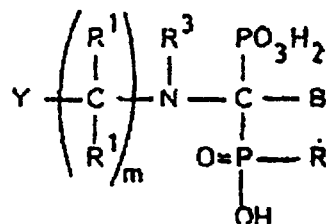
Synthesis of N-(1-(5-amino-2-methyl-1-oxo)-pentyl)-Aminomethane Phosphonomethylphosphinic Acid

A 10% aqueous solution of sodium N-(2'-(3'-methyl)-pyridyl)-amino methane-1-phosphono-1-methylphosphinate (10 g) is refluxed for 72 hours under a nitrogen atmosphere. After noting approximately a 75% conversion to new material, pure N-(1-(5-amino-2-methyl-1-oxo)-pentyl)-aminomethane-1-phosphono-1-methylphosphinic acid is isolated on a

preparative HPLC silica gel column on elution with approximately 91 : 9 MeOH/H₂O. The product isolated is reported as a 1 : 1 mixture of diastereoisomers. ³¹P NMR (D₂O, pD = 12) : 35, 12 ppm. ¹³C NMR (10% in D₂O) : 180.4, 52.2 (2 overlapping dd's), 42.5, 41.4, 32.4, 26.9, 19.2, 17.6 (d, J = 96). ¹H NMR (1% in D₂O) : 4.35 (1H, m), 3.00 (2H, m), 2.55 (1H, m), 1.58 (2H, m), 1.53 (1H, m), 1.39 (1.5H, d, J = 14.0), 1.36 (1.5H, d, J = 14.0), 1.17 (1.5H, d, J = 6.8), 1.16 (1.5H, d, J = 6.8).

Claims

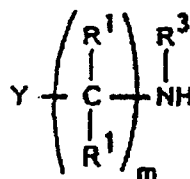
1. A process for making aminomethylene phosphonoalkylphosphinate compounds having the chemical structure :



said process comprising :

(a) heating a substantially anhydrous mixture comprising :

(1) an amine having the chemical structure :



wherein

(i) m is an integer from 0 to 10 ;

(ii) each R¹ is independently hydrogen, fluoro, lower alkyl, unsubstituted amino or the amide thereof derived from a carboxylic acid of a lower alkyl group, amino substituted with one lower alkyl group or the amide thereof derived from a carboxylic acid of a lower alkyl group, hydroxy, —CO₂H or the pharmaceutically-acceptable salts thereof or the ester thereof derived from an alcohol of a lower alkyl group or the unsubstituted amide thereof or the amide thereof substituted with one or two lower alkyl groups, ether having a lower alkyl group, —PO₃H₂ or the pharmaceutically-acceptable salts thereof, or nitro, or two R¹'s on the same carbon atom are =O or =NR⁹ (where R⁹ is unsubstituted lower alkyl or may be hydrogen when there is another nitrogen atom attached to the same carbon atom as the =NR⁹ moiety), or two R¹'s on adjacent carbon may be replaced by an additional bond between the carbon atoms ; except that R¹'s are not such that there is a halogen and an oxygen or sulfur or nitrogen singly bonded to the same carbon atom or such that two of an oxygen or sulfur or nitrogen are singly bonded to the same carbon atom.

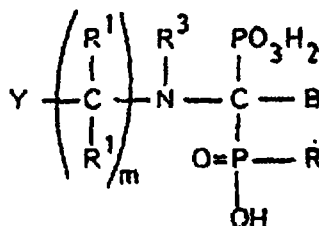
(iii) R³ is hydrogen or lower alkyl ; and

(iv) Y is hydrogen, fluoro ; cyano ; heterocycle ; aryl ; heteroaryl ; unsubstituted amino, or the amide thereof derived from a carboxylic acid of an alkyl, heterocycle, aryl or heteroaryl group ; amino substituted with one alkyl, heterocycle, aryl or heteroaryl group or the amide thereof derived from a carboxylic acid of an alkyl group ; hydroxy ether having an alkyl, heterocycle, aryl or heteroaryl group ; thiol ; thioether having an alkyl, heterocycle, aryl or heteroaryl group ; —SO₃H, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, or the amide thereof substituted with one or two alkyl groups ; —CO₂H, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, or the amide thereof substituted with one or two alkyl groups ; PO₃H₂, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsub-

preparative HPLC silica gel column on elution with approximately 91 : 9 MeOH/H₂O. The product isolated is reported as a 1 : 1 mixture of diastereoisomers. ³¹P NMR (D₂O, pD = 12) : 35, 12 ppm. ¹³C NMR (10% in D₂O) : 180.4, 52.2 (2 overlapping dd's), 42.5, 41.4, 32.4, 26.9, 19.2, 17.6 (d, J = 96). ¹H NMR (1% in D₂O) : 4.35 (1H, m), 3.00 (2H, m), 2.55 (1H, m), 1.58 (2H, m), 1.53 (1H, m), 1.39 (1.5H, d, J = 14.0), 1.36 (1.5H, d, J = 14.0), 1.17 (1.5H, d, J = 6.8), 1.16 (1.5H, d, J = 6.8).

