PATENT SPECIFICATION (11) 1 580 899

1 580 899

(21) Application No's. 31339/76 (22) Filed 27 Jul. 1976
42222/76 11 Oct. 1976
25700/77 20 Jun. 1977

(19)

(23) Complete Specification Filed 26 Jul. 1977

(44) Complete Specification Published 10 Dec. 1980

(51) INT. CL. [3] C07F 9/38
A61K 31/66

(52) Index at Acceptance
C2P 1L1 2E11A 2E11B 2E12B 2E13 2E14
2E18B 2E18C 2E19A 2E19B 2E19C
2E19D 2E19E 2E19F 2E26A 2E26B
2E26E 2L11A 2L11B 2L12B 2L14
2L18B 2L19C 2L19F 2L19G 2L26B
2L26E 2L26F 2L30B 2L30C 3B11A
3B11B 3B13 3B14A 3B16 3B18B 3B19C
3B19D 3B21 5A 5B 7 9 A1 A
C2C 1382 20Y 215 220 227 22Y 247
256 25Y 280 30Y 313 314 31Y 321
32Y 339 342 345 346 34Y 351 355
364 366 36Y 385 510 51X 534 574
620 625 62X 652 662 670 699 718
AA KS LY MV SG

(54) HYDROXYAMINOHYDROCARBONPHOSPHONIC ACID DERIVATIVES AND PRODUCTION AND USE THEREOF

(71) We, FUJISAWA PHARMACEUTICAL CO., LTD., a Corporation of Japan, of No. 3,4-chome, Doshomachi, Higashi-ku, Osaka-shi, Japan do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:-

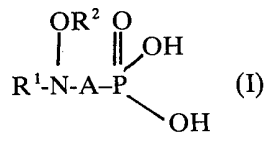
This invention relates to new hydroxyaminohydrocarbonphosphonic acid derivatives. More particularly, it relates to new hydroxyaminohydrocarbonphosphonic acid derivatives and, the esters and salts thereof, which have antimicrobial activities against various pathogenic microorganisms, to processes for preparation thereof, and to a pharmaceutical composition comprising the same, and to a method of use of the same for the therapeutical treatment of infectious diseases in non-human animals.

Accordingly, it is one object of this invention to provide new hydroxyaminohydrocarbonphosphonic acid derivatives, and the esters and salts thereof which are useful as antibiotics as well as intermediates for preparing antimicrobial substances.

Another object of this invention is to provide methods for preparation of hydroxyaminohydrocarbonphosphonic acid derivatives and the esters and salts thereof, comprising synthetic processes for preparation of the same and fermentation processes for production of some of those compounds by culturing strains belonging to the genus Streptomyces in a nutrient medium.

A further object of this invention is to provide pharmaceutical compositions comprising one or more active ingredient(s) selected from the group of hydroxyaminohydrocarbonphosphonic acid derivatives, and the esters and salts thereof.

Hydroxyaminohydrocarbonphosphonic acid derivatives of this invention are represented by the following general formula:



(I)

wherein R^1 is hydrogen or acyl,
R^2 is hydrogen, lower alkyl, ar(lower)alkyl wherein the aryl moiety may be substituted or acyl, and
A is lower alkylene, lower alkenylene or hydroxy(lower)alkylene,

or the esters at the phosphono group thereof or the pharmaceutically acceptable salts thereof.

Particulars of the above definitions and suitable examples thereof will be explained as follows:

As to the term "lower" used in the specification and claims, it is to be understood that "lower" is intended to mean 1 to 6 carbon atom(s), unless otherwise provided.

(1) Re: acyl for R^1 and R^2

Generally, "acyl" may be an acyl group derived from an acid such as an organic carboxylic acid, carbonic acid, carbamic acid, the thio acid or imidic acid corresponding to each of the preceding acids, or an organic sulfonic acid, each of which includes an aliphatic, an aromatic and/or a heterocyclic groups in its molecule; carbamoyl; or carbamimidoyl.

Suitable examples of said acyl are illustrated below. Aliphatic acyl means an acyl group derived from an aliphatic acid and includes:-

lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl and pivaloyl);

lower alkenoyl having 3 - 6 carbon atoms (e.g. acryloyl, methacryloyl and crotonoyl);

lower alkylthio(lower)alkanoyl (e.g. methylthioacetyl and ethylthioacetyl);

lower alkanesulfonyl (e.g. mesyl, ethanesulfonyl and propanesulfonyl);

lower alkoxycarbonyl having 2 - 6 carbon atoms (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl and isobutoxycarbonyl);

lower alkylcarbamoyl having 2 - 6 carbon atoms (e.g. methylcarbamoyl);

(N-lower alkyl)thiocarbamoyl having 2 - 6 carbon atoms [e.g. (N-methyl)thiocarbamoyl];

lower alkylcarbamimidoyl (e.g. methylcarbamimidoyl); oxalo;

lower alkoxalyl having 2 - 6 carbon atoms (e.g. methoxalyl, ethoxalyl, propoxalyl).

In the above exemplified aliphatic acyl, the aliphatic hydrocarbon moiety, particularly alkyl group and alkane moiety may have optionally one or more suitable substituent(s) such as amino, halogen (e.g. fluorine, chlorine and bromine), hydroxy, hydroxyimino, carboxy, alkoxy (e.g. methoxy, ethoxy and propoxy), alkoxycarbonyl, acylamino (e.g. benzyloxycarbonylamino), acyloxy (e.g. acetoxy and benzoyloxy), and preferred aliphatic acyl having such substituents may be exemplified by alkanoyl substituted by amino, carboxy, amino and carboxy, halogen or acylamino.

Aromatic acyl means an acyl group derived from an acid having substituted or unsubstituted aryl group, in which the aryl group may include phenyl, tolyl, xylyl or naphthyl, and suitable examples thereof are illustrated as follows.

aroyl (e.g. benzoyl, toluoyl, xyloyl and naphthoyl, phthaloyl);

ar(lower)alkanoyl (e.g. phenylacetyl);

ar(lower)alkenoyl (e.g. cinnamoyl);

aryloxy(lower)alkanoyl (e.g. phenoxyacetyl);

arylthio(lower)alkanoyl (e.g. phenylthioacetyl);

arylamino(lower alkanoyl (e.g. N-phenylglycyl);

arenesulfonyl (e.g. benzenesulfonyl, tosyl and naphthalenesulfonyl);

aryloxycarbonyl (e.g. phenoxycarbonyl and naphthyloxycarbonyl);

ar(lower)alkoxycarbonyl (e.g. benzoyloxycarbonyl);

arylcarbamoyl (e.g. phenylcarbamoyl, naphthylcarbamoyl);

arylglyoxyloyl (e.g. phenylglyoxyloyl)

In the above exemplified aromatic acyl, the aromatic hydrocarbon moiety (particularly aryl moiety) and/or aliphatic hydrocarbon moiety (particularly alkane moiety) may have optionally one or more suitable substituent(s), such as the same as those exemplified as the suitable substituent for alkyl group and alkane moiety as mentioned above. Particularly, and preferred aromatic acyl having such substituents may be exemplified by aroyl substituted by halogen and hydroxy, or halogen and acyloxy, and ar(lower)alkanoyl substituted by hydroxy, hydroxyimino or dihaloalkanoyloxyimino.

arylthiocarbamoyl (e.g. phenylthiocarbamoyl);

arylcarbamimidoyl (e.g. phenylcarbamimidoyl).

Heterocyclic acyl means an acyl group derived from an acid having heterocyclic group and includes:-

heterocyclic carbonyl, in which the heterocycle moiety is 5 to 6 membered heterocycle containing at least one hetero atom selected from nitrogen, oxygen and sulfur (e.g. thenoyl, furoyl, pyrrolecarbonyl or nicotinoyl);

heterocycle(lower) alkanoyl, in which the heterocycle moiety is 5 to 6 membered heterocycle containing at least one hetero atom selected from nitrogen, oxygen and sulfur (e.g. thienylacetyl, furylacetyl, imidazolylpropionyl, tetrazolylacetyl and 2-(2-amino-4-thiazolyl) -2-methoxyiminoacetyl).

In the above exemplified heterocyclic acyl, heterocycle moiety and/or the aliphatic hydrocarbon moiety may have optionally one or more suitable substituent(s) such as the same as those exemplified as the suitable substituent for alkyl group and alkane moiety as mentioned

above.

(2) Re: lower alkyl for R^2

"Lower alkyl" may include a straight or branched alkyl group containing up to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl and hexyl.

(3) Re: ar(lower, alkyl for R^2

"Ar(lower)alkyl" may include mono-, di- or triphenyl(lower)alkyl such as benzyl, phenethyl, benzhydryl and trityl, of which arene moiety may have optionally one or more suitable substituent(s) such as alkoxy (e.g. methoxy and ethoxy), halogen (e.g. fluorine, chlorine and bromine) and nitro.

(4) Re: lower alkylene for A

"Lower alkylene" may include a straight or branched (lower) alkylene group containing up to 6 carbon atoms, which can also be represented by the formula:- (C_nH_{2n})- wherein n is an integer of 1 to 6, such as methylene, ethylene, trimethylene, methylethylene, tetramethylene, 1-methyltrimethylene, 2-ethylethylene, pentamethylene, 2-methyltetramethylene, isopropylethylene or hexamethylene, and particularly the preferred may be alkylene having up to 4 carbon atoms and the most preferred may be one having 3 carbon atoms (e.g. trimethylene.)

(5) Re: lower alkenylene for A

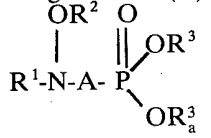
"Lower alkenylene" may include a straight or branched (lower)alkenylene group containing up to 6 carbon atoms, which can also be represented by the formula:- (C_nH_{2n-2}) wherein n is an integer of 2 to 6, such as vinylene, propenylene (e.g. 1-propenylene, 2-propenylene), 1-methylpropenylene, 2-methylpropenylene, butenylene, 2-ethylpropenylene, pentenylene and hexenylene, and particularly the preferred may be alkenylene having up to 5 carbon atoms and most preferred may be one having 3 carbon atoms [e.g. 1-propenylene].

(6) Re: hydroxy(lower)alkylene for A

"Hydroxy(lower) alkylene" may include a straight or branched (lower)alkylene group containing up to 6 carbon atoms, whose optional carbon is substituted with one hydroxy group and said hydroxyalkylene can also be represented by the formula:- (C_nH_{2n-1}) (OH)- wherein n is an integer of 1 to 6. Suitable examples of said hydroxyalkyelene may include hydroxymethylene, hydroxyethylene (e.g. 1-hydroxyethylene and 2-hydroxyethylene), hydroxytrimethylene (e.g. 1-hydroxytrimethylene, 2-hydroxytrimethylene and 3-hydroxytrimethylene), hydroxytetramethylene (e.g. 2-hydroxytetramethylene), 2-hydroxy-2- methyltrimethylene, hydroxypentamethylene (e.g. 2-hydroxypentamethylene), hydroxyhexamethylene (e.g. 2-hydroxyhexamethylene). Particularly, as to such hydroxyalkylene, the preferred may be hydroxy(lower)alkylene containing up to 4 carbon atoms and the most preferred may be one containing 3 carbon atoms (e.g. 2-hydroxytrimethylene).

Suitable examples of the esters at the phosphono group of the object compound (I) may include conventional mono- and di-ester, and preferred examples of such ester may include lower alkyl ester (e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester and hexyl ester); an ar(lower)alkyl ester (e.g. benzyl ester, phenethyl ester, benzhydryl ester and trityl ester), an aryl ester (e.g. phenyl ester, tolyl ester and naphthyl ester), aroyl(lower)alkyl ester (e.g. phenacyl ester); and an ester of silyl compound [e.g. trialkylhalosilane, dialkyldihalosilane, alkyltrihalosilane, dialkylarylhalosilane, trialkoxyhalosilane, dialkylaralkylhalosilane, dialkoxydihalosilane and trialkoxyhalosilane).

In the above ester, the alkane and/or arene moiety may optionally bear at least one suitable substituent such as halogen, alkoxy, hydroxy or nitro. In this respect, it is to be noted that the ester at the phosphono group of the object compound (I) can be represented by the following formula (I') for convenience' sake.



(I')

wherein R^3 is hydrogen or a residue of the ester, and

R^3_a is a residue of the ester

Suitable examples of the salts of the object compound (I) and the esters may include an acid addition salt with an organic or inorganic acid (e.g. hydrochloride, hydrobromide, sulfate, nitrate, methanesulfonate, p-toluenesulfonate, acetate, lactate, maleate, fumalate, oxalate, tartarate, benzoate), a salt with an organic or inorganic base (e.g. sodium salt, potassium salt, calcium salt, alminum salt, ammonium salt, magnesium salt, triethylamine salt, ethanolamine salt, dicyclohexylamine, salt, ethylenediamine salt, N,N'-dibenzyl ethylenediamine salt) and

a salt with an amino acid (e.g. arginine salt, aspartic acid salt, glutamic acid salt).

It is to be understood that the object compound (I) may include geometric isomers (i.e. cis-and trans-isomers, and syn- and anti-isomers), and optical isomers (d- and ℓ-isomers, or their mixture) according to the chemical structure thereof.

According to this invention, the object compound (I), the ester at the phosphono group thereof and salt thereof can be prepared by various processes, details of which will be explained as follows.

Production of hydroxyaminohydrocarbonphosphonic acid derivates

Production by Synthetic processes

The compound (I), and the esters at the phosphono group thereof and the salts thereof can be produced by various synthetic processes, which can be classified as follows.

I. Processes for construction of skeletal structure
   (1) Formation of C-P bond
   (2) Formation of C-N bond
   (3) Formation of hydroxyamino function

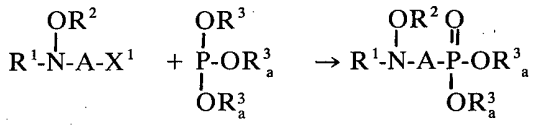
II. Process for transformation of functional groups
   (1) Hydrolysis (I)
   (2) Hydrolysis (II)
   (3) N-Acylation
   (4) O-Acylation
   (5) Esterification
   (6) Formation of C-S bond

Each of these processes will be illustrated hereinafter.

i. Processes for construction of skeletal structure

(I) Formation of C-P bond

The reaction of this process can be illustrated by the following scheme:



(II) (III) (Ia)

wherein R^1, R^2 and A are each as defined above;
R^3 is hydrogen or a residue of the ester;
R^3_a is a residue of the ester, and
X^1 is an acid residue.

Preferred examples of the acid residue for X^1 of the starting compound (II) may include halogen (e.g. chlorine, bromine, iodine), alkanesulfonyloxy (e.g. mesyloxy, ethanesulfonyloxy), arenesulfonyloxy (e.g. benzenesulfonyloxy, tosyloxy).

A residue of the ester for R^3 and R^3_a of the starting compound (III), as illustrated hereinabove in the explanation of the object compound (I), may include lower alkyl, ar(lower)alkyl and aryl, and preferred examples are the same as those illustrated hereinabove. Among such residue of the ester, lower alkyl is preferable.

Further, it is to be understood that preferred examples of the groups as defined for R^1, R^2 and A are the same as those illustrated hereinabove in the explanation of the object compound (I), respectively.

In this process, the object compound (Ia) can be prepared by reacting the compound (II) or the acid addition salt thereof with the compound (III). Suitable examples acid addition salt of the compound (II) are the same as those illustrated hereinabove in the explanation of the salt of the compound. (I).

The starting compound (II) includes known and novel ones. The known compounds, e.g. N-(3-bromopropyl)- N-benzyloxy- p-toluenesulfonamide, are prepared by the method described in Bulletin of the Chemical Society of Japan Vol. 45, page 1462 (1972), and the other new compounds can also be prepared in the similar manner thereto. The detailed method for preparing said new compound is to be referred to Preparation of starting compounds as described hereinafter.

The reaction of this process can be conducted in the presence or absence of solvents. Preferred solvents may inlcude conventional ones such as benzene, toluene, xylene, pyridine, dimethylsulfoxide, N,N-dimethylformamide. The reaction is conducted usually at ambient temperature or with heating.

The reaction of this process can also be conducted in the presence of an organic or

inorganic base such as alkali metal (e.g. lithium, sodium, potassium), alkaline earth metal (e.g. calcium, magnesium), alkali metal hydride (e.g. sodium hydride), alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate), alkali metal alkoxide (e.g. sodium methoxide, sodium ethoxide, potassium t-butoxide), trialkylamine (e.g. triethylamine), pyridine, diazabicyclo compound (e.g. 1,5-diazabicyclo[3,4,0] nonene-5, 1-5-diazabicyclo [5,4,0] undecene-5), quaternary ammonium salt (e.g. Triton B (Registered Trade Mark)).

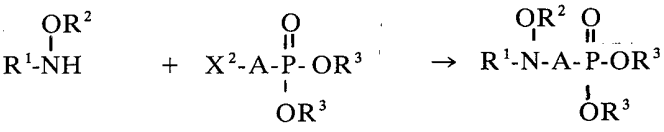
Optimum reaction conditions can be selected from the above reaction conditions according to kinds of the starting compound, solvent, and/or base to be used.

For example, in the case of using dialkyl phosphonate as a starting compound, i.e. the compound (III), wherein R^3 is hydrogen and R^3_a is a residue of ester, the reaction can preferably be conducted in the presence of a solvent and a base. On the other hand, in the case of using trialkylphosphite as a starting compound, i.e. the compound (III) wherein R^3 and R^3_a are each a residue of ester, the reaction can usually be conducted in the absence of solvent and base.

The object compound (Ia) can be isolated and purified in a conventional manner (e.g. evaporation, extraction, chromatography, salt formation, crystallization)

(2) Formation of C-N bond

The reaction of this process can be illustrated by the following scheme:



(V) (IV) (Ib)

wherein R^1, R^2, R^3 and A are each as defined above, and

X^2 is an acid residue.

Preferred examples of the acid residue for X^2 of the compound (IV) are the same as those illustrated for X^1 hereinabove. Further, it is to be understood that preferred examples of the groups as defined for R^1, R^2, R^3 and A are the same as those illustrated hereinbefore, respectively.

In this process, the object compound (Ib) or the salt thereof also be prepared by reacting the compound (IV) or the salt thereof with the compound (V) or the salt thereof. Suitable examples of the salts of the compounds (Ib), (IV) and (V) are the same as those illustrated hereinabove in the explanation of the salt of the compound (I).

The starting compound (IV) includes known and novel ones. The known compounds, e.g. diethyl 3-bromopropyl phosphonate, and 3-bromopropyl phosphonic acid, are prepared by the method described in Journal of the Americal Chemical Society Vol. 66, page 1511 (1944), and the other new compounds can also be prepared in the similar manner thereto.

The other starting compound (V) also includes known and novel ones. The known compounds, e.g. N-benzyloxy-p-toluenesulfonamide, are prepared by the method described in Bulletin of the Chemical Society of Japan Vol. 45, page 1462 (1972), and the other new compounds can be prepared in the similar manner thereto. The detailed method for preparation of the starting compounds (IV) and (V) is to be referred to Preparation of starting compounds as described hereinafter.

The reaction of this process is usually conducted in a conventional solvent such as methanol, ethanol, propanol, benzene, toluene, pyridine, dimethylsulfoxide, N,N-dimethylformamide. There is no limitation to this reaction temperature and this reaction may be preferably conducted at ambient temperature or with heating.

The reaction of this process can preferably be conducted in the presence of an organic or inorganic base such as alkali metal (e.g. sodium), alkaline earth metal (e.g. calcium), alkali metal hydride (e.g. sodium hydride), alkali metal alkoxide (e.g. sodium ethoxide), alkali metal hydroxide (e.g. sodium hydroxide), alkali metal bicarbonate (e.g. sodium bicarbonate), trialkylamine (e.g. triethylamine), diazabicyclo compound (e.g. 1,5-diazabicyclo [3,4,0] nonene-5, 1,5-diazabicyclo [5,4,0] undecene-5, etc.)

When a starting compound (IV) wherein A is hydroxyalkylene group is used in this reaction, it is preferably to conduct the reaction by protecting said hydroxy group with an easily removable group such as tetrahydropyranyl. In such a case, the object compound (Ib) may be obtained in the form of a compound (IV) having protected hydroxy group on the

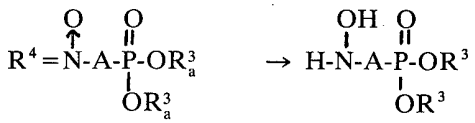
alkylene group thereof. And such a protective group can easily be hydrolyzed in a conventional manner as described in the working examples hereinafter.

Optimum reaction conditions can be selected from the above reaction conditions according to kinds of starting compound, solvent, and/or base to be used.

The object compound [Ib] of the salt thereof can be isolated and purified in a conventional manner as explained in the foregoing Process I(1) and the following Process I(3), respectively.

(3) Formation of hydroxyamino function

The reaction of this process can be illustrated by the following scheme:



(VII) (Ic)

wherein R^3, R^3_a, and A are each as defined above, and

R^4 is alkylidene.

Preferred examples of alkylidene for R^4 of the starting compound (VII) may include a lower and higher alkylidene such as methylene, ethylidene, propylidene, isoporpylidene, butylidene, isobutylidene, pentylidene, hexylidene, heptylidene, octylidene, nonylidene, decylidene.

Further, it is to be understood that preferred examples of the groups as defined for R^3_a, R^3 and A are the same as those illustrated hereinbefore.

In this process, the object compound (Ic) can be prepared by subjecting the compound (VII) to hydrolysis.

The starting compound (VII) is novel and can be prepared, for example, by reacting an alkanal - or alkanone-oxime with the compound (IV) wherein R^3 is a residue of the ester as mentioned in the foregoing Process (I)(2). The detailed method for preparation of the starting compound (VII) is to be referred to Preparation of starting compounds as described hereinafter.

The hydrolysis is conducted in a conventional manner, and preferably conducted in the presence of an acid. Preferred examples of the acid are an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid and an organic acid such as formic acid or trifluoroacetic acid.

The hydrolysis is usually carried out in any solvent which does not have an adverse influence on the reaction, e.g. water, methanol, ethanol, propanol, isopropanol, acetic acid, and preferably carried out at ambient temperature or under heating.

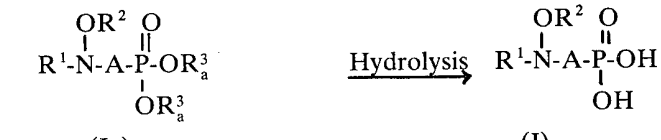
It is noted that in this process, the ester (i.e. - OR^3_a wherein R^3_a is a residue of the ester) group at the phosphono group of the compound (VIII) may be occasionally hydrolyzed to produce phosphonic acid compound (Ic), wherein R^3 is hydrogen together with the hydrolytic cleavage of the C=N bond, and this case is also included within the scope of this process.

The object compound (Ic) can be isolated and purified in a conventional manner and can also be transformed into an acid addition salt with an organic or inorganic acid, such as formate, acetate, trifluoroacetate, p-toluenesulfonate, hydrochloride, hydrobromide, sulfate, and further, in case that the object compound (Ic) is produced as a free phosphonic acid, it can also be transformed into an organic or inorganic base such as sodium salt, potassium salt, calcium salt, triethylamine salt, ethanolamine salt.

II. Process for transformation of function groups

(1) Hydrolysis (I)

The reaction of this process can be illustrated by the following scheme:



(Ia) (I)

wherein R^1, R^2, R^3_a and A are each as defined above.

It is to be understood that preferred examples of the groups as defined for R^1, R^2, R^3_a and A are the same as those illustrated hereinbefore.

In this process, the object compound (I) can be prepared by hydrolyzing compound (Ia) or the acid addition salt thereof. Suitable examples of the acid addition salt are the same as those illustrated hereinabove in the explanation of the salt of the compound (I).

The method of this hydrolysis includes conventional ones such as a hydrolysis in the presence of an organic or inorganic acid and a combination method comprising transformation of the ester excepting silyl ester of compound (Ia) into a silyl ester and subsequent hydrolysis of the residue silyl ester.

The hydrolysis can preferably be conducted in the presence of an organic or inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, trifluoroacetic acid, formic acid, which can be used in a conventional hydrolysis under acidic conditions.

The hydrolysis is usually conducted in a conventional solvent such as water, methanol, ethanol, propanol, isopropanol, acetic acid, and preferably at ambient temperature or under heating.

Further, in case that the ester of the compound (Ia)(i.e. $-OR^3_a$ wherein R^3_a is a residue of the ester) is the lower alkyl ester (i.e. OR^3_a wherein R^3_a is lower alkyl) or the ar(lower) alkyl ester (i.e. $-OR^3_a$ wherein R^3_a is ar(lower)alkyl), the object compound (I) can also be prepared by transforming said lower alkyl ester or ar(lower)alkyl ester into the silyl ester (i.e. $-OR^3_a$ wherein R^3_a is a residue of the silyl compound) by the reaction of the compound (Ia) and a silyl compound as the first step and then by subsequent hydrolysis of the resultant silyl ester as the second step.

The silyl compound to be used in the first step for the combination method may include trialkylhalosilane, dialkyldihalosilane, alkyltrihalosilane, dialkylaryl halosilane, triarylhalosilane, dialkylaralkyl halosilane, dialkoxydihalosilane, trialkoxyhalosilane.

The reaction of the compound (Ia) with the silyl compound is usually carried out in the presence of or absence of solvents under anhydrous condition. Preferred solvents may include tetrahydrofuran, dioxane, benzene, pyridine, chloroform, dichloromethane, N,N-dimethylformamide, dimethylsulfoxide.

There is no limitation to the reaction temperature for the reaction of compound (Ia) with a silyl compound and this reaction is preferably conducted either with cooling or warming.

The silyl compound is preferably used in an amount of 2 or more molar equivalents to 1 mole of the compound (Ia).

The subsequent hydrolysis can be conducted in a similar manner to one as illustrated above for the direct hydrolysis method of this process and is preferably conducted by treating said reaction mixture, without any isolation of the resultant product, directly with water.

In this process, the functional group of compound (Ia), i.e. acyl group(s) as defined for R^1 and/or R^2, or aralkyl group(s) as defined for R^2, may occasionally be removed off to transform into hydrogen together with the hydrolysis of the object phosphonic acid ester linkage, and these cases are also included within the scope of this process.