Claims

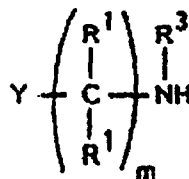
1. A process for making aminomethylene phosphonoalkylphosphinate compounds having the chemical structure :



said process comprising :

(a) heating a substantially anhydrous mixture comprising :

(1) an amine having the chemical structure :



wherein

(i) m is an integer from 0 to 10 ;

(ii) each R¹ is independently hydrogen, fluoro, lower alkyl, unsubstituted amino or the amide thereof derived from a carboxylic acid of a lower alkyl group, amino substituted with one lower alkyl group or the amide thereof derived from a carboxylic acid of a lower alkyl group, hydroxy, —CO₂H or the pharmaceutically-acceptable salts thereof or the ester thereof derived from an alcohol of a lower alkyl group or the unsubstituted amide thereof or the amide thereof substituted with one or two lower alkyl groups, ether having a lower alkyl group, —PO₃H₂ or the pharmaceutically-acceptable salts thereof, or nitro, or two R¹'s on the same carbon atom are =O or =NR⁹ (where R⁹ is unsubstituted lower alkyl or may be hydrogen when there is another nitrogen atom attached to the same carbon atom as the =NR⁹ moiety), or two R¹'s on adjacent carbon may be replaced by an additional bond between the carbon atoms ; except that R¹'s are not such that there is a halogen and an oxygen or sulfur or nitrogen singly bonded to the same carbon atom or such that two of an oxygen or sulfur or nitrogen are singly bonded to the same carbon atom.

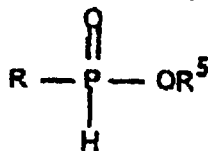
(iii) R³ is hydrogen or lower alkyl ; and

(iv) Y is hydrogen, fluoro ; cyano ; heterocycle ; aryl ; heteroaryl ; unsubstituted amino, or the amide thereof derived from a carboxylic acid of an alkyl, heterocycle, aryl or heteroaryl group ; amino substituted with one alkyl, heterocycle, aryl or heteroaryl group or the amide thereof derived from a carboxylic acid of an alkyl group ; hydroxy ether having an alkyl, heterocycle, aryl or heteroaryl group ; thiol ; thioether having an alkyl, heterocycle, aryl or heteroaryl group ; —SO₃H, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, or the amide thereof substituted with one or two alkyl groups ; —CO₂H, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, or the amide thereof substituted with one or two alkyl groups ; PO₃H₂, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsub-



stituted amide thereof, or the amide thereof substituted with one or two alkyl groups ; $-(R^8)PO_2H$ (where R^8 is hydrogen or unsubstituted lower alkyl), the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of an alkyl group, the unsubstituted amide thereof, or the amide thereof substituted with one or two alkyl group ; carbamate, unsubstituted or substituted with one or two alkyl groups ; or peptidyl ;

(2) an ester of an alkyl phosphite having the chemical structure :

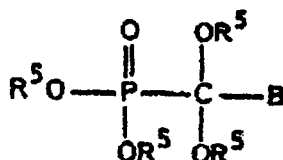


wherein

(i) R is hydrogen or alkyl ; and

(ii) R^5 is alkyl ;

(3) an ester of an phosphonate acetal having the chemical structure :



wherein

(i) B is hydrogen ; fluoro ; unsubstituted or substituted lower alkyl ; unsubstituted or substituted cycloalkyl having from 3 to 7 atoms in the ring ; unsubstituted or substituted heterocycle having from 3 to 7 atoms in the ring ; unsubstituted or substituted phenyl ; and $-\text{CO}_2\text{H}$, the pharmaceutically-acceptable salts thereof, the ester thereof derived from an alcohol of a lower alkyl group, the unsubstituted amide thereof, or the amide thereof substituted with one or two lower alkyl groups ; and

(ii) R^5 is alkyl ;

(b) and then adding water to said mixture.