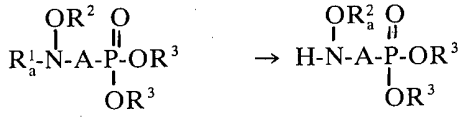
When, in this reaction, there is used a starting compound (Ia) wherein A is hydroxyalkylene group, in which the hydroxy group is protected with an easily removable protective group such as pyranyl, such a protective group can usually be removed off by the hydrolysis of this process to provide the object compound (I) wherein A is hydroxyalkylene group, and this case is also included within the scope of this process.

The object compound (I) can be isolated and purified in a conventional manner in the free form or in the form of salt with an organic or inorganic acid, such as p-toluenesulfonate, hydrochloride, hydrobromide, sulfonate, or of salt with an organic or inorganic base, such as sodium salt, potassium salt, calcium salt, triethylamine salt.

Further, a salt of the compound (I) can also be transformed, on the occasion of demand, into another salt of the same and reversely converted in the free form of the same in a conventional manner.

(2) Hydrolysis (II)

The reaction of this process can be illustrated by the following scheme:



(Id) (Ie)

wherein R^2, R^3 and A are each as defined above, R_a^1 is acyl, and R_a^2 is hydrogen or alkyl.

Preferred examples of the acyl for R_a^1 are the same as those hereinabove illustrated for the acyl in R^1.

It is to be understood that preferred examples of the groups as defined for R^2, R^3 and A of the compound (Id) are the same as those illustrated hereinbefore. Suitable examples of the salt of the compound (Id) are the same as those illustrated hereinabove for the salt of the compound (I).

In this process, the object compound (Ie) can be prepared by hydrolyzing the compound (Id).

The hydrolysis is usually conducted in a conventional solvent such as water, methanol, ethanol, propanol, isopropanol, acetic acid and preferably at ambient temperature or with heating.

The hydrolysis can preferably be conducted in the presence of an organic or inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, trifluoroacetic acid, formic acid, and an organic or inorganic base such as alkali metal hydroxide (e.g. lithium hydroxide, sodium hydroxide, potassium hydroxide), alkali metal alkoxide (e.g. lithium methoxide, sodium ethoxide, potassium t-butoxide), a quaternary ammonium salt (e.g. tetramethylammonium hydroxide, tetraethylammonium hydroxide, dimethyldi benzylammonium hydroxide.

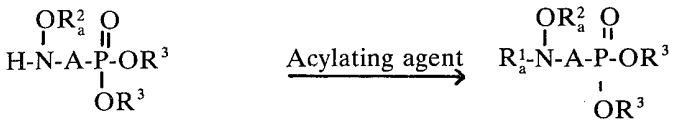
In this process, one or two of the ester at the phosphono group (i.e. $-OR^3$ wherein R^3 is a residue of the ester of compound (Id) may occasionally be subjected to hydrolysis to be transformed into the hydroxy group (i.e. $-OR^3$ wherein R^3 is hydrogen), and this case is also included within the scope of this process.

The object compound (Ie) can be isolated and purified in a conventional manner in the free form or in the form of salt with an organic or inorganic acid, such as p-toluenesulfonate, hydrochloride, hydrobromide, sulfate, or of salt with an organic or inorganic base, such as sodium salt, potassium salt, calcium salt and triethylamine salt.

Further, a salt of the compound (Ie) can also be transformed, on the occasion of demand, into another salt of the same and reversely converted into the free form of the same in a conventional manner.

(3) N-Acylation

The reaction of this process can be illustrated by the following scheme:



(Ie) (If)

wherein R_a^1, R_a^2 and R^3 and A are each as defined above.

In this process, the object compound (If) or the salt thereof can be prepared by reacting the starting compound (Ie) or the salt thereof with an acylating agent. Suitable examples of the salt of the compounds (If) and (Ie) are the same as those hereinabove illustrated for the salts of the compound (I).

The starting compound (Ie) can preferably be prepared by the foregoing process II (2).

It is to be understood that preferred examples of the groups as defined for R_a^2, R^3 and A of the compound (Ie) are the same as those illustrated hereinbefore.

The acylating agent to be used in this reaction includes an organic acid (R_a^1- OH wherein R_a^1 is acyl group) such as monobasic or dibasic organic carboxylic acid, an organic carbonic acid or an organic carbamic acid and the corresponding thio acid or imidic acid; and an organic sulfonic acid, more particularly, aliphatic, aromatic or heterocyclic carboxylic acid, and the corresponding carbonic, carbamic, thiocarboxylic, thiocarbonic, thiocarbamic, carboximidic, carbamimidic acid, and sulfonic acid; their reactive derivatives; and also includes an isocyanate (e.g. potassium-, alkyl- or aryl- isocyanate), isothiocyanate (e.g. alkyl isothiocyanate) and an isothiourea (e.g. ethyl isothiourea).

And suitable examples of these organic acids are to be referred to the corresponding organic acids to those comprising the acyl groups as exemplified hereinabove in details in the descriptions of suitable examples of acyl groups for R^1 of the compound (I).

Said organic acid as an acylating agent can be used in the form of an activated organic acid, i.e. as a reactive derivative of the acid. As such reactive derivatives of said organic acids, there may be exemplified an acid halide, an acid azide, an acid anhydride, an activated amide, an activated ester, and additionally isocyanate and isothiocyanate can preferably be used as

reactive derivative of carbamic and thiocarbamic acids, respectively.

Preferred examples of such reactive derivatives are illustrated by:

an acid halide (e.g. acid chloride, acid bromide,);

an acid azide;

an acid anhydride including a mixed acid anhydride with an acid such as dialkylphosphoric acid, phenylphosphoric acid; diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, mono-alkylcarbonic acid, aliphatic carboxylic acid (e.g., acetic acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid or trichloroacetic acid), aromatic carboxylic acid (e.g., benzoic acid), and symmetrical acid anhydride;

an activated amide with pyrazole, imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; and

an activated ester such as methyl thioester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, or ester with N, N-dimethylhydroxylamine, 1-hydroxy-2- (1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide or 1-hydroxy-6- chlorobenzotriazole.

The above reactive derivatives are selected according to the kind of the acid to be used.

In the reaction, when free acid is used as an acylating agent, the acylation reaction may preferably be conducted in the presence of condensing agent such as carbodiimidic compound (e.g. N, N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinoethylcarbodiimide, N-cyclohexyl-N'-(4-diethylaminocyclohexyl) carbodiimide, N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl) carbodiimide), N,N'-carbonyldi(2-methylimidazole), pentamethyleneketene-N-cyclohexylimine, diphenylketene-N-cyclohexylimine, alkoxyacetylene, 1-alkoxy-1-chloroethylene, trialkyl phosphite, ethyl polyphosphate, isopropyl polyphosphate, phosphorus compound (e.g. phosphorus oxychloride, phosphorus trichloride), thionyl chloride, oxalyl chloride, 2-ethyl-7- hydroxybenzisoxazolium salt, 2-ethyl-5-(m-sulfophenyl) isoxazolium hydroxide, (chloromethylene)- dimethylammonium chloride, 2,2,4,4,6,6,- hexachloro-1,3,5,2,4,6- triazatriphosphorine, 1-benzenesulphonyloxy-6- chloro- 1H-benzotriazole, p-toluenesulfonyl chloride, isopropoxy-benzenesulfoxyl chloride, or a mixed condensing agent such as triphenylphosphine and a carbon tetrahalide (e.g. carbon tetrachloride, carbon tetrabromide or a complex of N,N-dimethylformamide with phosphoryl chloride, phosgene or thionyl chloride.

The reaction is usually conducted in a solvent such as water, methanol, ethanol, propanol, acetone, ethyl ether, dioxane, acetonitrile, ethylacetate, N,N-dimethyl-formamide, dimethylsulfoxide, tetrahydrofuran, dichloromethane, chloroform or pyridine, N- methylmorpholine, N-methylpyrrolidine and other conventional solvents, and a mixture thereof.

The reaction can also be conducted preferably in the presence of an organic or inorganic base such as alkali metal (e.g. sodium), alkaline earth metal (e.g. calcium), alkali or alkaline earth metal hydride (e.g. sodium hydride, calcium hydride), alkali or alkaline earth metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide), alkali earth metal carbonate or bicarbonate (e.g. sodium carbonate, potassium carbonate, sodium bicarbonate), alkali or alkaline earth metal alkoxide (e.g. sodium ethoxide, lithium methoxide, magnesium methoxide), trialkylamine (e.g. triethylamine), pyridine, bicyclodiaza compound (e.g. 1,5-diazabicyclo[3,4,0] nonene-5, 1,5-diazabicyclo [5,4,0]undecene-5].

And, among said base, a liquid one can also be used as a solvent.

There is no limitation to this reaction temperature and this reaction may preferably be conducted with cooling or at ambient temperature.

When this acylation reaction is conducted by using the starting compound (Ie), wherein R_a^2 is hydrogen, and an excess amount of the acylating agent, there mayoccasionally produce N,O-diacylated compound, i.e., a compound of the formula corresponding to the formula (If) wherein R_a^2 is also acyl, together with the object N- monoacyl compound (If) wherein R_a^2 is hydrogen, and in such case, N,0-diacylated compound can easily be transformed into the object N-monoacyl compound by treating it with aqueous alkaline solution. These cases are also included within the scope of this process.

In case that the acyl group for R_a^1 of the object compound (If) prepared by this process is an acyl bearing functional group(s), such as alkoxycarbonyl, acylamino, acyloxy group (e.g. alkoxalyl, acylaminoalkanoyl, acyloxyalkanoyl, acyloxyaroyl), said object compounds can also be transformed by hydrolysis into the corresponding acyl compound of which acyl group for R_a^1 is an acyl bearing the corresponding functional group(s) such as carboxy, amino, hydroxy (e.g. oxalo, aminoalkanoyl, hydroxyalkanoyl, hydroxyaroyl,).

The hydrolysis is usually conducted in a conventional solvent such as water, methanol, ethanol, propanol, isopropanol and preferably under rather mild conditions such as at ambient temperature or under cooling.

The hydrolysis can preferably be conducted in the presence of a base such as sodium hydroxide, potassium hydroxide, and of an acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, trifluoracetic acid, formic acid.

These cases are also included within the scope of this process.

In case that the acyl group for R_a^1 of the object compound (If) prepared by this process is an acyl having oxalyl (-COCO-) group (e.g. arylglyoxyloyl), said object compounds can also be transformed by a conventional reduction into the corresponding acyl compound of which acyl group for R_a^1 is an acyl having hydroxymethylenecarbonyl (-CH(OH)-CO-) group (e.g. arylglycoloyl).

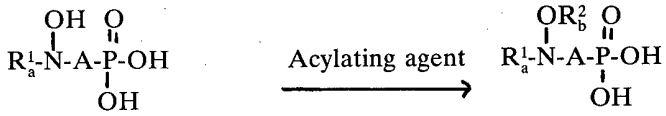
The reduction is preferably conducted with a reducing agent such as alkali metal borohydride (e.g. sodium borohydride), an alkali metal aluminum hydride (e.g. lithium aluminum hydride), a combination of alkali metal and alcohol, in a conventional solvent such as water, methanol, ethanol, ether tetrahydrofuran, benzene, at cooling to the boiling point of the solvent to be used.

These cases are also included within the scope of this process.

The reaction product (If) can be isolated and purified optionally in the form of free phosphonic acid or of salt with a base in a conventional manner as those illustrated hereinabove.

(4) O-Acylation

The reaction of this process can be illustrated by the following scheme:



(Ig) (Ih)

wherein R_a^1 and A are each as defined above, and R_b^2 is acyl.

In this process, the object compound (Ih) or the salt thereof can be prepared by reacting the compound (Ig) or the salt thereof with an acylating agent. Suitable examples of the salts of the compound (Ih) and (Ig) are the same as those illustrated hereinabove for the salt of the compound (I).

It is to be understood that preferred examples of the groups as defined for R_a^1 and A of the compound (Ig) are the same as those illustrated hereinbefore, respectively.

The acylating agent to be used in this reaction includes an organic acid (R_b^2 - OH, wherein R_b^2 is acyl group) and their reactive derivatives.

Suitable examples of the organic acid (R_b^2 - OH) and their reactive derivatives are the same as those illustrated in the explanations of the organic acid (R_a^1 - OH) and their reactive derivatives in the foregoing N-acylation process II (3).

The reaction of this acylation, and isolation and purification of the object compound (Ih) are also conducted in substantially the same manner as those illustrated in the foregoing N-Acylation process II (3).

(5) Esterification

The reaction of this process can be illustrated by the following scheme:

(Ii) (Ij)

wherein R_a^1, R^2, A, R^3 and R_a^3 are each as defined above.

In this process, the object compound (Ij) or the salt thereof can be prepared by reacting the compound (Ii) or the salt thereof or the reactive derivative at the phosphono group thereof with an esterifying agent. Suitable examples of the salts of the compounds (Ij) and (Ii) are the same as those illustrated hereinabove for the salt of the compound (I).

It is to be understood that preferred examples of the groups as defined for R_a^1, R^2, and A of the Compound (Ii) are the same as those illustrated hereinbefore.

Preferred example of reactive derivative of the compound (Ii) may include an acid halide,

an acid anhydride, an activated amide, an activated ester.

The esterifying agent to be used in this process may include an alcohol such as an lower alkanol (e.g. methanol, ethanol, propanol, isopropanol, butanol, pentanol, hexanol), an ar(lower)alkanol (e.g. benzylalcohol, phenethylalcohol, diphenylmethylalcohol), an arenol (e.g. phenol, cresol, p-chlorophenol), etc. and the reactive derivative thereof, and a silyl compound such as trialkylhalosilane, dialkyldihalosilane, alkyltrihalosilane, dialkylaryl-halosilane, triarylhalosilane, dialkylaralkylhalosilane, dialkoxydihalosilane, trialkoxy-halosilane.

As the reactive derivative of said lower alkanol, ar(lower)alkanol and arenol, there may be exemplified the corresponding halide (e.g. chloride, bromide, iodide), diazocompound (e.g. diazalkane, diazoaralkane), sulfonate (e.g. alkanesulfonate, arenesulfonate), sulfate or salt with an alkali metal or alkaline earth metal (e.g. lithium, sodium potassium, magnesium. More particularly, the preferred examples thereof may be: a halide such as an alkyl halide (e.g. methyl iodide, ethyl bromide, isopropyl bromide, butyl bromide, hexyl chloride) or an aralkyl halide (e.g. benzyl chloride, phenethyl bromide, diphenylmethyl chloride); a sulfonate such as an alkyl alkanesulfonate or alkyl arene sulfonate (e.g. methyl methanesulfonate, ethyl p-toluenesulfonate, propyl p-toluenesulfonate, hexyl p-toluenesulfonate) or an aralkyl alkanesulfonate or aralkyl arenesulfonate (e.g. benzyl p-toluenesulfonate, tolyl methanesulfonate); a sulfate such as a dialkylsulfate (e.g. dimethylsulfate, diethylsulfate).

The reaction is usually conducted in a solvent such as methanol, ethanol, propanol, isopropanol, ether, tetrahydrofuran, ethyl acetate, benzene, toluene, dimethyl-sulfoxide, N,N-dimethylformamide.

The reaction of this process can also be conducted in the presence of an organic or inorganic base. Preferred examples of such base are the same as those given in the explanation for N-Acylation process, II (3).

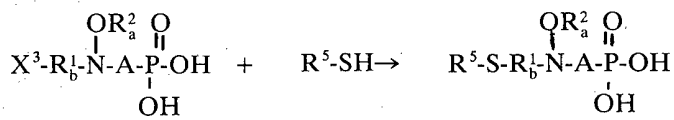
In case of the reaction of free phosphonic acid (Ii) or the salt thereof with an alcohol such as alkanol, ar(lower)alkanol or arenol as illustrated above, the reaction can preferably be conducted in the presence of a condensing agent. Preferred examples of such condensing agent may include those given in the explanation for N-Acylation process, II (3), and further, trichloroacetonitrile, p-toluenesulfonyl chloride, isopropylbenzenesulfonyl chloride, pivaloyl chloride, α-bromcyanoacetamide.

The reaction of this process is usually conducted with cooling or at ambient temperature.

The object compound (Ij) can be isolated and purified in a conventional manner as explained hereinabove.

(6) Formation of C-S bond

The reaction of this process can be illustrated by the following scheme:



(Ik) (VIII) (Iℓ)

wherein R^2_a and A are each as defined above, R^1_b, is 1- oxoalkylene, R^5 is lower alkyl and X^3 is an acid residue.

In this process, the object compound (Iℓ) or the salt thereof can be prepared by reacting the compound (Ik) or the salt thereof with the compound (VIII). Suitable examples of the salts of the compounds (Iℓ) and (Ik) are the same as illustrated hereinabove for the salt of the compound (I).

Preferred examples of the acid residue for X^3 of the compound (Ik) are the same as those illustrated for X^1 in the process I (1).

Preferred examples of 1-oxoalkylene for R^1_b of the compound (Ik) may include oxomethylene, 1-oxoethylene, 1-oxopropylene, 1-oxo-trimethylene, 1-oxo-tetramethylene, 1-oxo-2-isopropylethylene.

Preferred examples of alkyl for R^5 of the compound (VIII) may include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl which may have one or more suitable substituent(s) such as amino, carboxy.

The reaction of this process is usually conducted in a conventional solvent such as alcohol (e.g. methanol, ethanol, propanol), benzene, toluene, pridine, dimethylsulfoxide, N,N-dimethylformamide. The reaction is preferably conducted at ambient temperature or with

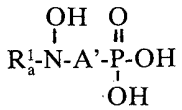
heating.

The reaction can preferably be conducted in the presence of an organic or inorganic base. Preferred examples of such a base are the same as those given in the explanation for N-Acylation process II (3).

The object compound (Iℓ) or the salt thereof can be isolated and purified in a conventional manner as explained hereinabove.

Production by Fermentation

Among the object compound of this invention, some specific compounds were found to be also produced by fermentation. And, said specific compounds can be represented by the following formula (I") and the salt thereof.



(1")

in which, $R^{1'}_a$ is acetyl, and A' is trimethylene ($-CH_2CH_2CH_2-$)

or 2-hydroxytrimethylene ($-CH_2CHCH_2-$), or $R^{1'}_a$ is formyl and A' is trimethylene ($-CH_2CH_2CH_2-$) or trans-1-propenylene)$-CH_2CH=CH-$).

Generally, the compound (I") as defined above is produced by culturing a microorganism belonging to the *genus Streptomyces* in a conventional manner. Particularly, the compound (I") is produced by culturing a microorganism belonging to the *genus Streptomyces* such as Streptomyces rubellomurinus, Streptomyces rubellomurinus subsp. indigoferus, Streptomyces lavendulae. More particularly, the compound (I") wherein $R^{1'}_a$ is acetyl and A' is trimethylene (hereinafter refered to FR-900098) is produced by fermentation of Streptomyces rubellomurinus and subspecies indigoferus thereof; the compounds (I") wherein $R^{1'}_a$ is formyl and A' is trimethylene (hereinafter referred to FR-31705) and $R^{1'}_a$ is formyl and A' is trans-1-propenylene are produced by fermentation of Streptomyces lavendulae; and the compound (I") wherein $R^{1'}_a$ is acetyl and A' is 2-hydroxytrimethylene is produced by fermentation of Streptomyces rubellomurinus subsp. indigoferus.

The fermentation of said microorganisms is conducted in a aqueous nutrient medium containing assimilable sources of carbon and nitrogen, preferably under aerobic conditions (e.g. shaking culture, submerged culture), the detail of which will be apparent in the following.

The preferred sources of carbon in the nutrient medium are carbohydrates such as glucose, fructose, glycerin and starch. Other sources which may be included are lactose, arabinose, xylose, dextrin, molasses.

The preferred sources of nitrogen are yeast extract, peptone, gluten meal, cottonseed meal, soybean meal, corn steep liquor, dried yeast, wheat germ, as well as inorganic and organic nitrogen compounds such as ammonium salts (e.g. ammonium nitrate, ammonium sulphate, ammonium phosphate), urea, amino acids.

The carbon and nitrogen sources, through advantageously employed in combination, need not be used in their pure form because less pure materials, which contain traces of growth factors and considerable quantities of mineral nutrients, are also suitable for use. When desired, there may be added to the medium mineral salts such as calcium carbonate, sodium or potassium phosphate, sodium or potassium chloride, magnesium salt, copper salt. If necessary, especially when the culture medium is foamed remarkably, a defoaming agent, such as liquid paraffin, fatty oil, plant oil, mineral oil and silicones may be added.

As in the case of the preferred methods used for the production of other antibiotics in massive amounts, submerged aerobic cultural conditions are preferred for the production of the compound (I") in massive amounted. For the production in small amounts, a shaking or surface culture in a flask or bottle is employed. Furthermore, then the growth is carried out in large tanks, it is preferable to use the vegetative form of the organism for inoculation in the production tanks in order to avoid growth lag in the process of production of the compound (I"). Accordingly, it is desirable first to produce a vegetative inoculum of the organism by inoculating a relatively small quantity of culture medium with spores or mycelia of the organism and culture them and to transfer the cultured vegetative inoculum aseptically to large tanks. The medium in which the vegetative inoculum is produced can be substantially the same as or different from medium utilized for the production of the compound (I").

Agitation and aeration of the culture mixture may be accomplished in a variety of ways. Agitation may be provided by a propeller or the similar mechanical agitation equipment, by revolving or shaking the fermenter, by various pumping equipment or by the passage of sterile air through the medium. Aeration may be effected by passing sterile air through the

fermentation mixture.

The fermentation is usually conducted at a temperature about between 20°C. and 40°C., preferably 30°C., for a period of 50 hours to 100 hours.

The compound (I") can be recovered from the culture medium by conventional means which are commonly used for the recovery of other known antibiotics.

In general, most of the compound (I") produced are found in the cultured broth, and accordingly the compound (I") can be separated from the filtrate, which is obtained by filtrating or centrifuging the broth, by a conventional method such as concentration under reduced pressure, lyophilization, extraction with solvent, pH adjustment, treatment with a resin (e.g. anion or cation exchange resin, non-ionic adsorption resin), treatment with an adsorbent (e.g. activated charcoal, silicic acid, silica gel, cellulose, almina), crystallization, recrystallization.

(I) Production of the compound (I") wherein $R^{1'}_a$ is acetyl and A' is $-CH_2-CH_2-CH_2-$, i.e. 3-(N-acetyl-N-hydroxyamino) propylphosphonic acid (hereinafter referred to as FR-900098):

The antibiotic FR-900098 can be produced by fermentation of an antibiotic FR-900098-producing strain belonging to genus Streptomyces such as Streptomyces rubellomurinus and Streptomyces rubellomurinus subsp. indigoferus in a nutrient medium.

(1) Re. The microorganisms:

The microorganisms which can be used for the production of the new antibiotic FR-900098 are strains of Streptomyces rubellomurinus newly isolated from a soil sample collected at Mt. Hira, Siga Prefecture, Japan, and of Streptomyces rubellomurinus subsp. indigoferus newly isolated from a soil sample collected at Koganei city, Tokyo, Japan.

A culture of the living organism of Streptomyces rubellomurinus has been deposited with an added to a permanent stock culture collection of the American Type Culture Collection, under ATCC No. 31215. Further, a culture of the organism has been deposited with Fermentation Research Institute, Agency of Industrial Science and Technology, Japan, under the receipt No. 3563.

A culture of the living organism of *Streptomyces rubellomurinus* subsp. *indigoferus* has been deposited with and added to a permanent stock culture collection of the American Type Culture Collection, under ATCC No. 31304. Further, a culture of the organism has been deposited with Fermentation Research Institute, Agency of Industrial Science and Technology, Japan, under the receipt number.

It is to be understood that the production of the new antibiotic is not limited to the use of the particular organism described herein, which is given only for illustrative purpose. That is, an artificial mutant as well as natural can also be used for the production the antibiotic. Such an artificial mutant is produced from the organism described herein by conventional means, such as X-rays, ultra-violet radiation N-methyl-N'-nitro-N-nitrosoguanidine, 2-amino-purine and nitrogen mustard oils.

1) Microbiological Property

1)-1 re. *Streptomyces rubellomurinus* ATCC 31215:

Streptomyces rubellomurinus ATCC 31215 has the following morphological, cultural and physiological characteristics:

1. *Morphological characteristics:-*

The morphology of the culture was microscopically observed with the mycelium grown on each of sucrose-nitrate, agar, glycerol-asparagine agar, yeast-malt extract agar and oatmeal agar, at 30°C for 10 - 14 days.

(1) Type of branching of spore-forming hyphae:
Monopodial branching

(2) Form of spore-forming hyphae:
Straight or Curved (Rectiflexibiles)

(3) Number of spore:
10 - 50 spores

(4) Surface appearance and size of spore:
Smooth, 0.4 - 0.8 x 1.1 - 1.6 micron

(5) Existence of zoospore:
Not observed

(6) Existence of sporangium:
Not observed

(7) Formation of spores:
At aerial mycelium

2. *Cultural characteristics:-*

The strain has the following cultural characteristics when grown on media as indicated below at 30°C for 10 - 14 days.