2. The process of Claim 1 wherein

(a) each R^1 is hydrogen, methyl, ethyl, hydroxy, unsubstituted amino, or two R^1 's on the same carbon atom are $=\text{O}$ or $=\text{NR}^2$, or two R^1 's on adjacent carbon atoms are replaced by an additional bond between the carbon atoms ; and

(b) R^3 is hydrogen ;

(c) each R^5 is lower alkyl ;

(d) R is unsubstituted lower alkyl or lower alkyl substituted with fluoro, unsubstituted or substituted phenyl, unsubstituted or substituted pyridinyl, unsubstituted amino, amino substituted with one lower alkyl group, hydroxy, or carboxy, or combinations thereof ; preferably unsubstituted, straight-chain, saturated lower alkyl ; and

(e) B is hydrogen, methyl, ethyl, $-\text{CO}_2\text{H}$ or the pharmaceutically-acceptable salts thereof, $-\text{CO}_2\text{CH}_3$, or $-\text{CONH}_2$; preferably hydrogen.

3. The process of Claim 2 wherein

(a) m is an integer from 1 to 5 ; and

(b) Y is unsubstituted amino or the amide thereof derived from a carboxylic acid of a lower alkyl group, amino substituted with one lower alkyl group or the amide thereof derived from a carboxylic acid of a lower alkyl group, hydroxy, $-\text{CO}_2\text{H}$ or the pharmaceutically-acceptable salts thereof or the ester thereof derived from an alcohol of a lower alkyl group or the unsubstituted amide thereof or the amide thereof substituted with one or two lower alkyl groups ; preferably amino substituted with one methyl group, or unsubstituted amino.

4. The process of Claim 2 wherein Y is hydrogen, hydroxy, amino substituted with one methyl group, or unsubstituted amino.

5. The process of Claim 4 wherein



(a) m is an integer from 0 to 2 ; preferably 0 ;

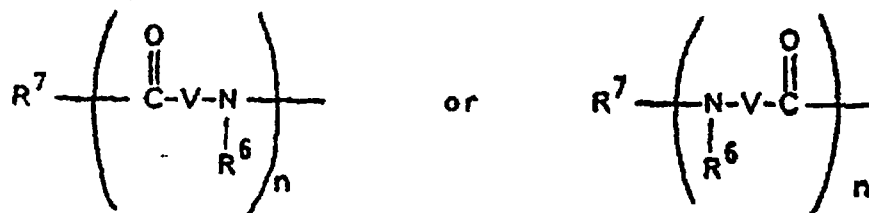
(b) Y is unsubstituted or substituted cycloalkyl, heterocycle, aryl or heteroaryl ; preferably phenyl, pyrrolidinyl, pyrrolyl, pyridinyl, piperidinyl, piperidinylidene, pyridazinyl, pyrimidinyl, pyrazinyl or morpholinyl, wherein said Y is unsubstituted or monosubstituted with methyl, ethyl, fluoro, trifluoromethyl, hydroxy, (N-methyl)amino, methyl ether, $-\text{CO}_2\text{H}$ or the pharmaceutically-acceptable salts thereof, $-\text{CO}_2\text{CH}_3$, or $-\text{CONH}_2$.

6. The process of Claim 5 wherein Y is pyridinyl attached at the 2-position, and is unsubstituted or monosubstituted with a methyl or amino at the 3-, 4- or 5-position.

7. The process of Claim 6 wherein in a subsequent reaction step said pyridinyl is hydrogenated to piperidinylidene.

8. The process of Claim 5 wherein Y is piperidinyl attached at the 2-position, and is unsubstituted or monosubstituted with methyl.

9. The process of Claim 2 wherein Y is peptidyl having the following chemical structure :



wherein

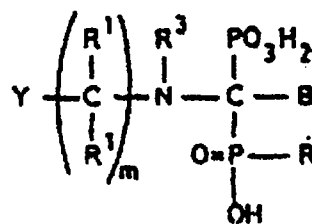
(a) n is an integer from 1 to 100 ; preferably from 1 to 6

(b) each R^6 and R^7 is independently hydrogen or lower alkyl ; preferably hydrogen ; and

(c) each V is independently unsubstituted or substituted lower alkyl, or independently each R^6 and V together with the included nitrogen atom to which they are bound, form a 5- or 6-membered ring which is unsubstituted or substituted ; preferably wherein each V or rings in which they are incorporated are moieties found in naturally-occurring amino acid moieties.

Patentansprüche

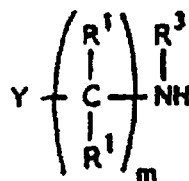
1. Verfahren zur Herstellung von Aminomethylenphosphonoalkylphosphinat-verbindungen mit der chemischen Struktur :



welches Verfahren umfaßt :

(a) Erhitzen eines im wesentlichen wasserfreien Gemisches, umfassend :

(1) ein Amin mit der chemischen Struktur :



worin

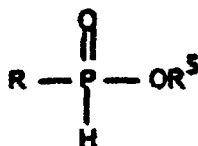
(i) m eine ganze Zahl von 0 bis 10 bedeutet ;

(ii) jeder Rest R^1 unabhängig voneinander Wasserstoff, Fluor, Niederalkyl, unsubstituiertes Amino oder das von einer Carbonsäure einer niederen Alkylgruppe abgeleitete Amid hievon, Amino, das mit einer Niederalkylgruppe substituiert ist, oder das von einer Carbonsäure einer Niederalkylgruppe abgeleitete Amid hievon, Hydroxy, $-\text{COOH}$ oder die pharmazeutisch annehmbaren Salze hievon oder der von einem Alkohol einer Niederalkylgruppe abgeleitete Ester hievon oder das unsubstituierte Amid hievon oder das mit einer oder mit zwei Niederalkylgruppen substituierte Amid hievon, Ether mit einer Niederalkylgruppe, $-\text{PO}_3\text{H}_2$ oder die pharmazeutisch annehmbaren Salze hievon oder Nitro bedeutet, oder zwei Reste R^1 am gleichen Kohlenstoffatom für $=\text{O}$ oder $=\text{NR}^9$ stehen (worin R^9 unsubstituiertes Niederalkyl ist oder Wasserstoff darstellt, wenn ein anderes Stickstoffatom an das gleiche Kohlenstoffatom wie der $=\text{NR}^9$ -Rest gebunden ist), oder zwei Reste R^1 an benachbarten Kohlenstoffatomen durch eine zusätzliche Bindung zwischen den Kohlenstoffatomen ersetzt sein können ; mit der Ausnahme, daß die Reste R^1 nicht solche sind, daß ein Halogen und ein Sauerstoff oder Schwefel oder Stickstoff einfach an das gleiche Kohlenstoffatom gebunden sind, oder nicht solche sind, daß zwei der Reste Sauerstoff oder Schwefel oder Stickstoff einfach an das gleiche Kohlenstoffatom gebunden sind ;

(iii) R^3 für Wasserstoff oder Niederalkyl steht ; und

(iv) Y Wasserstoff, Fluor ; Cyano ; einen Heterocyclus ; Aryl ; Heteroaryl ; unsubstituiertes Amino oder das von einer Carbonsäure eines Alkyls, Heterocyclus, Aryls oder einer Heteroarylgruppe abgeleitete Amid hievon ; mit einer Alkyl-, Heterocyclus-, Aryl- oder Heteroarylgruppe substituiertes Amino oder das von einer Carbonsäure einer Alkylgruppe abgeleitete Amid hievon ; Hydroxy ; Ether mit einer Alkyl-, Heterocyclus-, Aryl- oder Heteroarylgruppe ; Thiol ; Thioether mit einer Alkyl-, Heterocyclus-, Aryl- oder Heteroarylgruppe ; $-\text{SO}_3\text{H}$, die pharmazeutisch annehmbaren Salze hievon, den von einem Alkohol einer Alkylgruppe abgeleiteten Ester hievon, das unsubstituierte Amid hievon oder das mit einer oder mit zwei Alkylgruppen substituierte Amid hievon ; $-\text{COOH}$, die pharmazeutisch annehmbaren Salze hievon, den von einem Alkohol einer Alkylgruppe abgeleiteten Ester hievon, das unsubstituierte Amid hievon oder das mit einer oder mit zwei Alkylgruppen substituierte Amid hievon ; $-\text{PO}_3\text{H}_2$, die pharmazeutisch annehmbaren Salze hievon, den von einem Alkohol einer Alkylgruppe abgeleiteten Ester hievon, das unsubstituierte Amid hievon oder das mit einer oder mit zwei Alkylgruppen substituierte Amid hievon ; $-(R^6)\text{PO}_2\text{H}$ (worin R^6 Wasserstoff oder unsubstituiertes Niederalkyl bedeutet), die pharmazeutisch annehmbaren Salze hievon, den von einem Alkohol einer Alkylgruppe abgeleiteten Ester hievon, das unsubstituierte Amid hievon oder das mit einer oder mit zwei Alkylgruppen substituierte Amid hievon ; unsubstituiertes oder mit einer oder mit zwei Alkylgruppen substituiertes Carbamat ; oder Peptidyl bedeutet ;