	Medium	*Aerial mycelium*	*Vegetative growth*	*Soluble pigment*
(1)	Sucrose-nitrate agar	very thin, white	colorless, small colonies	none
(2)	Glucose-asparagine agar	pinkish gray, short cottony	pale yellow, small colonies	none or trace
(3)	Glycerol-asparagine agar	none	scant growth	none
(4)	Starch-inorganic salts agar	gray-pinkish gray, short cottony	pale yellow, colonies	none
(5)	Tyrosine agar	none	scant growth	none
(6)	Nutrient agar	none	scant growth	none
(7)	Yeast-malt extract agar	white-pink, short cottony	pale yellow, small colonies	none
(8)	Oatmeal agar	pinkish gray, short cottony	pale yellow, small colonies	none
(9)	Glucose-peptone gelatin stab*	white-pink, short cottony	colorless	none
(10)	Milk	faint growth on surface	pale yellow	none or trace
(11)	Peptone-yeast iron agar	none	scant growth	none

* at ambient temperature for 20 days

3. *Physiological characteristics:*

(1) Range of temperature for growth (on Bennett's agar slants):
12 - 40°C., optimum : 27°C

(2) Liquefection of gelatin (on glucose - peptone gelatin stab):
negative

(3) Hydrolysis of starch (on starch - inorganic salts agar):
positive

(4) Coagulation and peptonization of skim milk:
Coagulation : positive
Peptonization : weak

(5) Production of melanoid pigment (on tyrosine agar, peptone - yeast iron agar and trypton - yeast extract broth):
negative

(6) Cell-wall pattern:
I type (containing LL-diaminopimelic acid)

(7) Carbon source utilization patterns (on Pridham-Gottlieb agar)

Carbon source	*Growth*
L-Arabinose	+ +
D-Xylose	+
D-Glucose	+ +
D-Fructose	+
Sucrose	±
Inositol	−
L-Rhamnose	−
Raffinose	±
D-Mannitol	−
D-Mannose	−
Salicin	−

Note) + + = Very good utilization
+ = Good utilization
± = Doubtful utilization
− = No utilization

As result of looking up the strain possessing the characteristics as mentioned above referring to the literatures, "Bergey's Manual of Determinative Bacteriology" eighth edition (1975), "The Actinomycetes" Vol. II (1961) written by S.A. Waksman and "The International Streptomyces Project Reports" written by E.B. Shirling and D. Gottlieb {Cf. International Journal of Systematic Bacteriology Vol. 18, pages 69 and 279 (1968), Vol. 19, page 391 (1969) and Vol. 22, page 265 (1972)}, *Streptomyces sindenensis, Streptomyces xanthocidicus* and *Streptomyces exfaliatus* have been detected as species having relatively analogous characteristics to those of the strain ATCC No. 31215.

The strain ATCC No. 31215, however, is different from these anologous species in the following respects.

i) *Streptomyces sindenensis:*

Mature spore chains of *Streptomyces sindenensis* are generally short. Spores of the species are poor on starch-inorganic salts agar. Aerial mycelia of the species are slightly formed on glycerol-asparagine agar. A strain of the species can assimilate D-mannitol.

ii) *Streptomyces xanthocidicus:*

Aerial mycelia of *Streptomyces xanthocidicus* are abundant on each of glycerol-asparagine agar and yeast-malt extract agar. Some strains of the species produce melanoid pigments. A strain of the species can relatively strong assimilate sucrose and raffinose.

iii) *Streptomyces exfoliatus*

Aerial mycelia of *Streptomyces exfoliatus* are formed on glycerol-asparagine agar. Spores of the species are very abundant on yeast-malt extract agar. A strain of the species can relatively strong assimilate sucrose and raffinose. Fragmentation and spore formation of the species on substrate mycelium are each not observed.

In view of the result of the above observation and in view of the fact that the strain ATCC 31215 is capable of producing the new antibiotic FR-900098, the strain ATCC 31215 can be judged as a new species belonging to the genus *Streptomyces* and then has designated as *Streptomyces rubellomurinus.*

1)-2 re. *Streptomyces rubellomurinus subsp. indigoferus* ATCC 31304:

Streptomyces rubellomurinus subsp. *indigoferus* ATCC 31304 has the following morphological, cultural and physiological characteristics:-

1. *Morphological characteristics:*

Microscopic observations were made on cultures which were grown at 27°C for from 10 to 14 days on sucrose-nitrate agar, glycerin-asparagine agar, yeast-malt extract agar, oatmeal agar, and inorganic salts-starch agar.

(1) Sporophore morphology: monopodial branching, rectiflexibles

Spore chains are generally long, with more than 10 spores per chain.

(2) Spore surface: smooth

(3) Spore size : 0.4-0.9 X 1.0-1.6 micron

(4) Neither fragmentation of hyphae nor formation of spores occur in the substrate mycelium. Sporangium and zoospore are not observed.

2. *Cultural characteristics:*

The strain has the following cultural characteristics when grown on media as indicated below at 27°C for 10 days.

	Medium	*Aerial mycelium*	*Vegetative growth*	*Soluble pigment*
(1)	Sucrose-nitrate agar	white togray, very thin, powdery	colorless, small colonies	none
(2)	Glucose-asparagine agar	pinkish gray, short cottony	pale yellow, small colonies	none or trace of yellow
(3)	Glycerin-asparagine agar	none	scant growth	none
(4)	Starch-inorganic salts agar	mouse gray to pinkish gray, short cottony	pale yellow to pale yellowish brown, small colonies	none or trace of yellow
(5)	Tyrosine agar	none	scant growth	none
(6)	Nurient agar	none	scant growth	none
(7)	Yeast-malt extract agar	white, thin powdery	pale yellow to pale yellowsih brown, wrinkled margin, indigo color	none
(8)	Oatmeal agar	Pinkish gray, short cottony	pale yellow, small colonies	none
(9)	Bennett's agar	white to pinkish gray, powdery	pale yellow to slightly indigo color,small colonies	none
(10)	Glucose-peptone gelatin stab.	white to pink, short cottony	colorless, faint growth	none
(11)	Peptone-yeast iron agar	none	colorless to slightly indigo color, faint growth	none
(12)	Milk	white, very thin powdery	pale yellow, growth on surface ring	none or trace

3. *Physiological properties:*
(1) Range of temperature for growth (on Bennett's agar slants):
12-40°C, optimum : 27°C
(2) Liquefaction of gelatin (on glucosepeptone gelatin stab):
negative
(3) Hydrolysis of starch (on starch-inorganic salts agar):
strongly hydrolyzed
(4) Coagulation and peptonization of skim milk:
Coagulation followed weak peptonization
(5) Production of melanoid pigment (on tyrosine agar, peptone-yeast iron agar and trypton-yeast extract broth):
negative
(6) Carbon source utilization patterns (on Pridham-Gottlieb agar):

3. *Physiological properties*:
(1) Range of temperature for growth (on Bennett's agar slats):
12 - 40°C, optimum : 27°C
(2) Liquefaction of gelatin (on glucose-peptone gelatin stab):
negative
(3) Hydrolysis of starch (on starch-inorganic salts agar):
strongly hydrolyzed
(4) Coagulation and peptonization of skim milk:
Coagulation followed weak peptonization
(5) Production of melanoid pigment (on tyrosine agar, peptone-yeast iron agar and trypton-yeast extract broth):
negative
(6) Carbon source utilization patterns (on Pridham-Gottlieb agar):

Carbon source	*Growth*
L-arabinose	+ +
cellulose	−
D-fructose	+
D-galactose	+
D-glucose	+
glycerin	+
inositol	−
lactose	−
D-maltose	+
D-mannitol	−
D-mannose	−
raffinose	−
L-rhamnose	−
salicin	−
Starch	+
sucrose	−
D-xylose	+

Symbol : +, positive utilization; −, no utilization

The above microscopic and cultural studies indicate that the strain ATCC 31304 belongs to the genus *Streptomyces*. Accordingly, a comparison of this organism was made with the published descriptions of *Streptomyces* species. From the above-mentioned information, the strain ATCC 31304 is considered to be closely resemble to *Streptomyces rubellomurinus* ATCC 31215. It was found, however, that this species was differentiated from the strain ATCC 31304 in the indigo color of vegetative mycelium on media contaning yeast extract. As a result of the comparisons, the strain ATCC 31304 is considered a subspecies of *Streptomyces rubellomurinus*, and the name *Streptomyces rubellomurinus* subsp. *indigoferus* is designated.

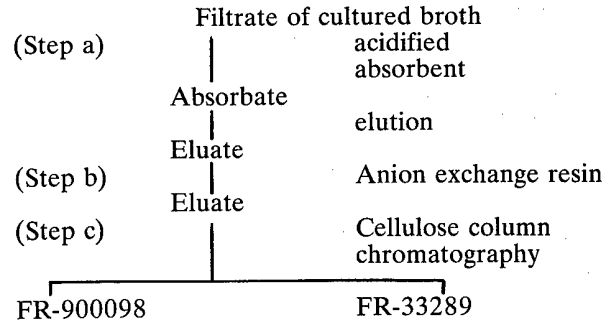
(2) Re. Fermentation

Fermentation for production of the antibiotic FR-900098 can be conducted by conventional means as mentioned hereinabove, and isolation of the antibiotic FR-900098 can also be conducted by conventional means as mentioned hereinabove.

However, as mentioned hereinafter, when Streptomyces rubellomurinus subsp. indigoferus is used for production of the antibiotic FR-900098, the antibiotic FR-33289 as well as FR-900098 are simultaneously produced in the cultured broth.

Accordingly, these two antibiotics may be separated out in a conventional manner such as chromatography means. The following is mentioned as one example of the separation

method.



re. Step a:
The filtrate is acidified in a conventional manner e.g. adjusted to pH 2.8 and the solution is passed through a column of an appropriate absorbent such as charcoal. Elution is carried out with an aqueous solvent (e.g. methanol, acetone).

re. Step b:
The eluate is passed through a column of an anion exchange resin (e.g. DEAE-Sephadex, Duolite A-6). Elution is carried out with, for example, aqueous sodium chloride (e.g. 0.3 N), aqueous ammonia (e.g. 0.2 M). The above operations (Step a and b) are advantageously repeated several times.

re. Step c:
The eluate is subjected to a column chromatography using cellulose with a suitable developing solvent (e.g. an aqueous propanol). And the antibiotic FR-900098 can be separated out, for example, by developing with 75% aqueous propanol, and FR-33289 can be separated out by developing with 70% aqueous propanol.

The antibiotic FR-900098 produced in the culture broth or separated out from the culture broth, can be isolated in the free form i.e. FR-900098 *per se* and when the solution or concentrate containing the antibiotic FR-900098 is treated with an alkali metal or alkaline earth metal (e.g. sodium or potassium hydroxide, or calcium carbonate) during the processes, e.g. extraction, isolation, or purification process, the antibiotic FR-900098 may be isolated in the form of its alkali metal or alkaline earth metal salt.

The antibiotic FR-900098 obtained in its free form may also be converted to its salt with a base such as an inorganic base (e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide, ammonia) or an organic base (e.g. ethanolamine, trimethylamine, dicyclohexylamine) in a conventional manner.

The salt of the antibiotic FR-900098 may be easily converted to the free form by treatment with an acid such as a mineral acid (e.g. hydrochloric acid) in a conventional manner.

(3) Re. The antibiotic FR-900098:

The antibiotic FR-900098 as obtained according to the afore-mentioned process, has as its monosodium salt, the following physical and chemical properties:

(a) Elemental Analysis (%):
C27.74 ; H5.03 ; N6.66
(the others: phosphorus and oxgen)

(b) MP : 193 - 194°C

(c) Specific rotation :
$[\alpha]_D^{25} = 0$ (C=1.0, in water)

(d) Ultraviolet absorption spectrum :
H_2O or 0.1NHCℓ
λ_{max} = end absorption
0.1N NaOH
λ_{max} = 230 nm (Shoulder)
$E^{1\%}_{1\,cm} = 325$

(e) Infrared absorption spectrum:
KBr
ν_{max} = 3450, 3400, 3350, 3100, 2930, 2800, 2420, 2320, 1615, 1570, 1495, 1450, 1420, 1370, 1310, 1280, 1240, 1220, 1200, 1180, 1160, 1090, 1080, 1050, 1040, 990, 980, 925, 910, 885, 810, 780, 760, 740, 710 cm^{-1}

(f) Solubility:
Very soluble ; water, methanol.
Sparingly soluble ; acetone, propanol.
Insoluble ; ethyl acetate, chloroform, benzene.

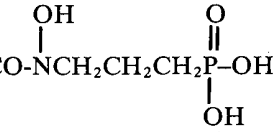
(g) Coloring reaction :
Positive ; each reaction with ferric chloride, potassium permanganate and iodine vapour.
Negative ; ninhydrin reaction and Molish's reaction.

(h) Form and color of crystals :
Colorless prisms (recrystallized from a mixture of methanol and acetone)

(i) Thin layer chromatography :
Carrier ; Eastman chromatogram Sheet Cellulose No. 13254 (trade name, made by Eastman Kodak Co.)

Developing solvent	*Rf value*
75% Aqueous propanol	0.5
n-Butanol saturated with water	0
70% Aqueous acetonitrile	0.4

From the analysis of the above physical and chemical properties and the result of further investigation for identification of chemical structure, the chemical structure of the antibiotic FR-900098 has been identified and assigned as follows.



[3-(N-acetyl-N-hydroxyamino) propylphosphonic acid]

(II). Production of the compound (I″) wherein $R^{1'}_a$ is formyl and A′ is $-CH_2-CH_2-CH_2-$, i.e. 3-(N-formyl-N-hydroxy -amino)propyl phosphonic acid (hereinafter referred to as FR-31705), and/or the compound (I″) wherein $R^{1'}_a$ is formyl and A′ is trans-l-propenylene, i.e. 3-(N-formyl-N-hydroxy -amino)-trans-l -propenylphosphonic acid (hereinafter referred to as FR-900136).

The antibiotic FR-31705 and/or antibiotic FR-900136 can be produced by fermentation of an antibiotic FR-31705- and/or antibiotic FR-900136- producing strain belonging to genus Streptomyces such as Streptomyces lavendulae in a nutrient medium.

(1) Re. The microorganism:

The microorganism which can be used for the production of the new antibiotics FR-31705 and/or FR-900136, is a strain of Streptomyces lavendulae newly isolated from a soil sample collected at Fukue city, Nagasaki prefecture, Japan.