(2) einen Ester eines Alkylphosphits mit der chemischen Struktur :

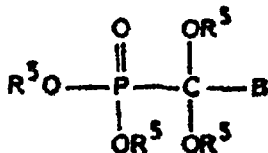


worin

(i) R für Wasserstoff oder Alkyl steht ; und

(ii) R^5 für Alkyl steht ;

(3) einen Ester eines Phosphonatacetal mit der chemischen Struktur :



worin

(i) B Wasserstoff ; Fluor ; unsubstituiertes oder substituiertes Niederalkyl ; unsubstituiertes oder substituiertes Cycloalkyl mit 3 bis 7 Ringatomen ; unsubstituierten oder substituierten Heterocyclus mit 3 bis 7 Ringatomen ; unsubstituiertes oder substituiertes Phenyl ; und $-\text{COOH}$, die pharmazeutisch annehmbaren Salze hievon, den von einem Alkohol einer Niederalkylgruppe abgeleiteten Ester hievon,



das unsubstituierte Amid hievon oder das mit einer oder mit zwei Niederalkylgruppen substituierte Amid hievon bedeutet ; und

(ii) R⁵ für Alkyl steht ;

(b) und anschließendes Zusetzen von Wasser zu dem genannten Gemisch.

5 2. Verfahren nach Anspruch 1, worin

(a) jeder Rest R¹ für Wasserstoff, Methyl, Ethyl, Hydroxy, unsubstituiertes Amino steht, oder zwei Reste R¹ am gleichen Kohlenstoffatom für =O oder =NR⁹ stehen, oder zwei Reste R¹ an benachbarten Kohlenstoffatomen durch eine zusätzliche Bindung zwischen den Kohlenstoffatomen ersetzt sind ; und

(b) R³ für Wasserstoff steht ;

10 (c) jeder Rest R⁵ Niederalkyl bedeutet ;

(d) R unsubstituiertes Niederalkyl oder Niederalkyl bedeutet, das durch Fluor, unsubstituiertes oder substituiertes Phenyl, unsubstituiertes oder substituiertes Pyridinyl, unsubstituiertes Amino, mit einer Niederalkylgruppe substituiertes Amino, Hydroxy oder Carboxy oder Kombination hievon substituiert ist ; vorzugsweise unsubstituiertes, geradkettiges, gesättigtes Niederalkyl darstellt ; und

15 (e) B für Wasserstoff, Methyl, Ethyl, —COOH oder die pharmazeutisch annehmbaren Salze hievon, —COOCH₃ oder —CONH₂ ; vorzugsweise für Wasserstoff steht.

3. Verfahren nach Anspruch 2, worin

(a) m eine ganze Zahl von 1 bis 5 bedeutet ; und

20 (b) Y für unsubstituiertes Amino oder das von einer Carbonsäure einer Niederalkylgruppe abgeleitete Amid hievon, mit einer Niederalkylgruppe substituiertes Amino oder das von einer Carbonsäure einer Niederalkylgruppe abgeleitete Amid hievon, Hydroxy, —COOH oder die pharmazeutisch annehmbaren Salze hievon oder den von einem Alkohol einer Niederalkylgruppe abgeleiteten Ester hievon oder das unsubstituierte Amid hievon oder das mit einer oder mit zwei Niederalkylgruppen substituierte Amid hievon ; vorzugsweise für mit einer Methylgruppe substituiertes Amino oder für unsubstituiertes Amino steht.

25 4. Verfahren nach Anspruch 2, worin Y für Wasserstoff, Hydroxy, mit einer Methylgruppe substituiertes Amino oder unsubstituiertes Amino steht.

5. Verfahren nach Anspruch 4, worin

(a) m eine ganze Zahl von 0 bis 2 ; vorzugsweise 0 bedeutet ;

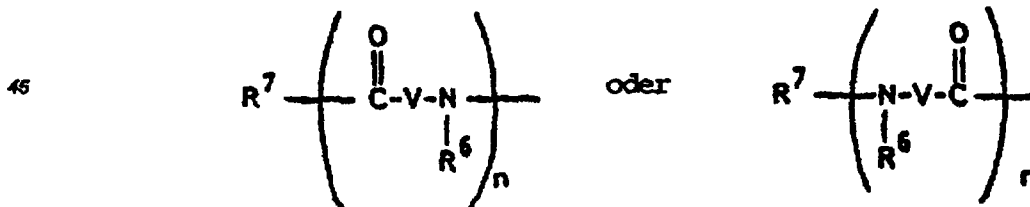
30 (b) Y unsubstituiertes oder substituiertes Cycloalkyl, einen Heterocyclus, Aryl oder Heteroaryl darstellt ; vorzugsweise Phenyl, Pyrrolidinyl, Pyrrolyl, Pyridinyl, Piperidinyl, Piperidinylden, Pyridazinyl, Pyrimidinyl, Pyrazinyl oder Morpholinyl ist, worin der Rest Y unsubstituiert oder durch Methyl, Ethyl, Fluor, Trifluormethyl, Hydroxy, (N-Methyl)amino, Methylether, —COOH oder die pharmazeutisch annehmbaren Salze hievon, —COOCH₃ oder CONH₂ einfach substituiert ist.

35 6. Verfahren nach Anspruch 5, worin Y in der 2-Stellung verknüpftes Pyridinyl ist und unsubstituiert oder mit einem Methyl- oder Aminorest an der 3-, 4- oder 5-Stellung einfach substituiert ist.

7. Verfahren nach Anspruch 6, worin in einer anschließenden Reaktionsstufe das Pyridinyl zu Piperidinylden hydriert wird.

8. Verfahren nach Anspruch 5, worin Y ein in der 2-Stellung verknüpftes Piperidinyl ist, das unsubstituiert oder einfach durch Methyl substituiert ist.

40 9. Verfahren nach Anspruch 2, worin Y für Peptidyl mit der folgenden chemischen Struktur :



50 steht, worin

(a) n eine ganze Zahl von 1 bis 100 ; vorzugsweise von 1 bis 6 bedeutet ;

(b) jeder Rest R⁶ und R⁷ unabhängig voneinander Wasserstoff oder Niederalkyl ; vorzugsweise Wasserstoff bedeutet ; und

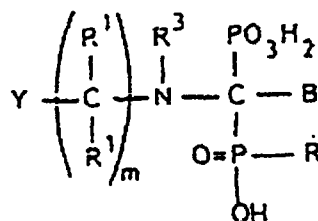
55 (c) jeder Rest V unabhängig voneinander unsubstituiertes oder substituiertes Niederalkyl darstellt, oder unabhängig voneinander jeder Rest R⁶ und V zusammen mit dem eingeschlossenen Stickstoffatom, an das die gebunden sind, einen 5- oder 6-gliedrigen Ring ausbilden, der unsubstituiert oder substituiert ist ; wobei vorzugsweise jeder Rest V oder Ringe, worin die Reste V enthalten sind, in natürlich vorkommenden



Aminosäureresten vorkommende Reste sind.

Revendications

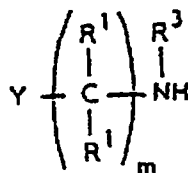
1. Procédé pour préparer des phosphonoalkylphosphinates d'aminométhylène, ayant la structure chimique :



ledit procédé comprenant :

(a) le chauffage d'un mélange sensiblement anhydre comprenant :

(1) une amine ayant la structure chimique :



dans laquelle

(I) m est un nombre entier valant de 0 à 10 ;