A culture of the living organism has been deposited with American Type Culture Collection under ATCC No. 31279 and with Fermentation Research Institute, Agency of Industrial Science and Technology, Japan under the receipt No. 3808.

It is to be understood that the production of FR-31705 and FR-900136 is not limited to use the specific organism described herein, which is given only for illustrative purpose. That is an artificial mutant as well as a natural mutant can also be used. Such an artificial mutant is produced from the microorganism as described herein by conventional means as mentioned hereinabove.

1) Microbiological Property

Streptomyces lavendulae ATCC 31279 has the following morphological, cultural and physiological characteristics:

1. Morphological characteristics:-

The morphology of the culture was microscopically observed with the mycelium grown on each of glycerolasparagine agar, yeast-malt extract agar, oatmeal agar and inorganic salts-starch agar.

(1) Type of branching of spore-forming hyphae:
Monopodial branching

(2) Form of spore-forming hyphae:
Retinaculiaperti: open loop, hook and occasionally rectus and spiral.

(3) Number of spore:
10 - 50 spores
(4) Surface appearance and size of spore:
Smooth, 0.5 - 1.2 x 1.4 - 2.0 micron
(5) Existence of zoospore:
Not observed
(6) Existence of sporangium:
Not observed
(7) Formation of spores:
At aerial mycelium
(8) Fragmentation of substrate mycelium:
Not observed

2. Cultural characteristics:

The strain has the following cultural characteristics when grown on media, as indicated below, at 30°C for 10 - 14 days.

Medium	*Aerial mycelium*	*Vegetative growth*	*Soluble pigment*
(1) Sucrose-nitrate agar	thin, white, short cottony	colorless, small colonies	none
(2) Glucose-asparagine agar	white, short cottony	pale yellow, small colonies	none
(3) Glycerol-asparagine agar	pinkish gray, short cottony	colorless-cream colored, small colonies	none
(4) Starch-inorganic salts agar	pinkish gray, short cottony	pale yellow small colonies	none
(5) Tyrosine agar	thin, white, powdery	colorless, small colonies	none
(6) Nutrient agar	none	cream-colored, wrinkled colonies	faint brown
(7) Yeast-malt extract agar	pinkish gray, short cottony	yellowish brown, wrinkled colonies	trace
(8) Oatmeal agar	pinkish gray, short cottony	pale yellow, small colonies	none
(9) Glucose-peptone gelation stab	white, powdery	yellowish brown, surface growth	brown
(10) Milk	none	cream-colored, ring	none
(11) Peptone-yeast-iron agar	none	colorless, wrinkled colonies	brownish black

3. *Physiological characteristics:*
(1) Range of temperature for growth (on Bennett's agar):
12 - 40°C, optimum : 26°C
(2) Liquefaction of gelatin (on glucose-peptone-gelatin stab):
negative
(3) Hydrolysis of starch (on starch-inorganic salts agar):
positive
(4) Coagulation and peptonization of skim milk:
Coagulation : negative
Peptonization: slowly petonized
(5) Production of melanoid pigment:
(a) Positive on peptone-yease-iron agar
(b) negative on tyrosine agar
(6) Carbon source utilization potterns (on Pridham-Gottlieb agar)

Carbon source	*Growth*
L-Arabinose	-
Cellulose	-
D-Fractose	-
D-Glucose	+
D-Galactose	+
Inositol	-
D-Mannose	±
D-Mannitol	-
L-Rhamnose	-
Raffinose	-
Sucrose	-
Salicin	+
D-Xylose	-

Symbols: +, Good utilization, ±, Doubtful utilization
-, No utilization

The above microbiological characteristics indicate that the strain ATCC 31279 belongs to the genus Streptomyces. And, as a result of looking up the strain possessing the characteristics as mentioned above referring to the literatures, "Bergey's Manual of Determinative Bacteriology" eighth edition (1975), "The Actinomycetes" Vol. II (1961) written by S. A. Waksman and "The International Streptomyces Project Reports" written by E. B. Shirling and D. Gottlieb [Cf. International Journal of Systematic Bacteriology Vol. 18, pages 69 - 189 and 279 - 392 (1968), Vol. 19, pages 391 - 512 (1969) and Vol. 22, pages 265 - 394 (1972)], it is confirmed that microbiological characteristics of the strain ATCC 31279 are identical with those of *Streptomyces lavendulae*.

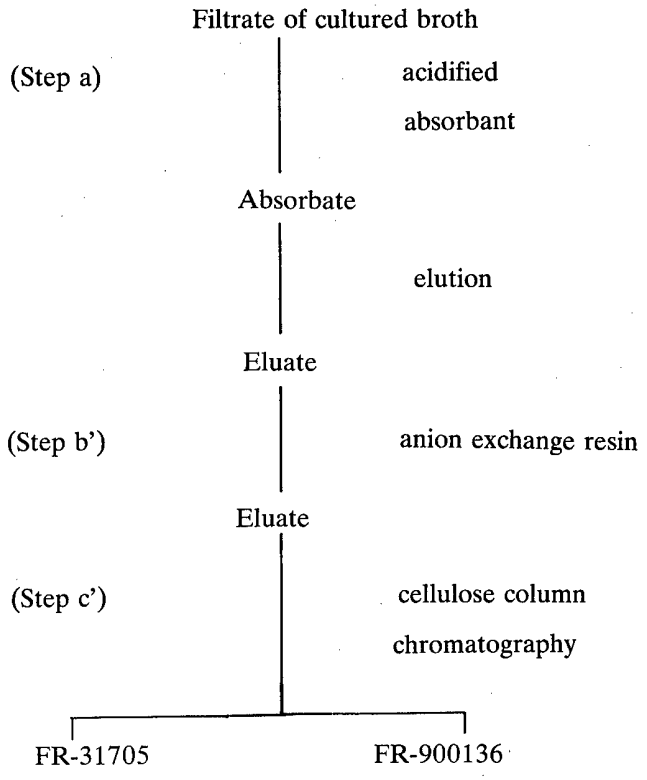
The above observation was confirmed also by comparison of the microbiological characteristics of the strain ATCC 31279 and that of a type-culture, *Streptomyces lavendulae* IAM 0009.

From the result of the above observation, the strain has been designated as *Streptomyces lavendulae*.

(2) Re. Fermentation:

Fermentation for production of the antibiotic FR-31705 and antibiotic FR-900136 can be conducted by conventional methods as mentioned hereinabove and isolation of these antibiotics can also be generically conducted by conventional means as mentioned hereinabove.

As mentioned above, the cultured broth contains both of the antibiotic FR-31705 and the antibiotic FR-900136, and accordingly these two antibiotics may be separated out in a conventional manner such as chromatography means. The following is illustrated as one example of the separation method.



re. Step a':
Filtrate is acidified in a conventional manner (e.g. adjusted to pH 2.0), and the solution is passed through a column of an appropriate adsorbent such as charcoal. Elution is carried out with an aqueous solvent (e.g. methanol, acetone).

re. Step b':
The eluate is passed through a column of an anion exchange resin (e.g. DEAE-Sephadex, Duolite A-6). Elution is carried out with, for example, aqueous sodium chloride (e.g. 0.3 M) and aqueous ammonia (e.g. 0.2 N).

re. Step c':
The eluate is subjected to a column chromatography using cellulose with a suitable developing solvent (e.g. an aqueous propanol). And FR-31705 can be separated out, for example, by developing with 97% aqueous propanol, and FR-900136 can be separated out by developing with 95% aqueous propanol.

The antibiotics FR-31705 and FR-900136 produced in the cultured broth or separated out from the cultured broth, can be isolated in the free form i.e. FR-31705 *per se*. Further, these antibiotics can also be isolated in the form of their alkali or alkaline earth metal salt by treating a solution containing the antibiotics with an alkali or alkaline earth metal (e.g. sodium or potassium hydroxide, or calcium carbonate) during the processes, e.g. the extraction, isolation or purification process.

These antibiotics obtained in their free forms may also be converted to their salts with bases such as an iorganic base (e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide, ammonia), and an organic base (e.g. ethanolamine, trimethylamine, dicyclohexylamine) in a conventional manner.

The salts of these antibiotics may easily be converted to the free form by treating them with an acid such as a mineral acid (e.g. hydrochloric acid) in a conventional manner.

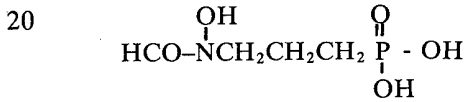
(3) Re. The antibiotics FR-31705 and FR-900136:

(3)-1 The antibiotic FR-31705

The antibiotic FR-31705 as obtained according to the afore-mentioned process, has as its monopotassium salt the following physical and chemical properties:

(a) Elemental Analysis (%):
C 21.62 ; H 4.07 ; N 6.36 ;
K 17.99
(b) MP : 202 - 204°C (dec.)
(c) Infra-red absorption spectrum:
nujol
ν_{max} = 2950, 2925, 2850, 2550, 2380, 1650, 1460, 1410, 1395, 1375, 1320, 1300, 1260, 1220, 1190, 1150, 1120, 940, 890, 810, 785, 700 cm^{-1}
(d) N.M.R. Spectrum
δ(ppm) in D_2O
1.25 - 2.3 (4H, m), 3.65 (2H, t, J=6Hz), 8.00 (s), 8.35 (s) } 1H

From the analysis of the above physical and chemical properties, and the result of further investigation for identification of chemical structure, the chemical structure of the antibiotic FR-31705 has been identified and assigned as follows.



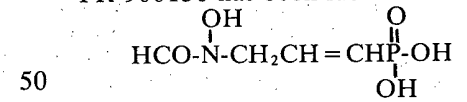
[3-(N-formyl-N-hydroxyamino) propylphosphonic acid]

(3)-2 The antibiotic FR-900136

The antibiotic FR-900136 as obtained according to the afore-mentioned process, has as its monopotassium salt has the following physical and chemical properties:

(a) Elemental Analysis (%):
C 21.32 ; H 3.26 ; N 6.00 ;
H_2O 1.49
(b) MP : 178 - 180°C (dec.)
(c) Infra-red absorption spectrum:
Nujol (Registered Trade Mark)
ν_{max} = 2960, 2930, 2870, 2600, 2350, 1660, 1530, 1460, 1440, 1400, 1380, 1365, 1290, 1250, 1180, 1125, 1070, 1010, 980, 960, 950, 890, 830, 780, 700 cm^{-1}
(d) N.M.R. Spectrum
δ(ppm) in D_2O
4.30 (2H, m), 6.01 (1H, m), 6.38 (1H, m), 8.02 (s), 8.38 (s) } 1H

From the analysis of the above physical and chemical properties and the result of further investigation for identification of chemical structure, the chemical structure of the antibiotic FR-900136 has been identified and assigned as follows.



[3-(N-formyl-N-hydroxyamino)-trans -l-propenylphosphonic acid]

(III). Production of the compound (I″) wherein $R^{1''}_a$ is acetyl and A′ is $-CH_2-\underset{OH}{CH}-CH_2-$, i.e. 3-(N-acetyl-N- hydroxyamino)-2 -hydroxypropylphosphonic acid (hereinafter referred to as FR-33289):

The antibiotic FR-33289 can be produced by fermentation of an antibiotic FR-33289-producing strain belonging to genus *Streptomyces* such as *Streptomyces rebellomurinus* subsp. *indigoferus* in a nutrient medium.

(1) Re. The microorganism:

As a preferred microorganism which can be used for the production of the new antibiotic FR-33289, there is exemplyfied *Streptomyces rubellomurinus* subsp. *indigoferus* ATCC 31304.

Microbiological property of the strain ATCC 31304 is described hereinabove, and is to be

referred to said explanation.

Further, it is to be noted that the *Streptomyces rubellomurinus* subsp. *indigoferus* ATCC 31304 can produce simultaneously both the antibiotic FR-900098 and the antibiotic FR-33289 in a cultured broth as mentioned hereinabove.

(2) Re. The fermentation:

Fermentation for production of the antibiotic FR-33289 can be conducted by conventional means as mentioned hereinabove, and isolation of the antibiotic can generically also be conducted by conventional means as mentioned hereinabove.

As mentioned above, the cultured broth contains both the antibiotic FR-900098 and the antibiotic FR-33289 and accordingly these two antibiotics may be separated out.

Preferred separation operations is the same as mentioned above.

(3) Re. The antibiotic FR-33289:

The antibiotic FR-33289 as obtained according to the afore-mentioned process, has its monosodium salt the following physical and chemical properties:

(a) Infra-red absorption spectrum:

KBr

ν_{max} = 3300, 2900, 2400, 1740, 1620, 1420, 1240, 1140, 1040, 900 cm^{-1}

(b) N.M.R. Spectrum:

δ(ppm) in D_2O

1.88 (2H, d.d. J=6 18Hz),
2.16 (3H, s),
3.66 - 3.9 (2H, m),
4.30 (1H, m)

(c) Coloring reaction :

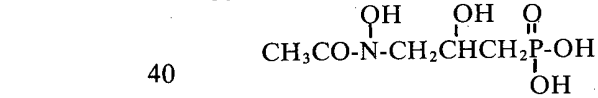
Positive : reaction with ferric chloride, potassium permanganate, and iodine vapour.

(d) Thin layer chromatography :

Carrier ; Eastman chromatogram Sheet Cellulose No. 13254 (trade name, made by Eastman Kodak Co.)