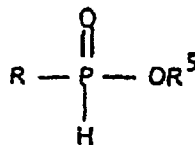
(II) chaque R¹ représente, indépendamment, un atome d'hydrogène ou de fluor, un groupe alkyle inférieur, amino non substitué ou son amide provenant d'un acide carboxylique à groupe alkyle inférieur, amino substitué par un groupe alkyle inférieur ou son amide provenant d'un acide carboxylique à groupe alkyle inférieur, un groupe hydroxy, —CO₂H ou ses sels pharmaceutiquement acceptables ou ses esters provenant d'un alcool à groupe alkyle inférieur ou son amide non substitué ou son amide substitué par un ou deux groupes alkyles, un groupe éther comportant un groupe alkyle inférieur, —PO₃H₂ ou ses sels pharmaceutiquement acceptables, ou un groupe nitro, ou bien deux R¹ fixés sur le même atome de carbone représentent =O ou =NR⁹ (où R⁹ représente un groupe alkyle inférieur non substitué ou peut représenter un atome d'hydrogène lorsqu'il existe un autre atome d'azote fixé sur le même atome de carbone que le fragment =NR⁹), ou bien deux R¹ fixés sur des atomes de carbone adjacents peuvent être remplacés par une liaison supplémentaire entre les atomes de carbone ; sauf que les R¹ ne sont pas tels qu'il y ait un atome d'halogène et un atome d'oxygène ou de soufre ou d'azote fixé par liaison simple au même atome de carbone ou bien qu'il y ait deux atomes d'oxygène ou de soufre ou d'azote fixés par une liaison simple sur le même atome de carbone ;

(III) R³ représente un atome d'hydrogène ou un groupe alkyle inférieur ; et

(IV) Y représente un atome d'hydrogène, un groupe fluoro ; cyano ; hétérocyclique ; aryle ; hétéro-aryle, amino non substitué ou son amide provenant d'un acide carboxylique à groupe alkyle, hétérocyclique, aryle ou hétéro-aryle ; amino substitué par un groupe alkyle, hétérocyclique, aryle ou hétéro-aryle, ou son amide provenant d'un acide carboxylique à groupe alkyle ; un groupe hydroxy ; éther ayant un groupe alkyle, hétérocyclique, aryle ou hétéro-aryle ; un groupe thiol ; thioéther comportant un groupe alkyle, hétérocyclique, aryle ou hétéro-aryle ; —SO₃H, ses sels pharmaceutiquement acceptables, ses esters provenant d'un alcool à groupe alkyle, son amide non substitué, ou son amide substitué par un ou deux groupes alkyles ; —CO₂H, ses sels pharmaceutiquement acceptables, ses esters provenant d'un alcool ayant un groupe alkyle, son amide non substitué ou son amide substitué par un ou deux groupes alkyles ; PO₃H₂, ses sels pharmaceutiquement acceptables, ses esters provenant d'un alcool comportant un groupe alkyle, son amide non substitué ou son amide substitué par un ou deux groupes alkyles ; —(R⁸)PO₂H (où R⁸ représente un atome d'hydrogène ou un groupe alkyle inférieur non subs-



titué), ses sels pharmaceutiquement acceptables, ses esters provenant d'un alcool ayant un groupe alkyle, son amide non substitué ou son amide substitué par un ou deux groupes alkyles ; un groupe carbamate, non substitué ou substitué par un ou deux groupes alkyles ; ou un groupe peptidyle ;
 (2) un ester d'un phosphite d'alkyle ayant la structure chimique :

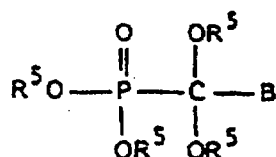


dans laquelle

(I) R représente un atome d'hydrogène ou un groupe alkyle ; et

(II) R⁵ représente un groupe alkyle ;

(3) un ester d'un acétal de phosphonate ayant la structure chimique :



dans laquelle

(I) B représente un atome d'hydrogène ; un groupe fluoro ; un groupe alkyle inférieur non substitué ou substitué ; un groupe cycloalkyle non substitué ou substitué, comportant de 3 à 7 atomes de carbone dans le noyau ; un hétérocycle non substitué ou substitué, comportant 3 à 7 atomes dans le noyau ; un groupe phényle non substitué ou substitué ; et —CO₂H, ses sels pharmaceutiquement acceptables, ses esters provenant d'un alcool comportant un groupe alkyle inférieur, son amide non substitué ou son amide substitué par un ou deux groupes alkyles inférieurs ; et

(II) R⁵ représente un groupe alkyle ;

(b) puis l'addition d'eau audit mélange.