Developing solvent	R_f
60% Aqueous propanol	0.6

From the analysis of the above and chemical properties and the result of further investigation for identification of chemical structure, the chemical structure of the antibiotic FR-33289 has been identified and assigned as follows.



[3-(N-acetyl-N-hydroxyamino)-2 -hydroxypropylphosphonic acid]

Biological Property of Hydroxyaminohydrocarbonphosphonic Acid Derivatives

Antimicrobial activity:-

The object compound, hydroxyaminohydrocarbon -phosphonic acid derivatives (I) and esters at the phosphono group thereof and salts thereof, have been found to possess strong antibacterial activity against pachogenic micro-organisms such as Gram positive and negative bacteria, including the genera *Bacillus*, *Sarcina*, *Escherichia*, *Proteus*, *Salmonella*, *Pseudomonas*, *Shigella* and *Enterobacter*. Accordingly, the object compound of this invention is useful for the treatment of infection disease caused by such pathogenic bacteria in human beings or animals. For illustrating purpose, the biological properties of some representative compounds of the object compound (I) are illustrated in the followings.

1. Monosodium salt of 3-(N-acetyl-N -hydroxyamino)-propylphosphonic acid:

Minimum Inhibitory Concentration (M.I.C.):-

M.I.C. test was conducted by the usual serial agar dilution method, using a nutrient agar which was incubated at 37°C. for 20 hours. M.I.C. value is expressed as the minimum concentration of the monosodium salt of 3-(N-acetyl-N-hydroxyamino) propylphosphonic acid (mcg/ml.) which inhibits growth of the microorganism. The results are as follows:

Test Microorganisms	*M.I.C. (mcg/ml.)*
Staphylococcus aureus FDA209P JC-1	> 1000
Bacillus subtilis ATCC6633	125
Sarcina lutea PCI 1001	8
Escherichia coli NIHJ JC-2	63
Escherichia coli 1341-29	32
Klebsiella pneumoniae NCTC 418	500
Proteus vulgaris IAM 1025	125
Proteus mirabilis 1	> 1000
Proteus morganii 30	> 1000
Proteus rettgeri 15	63
Pseudomonas aeruginosa IAM 1095	250
Salmonella typhi T-287	2
Shigella flexneri IaEW8	8
Serratia marcescens 5	250
Citrobacter freundii 20	500
Enterobacter aerogenes 10	32
Enterobacter cloacae 25	63

Protecting Effect in Experimental Mice Infections:-

The activity of monosodium salt of 3-N-acetyl-N-hydroxyamino) propylphosphonic acid in vivo against the species Escherichia coli was tested, using ICR-strain male mice of weighing 20-25g. Two groups, each of four mice, were fasted for 24 hours prior to the testing.

A suspension of a pathogenic bacteria, Escherichia coli strain No. 1341-29 in 2.5% aqueous Mucin solution (0.5 ml.) was intraperitoneally injected into each of all mice, respectively (Challenge Dose : 1 x 10^6 living cells/mouse), one group being used for protecting effect experiment and the other for control.

One hour after the infection, each mouse of the experimental group was subcutaneously injected with monosodium salt of 3-(N-acetyl-N -hydroxyamino) propylphosphonic acid (4 mg.) in water (0.5 ml.), the mouse of the control group being not treated with the antibiotic.

Animals in both of the groups were observed for death and survival for one week.

All mice of the experimental group were survived. On the other hand, all mice of the control group were dead.

Acute Toxicity:-

A solution of monosodium salt of 3-(N-acetyl-N -hydroxyamino) propylphosphonic acid in water (0.5 ml.) was intravenously injected into each of five mice (Dose : 5g/kg mouse), the result of which the all tested were normal for ten days after administration.

Hypolipidemic activity:-

The object compound (I) of this invention also has hypolipidemic activity such as hypochlosterolemic activity, and is useful as a therapeutic agent in the treatment of hyperlipemia.

For such an example, 3-(N-hydroxyamino) propylphosphonic acid, one of the object compound, showed nearly the same level of hypocholesterolemic activity as that of "Clofibrate", which is under marketing, as a result of a test using Wistar strain rats given a

high fat diet comprising cholesterol.

2. Monoammonium salt of 3-(N-formyl -N-hydroxyamino)- propylphosphonic acid:

Minimum Inhibitory Concentration (M.I.C.):-

M.I.C. test was conducted by the usual serial agar dilution method, (inoculum: 10^6 cells/ml.), using a nutrient agar which was incubated at 37°C. for 20 hours. M.I.C. value is expressed as the minimum concentration of the monoammonium salt of 3-(N-formyl-N -hydroxyamino)- propylphosphonic acid (mcg/ml.) which inhibits growth of microorganisms. The results are as follows:

Test Microorganisms	*M.I.C. (mcg/ml.)*
Staphylococcus aureus FDA209P JC-1	> 800
Bacillus substilis ATCC6633	6.25
Sarcina lutea PCI 1001	≦ 0.1
Escherichia coli NIHJ JC-2	200
Escherichia coli 1341-18(R)	12.5
Klebsiella pneumoniae NCTC 418	100
Proteus vulgaris IAM 1025	3.13
Proteus mirabilis 1432-75	6.25
Proteus morganii 1433-2	> 800
Proteus rettgeri 1434-3	1.56
Proteus inconstans 1436-21	3.13
Pseudomonas aeruginosa IAM 1095	0.78
Salmonella enteritidis 1891	0.39
Salmonella typhi 0-901	0.39
Salmonella paratyphi A-1015	12.5
Salmonella typhimurium 1406	25
Shigella flexneri IaEW8	12.5
Shigella sonnei I EW33	100
Serratia marcescens 1421-4	100
Citrobacter freundii 1381-3	3.13
Enterobacter aerogenes 1402-10	6.25
Enterobacter cloacae 1401-4	6.25

Protecting Effect in Experimental Mice Infections:-

(a) Test compound :

Monoammonium salt of 3-(N-formyl-N-hydroxy -amino) propylphosphonic acid

(b) Test animal :

Male mice of ICR-strain, aged 4 weeks and weighing 24 ± 1 g., were used. Each experimental group consists of 8 animals.

(c) Test method :

A prescribed amount of pathogenic bacteria, suspended in 5% aqueous Mucin solution (0.5 ml.), was intraperitoneally injected into the test animals.

Subsequently, the above test compound in water (0.25 ml.) was administered to each of the test animals, subcutaneously three times at 0, 1, 3 hours or orally once at 1 hour after the infection of pathogenic bacteria, respectively.

All test animals were observed for survival or death for 1 week and ED_{50} values were calculated by the probit method. The results are shown in the following table.

Table

Pathogenic bacteria	*Inoculated viable cells per mouse*	*ED_{50} (mg/mouse)*	
		subcutaneous administration	*oral administration*
Pseudomonas aeruginosa 1101-76	1.2×10^6	0.228	0.280
Eschericha coli 1341-67	6.9×10^7	0.167	2.559
Proteus mirabilis 1432-75	8.0×10^7	0.236	4.331

Acute Toxicity

(a) Test comound:
Monosodium salt of 3-(N-formyl -N-hydroxyamino) -propylphosphonic acid.

(b) Test animal
Male and Female mice of ICR-strain, aged 6 weeks were used.

(c) Observation times
One week

(d) Calculation method
Litchfield-Wilcoxon method

Animal	*Sex*	LD_{50} *(mg/kg.)* *oral administration*	*subscutaneous administration*
Mouse	male	> 11,000	8,050
	female	> 11,000	8,270
Rat	male	> 11,000	8,000

3. Monopotassium salt of 3-(N-formyl-N-hydroxyamino)-trans- l-propenylphosphonic acid:

Minimum Inhibitory Concentration (M.I.C.):-
M.I.C. test was conducted by an usual serial agar dilution method, (inoculum: 10^5 cells/ml.), using a nutrient agar which was incubated at 37°C for 18 hours. M.I.C. value is expressed as the minimum concentration of the monopotassium salt of 3-(N-formyl-N -hydroxyamino)-trans -l-propenylphosphonic acid (mcg/ml.) which inhibits growth of microorganisms. The results are as follows:

Test Microorganisms	*M.I.C. (mcg/ml)*
Staphylococcus aureus FDA209PJC-1	> 100
Bacillus subtilis ATCC6633	6.25
Sarcina lutea PCI 1001	0.2
Escherichia coli 1341-18(R^+)	25
Klebsiella pneumoniae NCTC 418	100
Proteus vulgaris IAM 1025	1.56
Proteus mirabilis 1432-75	0.39
Proteus morganii 1433-2	> 100
Proteus rettgeri 1434-3	6.25
Proteus inconstans 1436-21	25
Pseudomonas aeruginosa IAM 1095	1.56
Salmonella enteritidis 1891	6.25
Salmonella typhi 0-901	0.78
Salmonella paratyphi A-1015	25
Salmonella typhimurium 1406	12.5
Shigella flexneri IaEW8	50
Shigella sonnei I EW33	25
Serratia marcescens 1421-4	> 100
Citrobacter freundii 1381-3	12.5
Enterobacter aerogenes 1402-10	50
Enterobacter cloacae 1401-4	12.5

The Pharmaceutical Composition Comprising Hydroxyaminohydrocarbonphosphonic Acid Derivatives

The object compound (I) of this invention, hydroxyaminohydrocarbonphosphonic acid derivatives and the esters at the phosphono group thereof and the pharmaceutically acceptable salts thereof according to this invention, can be formulated for administration in any convenient way, analogously with known antibiotics, in admixture with a non-toxic pharmaceuticaly acceptable carrier.

A pharmaceutically acceptable salt of the compound (I) may include salt with an inorganic or organic base such as sodium salt, potassium salt, calcium salt, ammonium salt, ethanolamine salt, triethylamine salt, dicyclohexylamine salt, and salt with an inorganic or

organic acid such as hydrochloride, sulfate, citrate, maleate, fumarate, tartarate, p-toluenesulfonate, and further salt with an amino acid such as arginine salt, aspartic acid salt, glutanic acid salt.

Thus, the antimicrobial composition can be used in the form of pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains an active object compound in admixture with a pharmaceutical organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications. The active ingredient may be compounded, for example, with usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions or suspensions. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, karatin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes. The antimicrobial compositions can also contain preserving or bacteriostatic agents thereby keeping the active ingredient in the desired preparations table in activity. The active object compound is included in the antimicrobial composition in an amount sufficient ot produce the desired therapeutic effect upon the bacterially infected process or condition.

For applying this composition to human, it is preferably to apply in a form of intravenous, intramuscular or oral administration. While the dosage or therapeutically effective amount of the object compound of this invention varies from and also depends upon the age and condition of each individual patient to be treated, a daily dose of about 2-100 mg. of the active ingredient/kg. of a human being or an animal is generally given for treating diseases, and an average single dose of about 50 mg., 100 mg., 250 mg. and 500 mg. is generally administered

Preparation of starting compounds

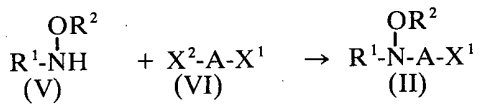
Starting compounds to be used in the preparation of the object compound (I) of this invention and the esters, and salts thereof, can be prepared by following processes:

1. Preparation of the starting compound (II)
   (1) Formation of C-N bond
2. Preparation of the starting compound (IV)
   (1) Formation of C-P bond (4) Halogenation (II)
   (2) Halogenation (I)
   (3) Dehydrohalogenation
3. Preparation of the starting compound (V)
   (1) O-Aralkylation
   (2) Acylation
4. Preparation of the starting compound (VII)
   (1) Formation of C-N bond

Each of these processes will be illustrated hereinafter.

1. Preparation of the starting compound (II)
   (1) Formation of C-N bond

The reaction of this process can be illustrated by the following scheme:



wherein R^1, R^2, X^1, X^2 and A are each as defined above.

In this process, the compound (II) can be prepared by reacting the compound (V) with the compound (VI).

Starting materials (V) include known and novel ones. The known compounds, e.g. N-benzyloxy -p-toluenesulfonamide, are prepared by the method described in Bulletin of the Chemical Society of Japan Vol. 45, page 1462 (1972) and the other new compounds can also be prepared in the similar manner thereto.

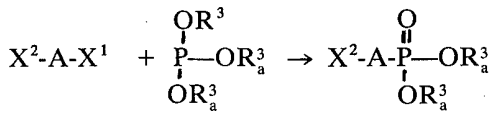
The reaction of this process is usually conducted in a solvent such as methanol, ethanol, propanol, benzene, toluene, pyridine, dimethylsulfoxide, N,N-dimethylformamide, and usually at ambient temperature or with heating.

The reaction of this process can preferably be conducted in the presence of an organic or inorganic base, preferred examples of which are the same as those given in explanation of the process I (I) for production of the object compound (I).

The reaction product can be purified and isolated in a conventional manner.

2. Preparation of the starting compound (IV)
   (1) Formation of C-P bond

The reaction of this process can be illustrated by the following scheme:



(VI) (III) (IVa)

wherein R^3, R^3_a, X^1, X^2 and A are each as defined above.

In this process, the compound (IVa) can be prepared by reaction the compound (VI) with the compound (III).

The reaction may be conducted in a solvent or without solvent. Preferred examples of the solvent may include methanol, ethanol, propanol, benzene, toluene, hexane, pyridine, dimethylsulfoxide, N,N-dimethylformamide.