2. Procédé selon la revendication 1, dans lequel

(a) chaque R¹ représente un atome d'hydrogène, un groupe méthyle, éthyle, hydroxy, amino non substitué, ou bien deux R¹ fixés sur le même atome de carbone représentent =O ou =NR³, ou bien deux R¹ fixés sur des atomes de carbone adjacents sont remplacés par une liaison supplémentaire entre les atomes de carbone ; et

(b) R³ représente un atome d'hydrogène ;

(c) chaque R⁵ représente un groupe alkyle inférieur ;

(d) R représente un groupe alkyle inférieur non substitué ou un groupe alkyle inférieur substitué par un atome de fluor, par un groupe phényle non substitué ou substitué, pyridinyle non substitué ou substitué, amino non substitué, amino substitué par un groupe alkyle inférieur, hydroxy ou carboxy, ou leurs combinaisons, de préférence un groupe alkyle inférieur saturé, linéaire, non substitué ; et

(e) B représente un atome d'hydrogène, un groupe méthyle, éthyle, —CO₂H ou ses sels pharmaceutiquement acceptables, —CO₂CH₃ ou —CONH₂ ; et de préférence B représente un atome d'hydrogène.

3. Procédé selon la revendication 2, dans lequel

(a) m est un nombre entier valant 1 à 5 ; et

(b) Y représente un groupe amino non substitué ou son amide dérivant d'un acide carboxylique à groupe alkyle inférieur, un groupe amino substitué par un groupe alkyle inférieur ou son amide dérivant d'un acide carboxylique à groupe alkyle inférieur, un groupe hydroxy, —CO₂H ou ses sels pharmaceutiquement acceptables ou ses esters provenant d'un alcool à groupe alkyle inférieur ou son amide non substitué ou son amide substitué par un ou deux groupes alkyles inférieurs ; de préférence un groupe amino substitué par un groupe méthyle, ou amino non substitué.

4. Procédé selon la revendication 2, dans lequel Y représente un atome d'hydrogène, un groupe hydroxy, amino substitué par un groupe méthyle, ou amino non substitué.

5. Procédé selon la revendication 4, dans lequel

(a) m est un nombre entier valant 0 à 2 et de préférence m est nul ;

(b) Y représente un groupe cycloalkyle, hétérocyclique, aryle ou hétéro-aryle, non substitués ou substitués ; de préférence un groupe phényle, pyrrolidinyle, pyrrolyle, pyridinyle, pipéridinyle, pipéridinylidène, pyrida-



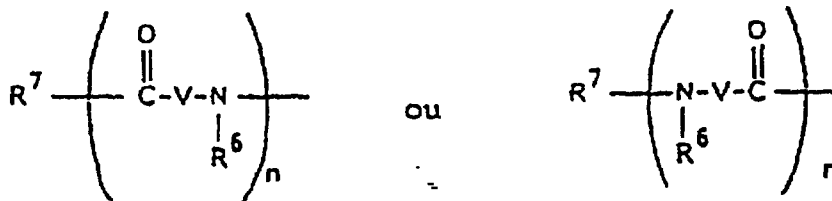
zinye, pyrimidinyle, pyrazinyle ou morpholinyle, dans lesquels Y n'est pas substitué ou est monosubstitué par un groupe méthyle, éthyle, fluoro, trifluorométhyle, hydroxy, (N-méthyl)amino, éther méthylique, $-\text{CO}_2\text{H}$ ou ses sels pharmaceutiquement acceptables, $-\text{CO}_2\text{CH}_3$ ou $-\text{CONH}_2$.

5 6. Procédé selon la revendication 5, dans lequel Y représente un groupe pyridinyle fixé en position 2, et qui n'est pas substitué ou est monosubstitué par un groupe méthyle ou amino fixé en position 3, 4 ou 5.

7. Procédé selon la revendication 6, dans lequel, dans une étape de réaction subséquente, on hydrogène ledit groupe pyridinyle en pipéridinylidène.

8. Procédé selon la revendication 5, dans lequel Y représente un groupe pipéridinyle fixé en position 2, et qui n'est pas substitué ou est monosubstitué par un groupe méthyle.

10 9. Procédé selon la revendication 2, dans lequel Y représente un groupe peptidyle ayant la structure chimique suivante :



formules dans lesquelles

(a) n est un nombre entier valant 1 à 100, de préférence 1 à 6 ;

25 (b) chaque R^6 et R^7 représente, indépendamment, un atome d'hydrogène ou un groupe alkyle inférieur et, de préférence, un atome d'hydrogène ; et

(c) chaque V est, indépendamment, un groupe alkyle inférieur, non substitué ou substitué, ou bien, indépendamment, chaque R^6 et V forment, avec l'atome d'azote inclus auquel ils sont fixés, un noyau pentagonal ou hexagonal qui n'est pas substitué ou qui est substitué, ; de préférence chaque V ou les noyaux auxquels ils sont incorporés est ou sont des fragments qu'on trouve dans des fragments d'acides aminés naturels.