The reaction is usually conducted at ambient temperature or with heating.

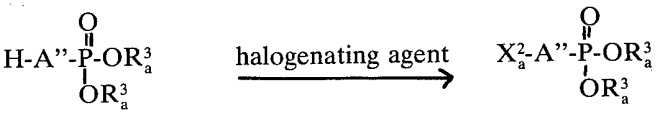
The reaction can be preferably conducted in the presence of an organic or inorganic base, preferred example of which are the same as those given in the explanation of the process I (1) for production of the object compound (I)

Optimum reaction conditions can be selected from the above reaction conditions according to kinds of starting compounds, solvent and/or base to be used.

The reaction production can be isolated and purified in a conventional manner.

(2) Halogenation

The reaction of this process can be illustrated by the following scheme:



(IX) (IVb)

wherein R^3_a is as defined above, X^2_a is halogen and A″ is alkenylene.

In this process, the compound (IVb) can be prepared by reacting the compound (IX) with a halogenating agent.

The starting material (IX) includes known and novel ones. The known compounds, e.g. diethyl l-propenylphosphonic acid can be prepared by the method described in Journal of General Chemistry of The USSR Vol. 33, page 429 (1963) and the other new compounds can also be prepared in the similar manner thereto.

The halogenating agent to be used in this reaction may include halogen (e.g. chlorine, bromine), N-haloimide (e.g. N-bromosuccinimide, N-chlorosuccinimide, N-bromophthalimide), alkyl hypohalite (e.g. t-butyl hypochlorite, amyl hypochlorite), hypohalogenous acid or its salt (e.g. hypochlorous acid, hypobromous acid, sodium hypochlorite), sulfuryl chloride, trichloromethanesulfuryl chloride.

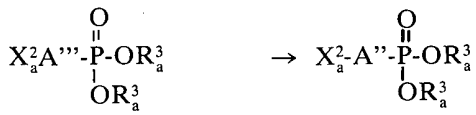
This halogenation usually results at so-called allylic position and is conducted in a conventional manner and preferably conducted in the presence of free-radical initiators such as light (e.g. ultra violet), peroxide (e.g. dibenzoyl peroxide, di-t-butyl peroxide), azo compound (e.g. azobisisobutyronitrile).

The reaction of this process is usually conducted in a solvent such as benzene, cyclohexane, at from ambient temperature to around at boiling point of the solvent to be used.

The reaction product (IVb) can be isolated and purified in a conventional manner.

(3) Dehydrohalogenation

The reaction of this process can be illustrated by the following scheme:



(X) (IVb)

wherein X^2_a, R^3_a and A″ are each as defined above and ABV is haloalkylene.

The haloalkylene for A‴ means an alkylene group bearing a halogen (e.g. chlorine, bromine, iodine).

In this process, the compound (IV_b) can be prepared by subjecting the compound (X) to so-called 1,2-dehydrohalogenation reaction.

The starting (X) includes known and novel ones. The known compounds, e.g. diethyl 2,3-dibromopropyl phosphonate can be prepared by the method described in Zhurnal Obshchei Khimii, Vol. 22 page 1052 (1952), and the other new compounds can also be prepared in the similar manner thereto.

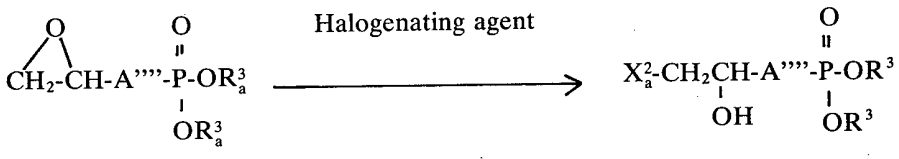
This reaction is conducted in a conventional manner and preferably conducted in the presence of an inorganic or organic base, preferred examples of which are the same as those given in the explanation of the process I (1) for production of the object compound (I).

This dehydrohalogenation is usually conducted in a conventional solvent such as methanol, ethanol, propanol, isopropyl alcohol, tert-butyl alcohol, acetone, chloroform, dichloromethane, ether, and preferably conducted either with cooling or heating.

The reaction product (IV_b) can be isolated and purified in a conventional manner.

(4) Halogenation (II)

The reaction of this process can be illustrated by the following scheme:



(XI) (XII)

wherein X^2, R^3 and R^3_a are each as defined above, and A‴ is alkylene.

In the process, the compound (XII) can be prepared by reacting the compound (XI) with a halogenating agent.

The starting material (XI) includes known and novel ones. The known compounds, e.g. diethyl 2,3-epoxypropylphosphonate can be prepared by the method described in Journal of the American Chemical Society, Vol. 77, page 6225 (1955), and the other new compounds can also be prepared in the similar manner thereto as described particularly hereinafter.

The halogenating agent to be used in this reaction may include hydrogen halide, a halosilyl compound such as trialkylhalosilane, dialkyldihalosilane, alkyltrihalosilane, dialkylarylhalosilane, triarylhalosilane, dialyklaralkylhalosilane, dialkoxy dihalosilane, trialkoxyhalosilane.

The reaction of this process is preferably conducted in the presence of or absence of solvents such as dichloromethane, chloroform, carbon tetrachloride, benzene, toluene either with ice-cooling or with heating up to the to boiling point of the solvent to be used.

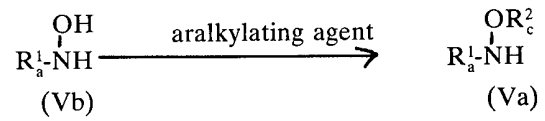
The reaction product (XII) can be isolated and purified in a conventional manner.

Moreover, when the reaction product (XII) is used as a starting compound of a further reaction, the hydroxy group of the compound (XII) can be protected with a easily removable group such as tetrahydropyranyl in a conventional manner as described particularly hereinafter.

3. Preparation of the starting compound (V)

(1) O-Aralkylation

The reaction of this process can be illustrated by the following scheme



(Vb) (Va)

wherein R^1_a is as defined above and R^2_c is aralkyl.

In this process, the compound (Va) can be prepared by reacting the compound (Vb) with an aralkylating agent.

Preferred examples of the aralkylating agent may include an aralkyl halide such as benzyl chloride, benzyl bromide, p-methoxybenzyl bromide, phenethyl iodide, benzhydryl chloride, trityl chloride; an aralkyl sulfonate such as aralkyl alkanesulfonate (e.g. benzyl methanesul-

fonate, phenethyl ethanesulfonate) or aralkyl arenesulfonate (e.g. benzyl p-toluenesulfonate, p-methoxybenzyl p-bromobenzenesulfonate, benzhydryl p-toluenesulfonate); and diaralkyl sulfate (e.g. dibenzylsulfate).

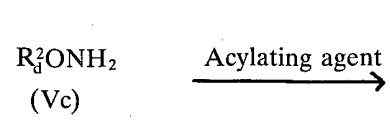
The reaction of this process is usually conducted in a solvent, such as methanol, ethanol, propanol, isopropanol, acetone, dioxane, tetrahydrofuran, N,N-dimethylformamide, ether, benzene, toluene, n-hexane, and usually at around ambient temperature or with cooling.

The reaction can also be conducted in the presence of an organic or inorganic base, preferred examples of which are the same as those given in the explanation of the process I(1) for production of the object compound (I)

The reaction product (Va) can be isolated and purified in a conventional manner.

(2) Acylation

The reaction of this process can be illustrated by the following scheme:



(Vc) (Vd)

wherein R_d^2 is hydrogen or aralkyl, R_e^2 is acyl or aralkyl and R_a^1 is as defined above.

In this process, the compound (Vd) can be prepared by reacting the compound (Vc) with an acylating agent.

The acylating agent to be used in this reaction are the same as those given in the explanation of N-acylation for the production of the object compound (I).

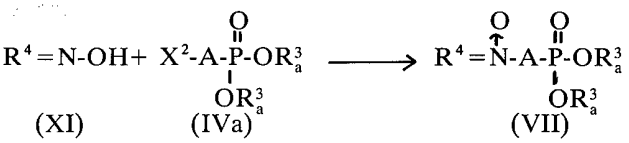
Further, the reaction conditions (e.g. reaction temperature, solvent, base, condensing agent), and purification and isolation of the reaction product (Vd) are the same as those given in the explanation of N-acylation for the production of the object compound (I).

In the acylation process, it is to be understood that there may be produced N-monoacyl, N,O-diacyl derivative or their mixture according to an amount of an acylating agent to be used in this reaction.

That is, the compound (Vc) wherein R_d^2 is hydrogen, is acylated with an acylating agent in an amount of one molar equivalent to provide mainly N-monoacyl derivative thereof and with nearly two moles of an acylating agent to provide mainly N,O-diacyl derivative thereof. In the case of the production of a mixture of N-monoacyl and N,O-diacyl derivatives in this reaction, each of the acyl derivatives can be purified and isolated from the reaction mixture in a conventional manner.

4. Preparation of the starting compound (VII)

The reaction of this process can be illustrated by the following scheme:



(XI) (IVa) (VII)

wherein R_a^3, R^4, X^2 and A are each as defined above.

In this process, the compound (VII) can be prepared by reacting the compound (XI) with the compound (IVa).

One of the starting compounds (XI) can be prepared, for example by reacting the corresponding carbonyl compound with hydroxylamine in a conventional manner.

The reaction of this process is usually conducted in a solvent such as methanol, ethanol, propanol, benzene, toluene, pridine, dimethylsulfoxide, N,N-dimethylformamide, at ambient temperature or with slight warming.

The reaction of this process can preferably be conducted in the presence of an organic or inorganic base, preferred examples of which are the same as those given in the explanation of the process I (1) for production of the object compound (I).

The reaction product can be isolated and purified in a conventional manner.

Suitable examples of some preparations of compound (II) are illustrated more specifically as follows.

(1) N-(p-methoxybenzyloxy)-p-toluenesulfonamide (61,4g) was added to a solution of sodium ethoxide in absolute ethanol (Na : 4.6g, absolute C_2H_5OH : 540 ml) and stirred at 70°C for 1.5 hours. After cooling to ambient temperature, 1,3-

dibromopropane (121.2g) was added to the mixture, and then the mixture was refluxed with stirring for 2 hours and filtered. The filtrate was concentrated under reduced pressure. To the residue was added a mixture of ethyl acetate and water, and the organic layer was separated, dried over magnesium sulfate and evaporated to dryness under reduced pressure to give an oil, which was crystallized from a mixture of ethyl acetate and n-hexane to give N-(3-bromopropyl)-N-(p-methoxybenzyloxy) -p-toluenesulfonamide (75.1g).
MP : 89.5~91.5°C
In substantially the same manner as described in the above example, there were obtained the following compounds.

(2) *Starting material*
Isobutyl N-(p-methoxybenzyloxy) carbamate (19.75g)
1,3-dibromopropane (47.1g)
Object compound
Isobutyl N-(3-bromopropyl)-N-(p -methoxybenzyloxy) carbamate (17.48g) in the form of oily substance.
Infrared Absorption Spectrum, (liquid film):
ν_{max} : 1720 (shoulder), 1705, 1610, 1590 cm^{-1} NMR Absorption Spectrum ($CDCl_3$):
δ(ppm)
0.95 (6H, d, J=7Hz)
1.8~2.4 (2H, m)
3.35 (2H, t, J=6Hz)
3.55 (2H, t, J=6Hz)
3.74 (3H, s)
3.94 (2H, d, J=6Hz)
4.77 (2H, s)
6.86 (2H, d, J=9Hz)
7.30 (2H, d, J=9Hz)

(3) *Starting material*
N-(p-methoxybenzyloxy) -p-toluenesulfonamide (18.4g)
1-Bromo-3-chloropropane (14.2g)
Object compound
N-(3-Chloropropyl)-N- (p-methoxylbenzyloxy) -p-toluenesulfonamide (20 g) in the form of crystals.
MP : 84~86°C

(4) *Starting material*
N-benzyloxy-p -toluenesulfonamide (27.7g)
1-Bromo-3-chloropropane (23.6g)
Object compound
N-(3-chloropropyl) -N-benzyloxy-p -toluenesulfonamide (32.65g)
MP : 84~87°C

Suitable working examples for some preparations of the compound (IV) are illustrated more specifically as follows:

(i) For formation of C-P bond:

(1) Sodium hydride dispersion (50% in mineral oil, 5.76g) was washed twice with dry petroleum ether (200ml) and suspended in dry benzene (400 ml). To this suspension was added dropwise dibutyl phosphonate (19.4 g) under reflux for 35 minutes and the mixture was refluxed for additional 2.5 hours. To the mixture was added 1-bromo-3-chloro-propane (23.63 g) and heating was continued for additional 7 hours under reflux with stirring. After cooling, the resultant mixture was washed twice with water (200 ml), dried over magnesium sulfate and concentrated under reduced pressure to give dibutyl 3-chloropropyl phosphonate (21.15 g) in the form of oily substance.
Infrared Absorption Spectrum (liquid film):
ν_{max} = 1270(shoulder), 1240 cm^{-1}
NMR Absorption Spectrum (neat):
Internal standard : TMS
δ(ppm)
0.91 (6H, t, J=7Hz)
1.2~2.2 (2H, t, J=6Hz)
3.65 (2H, t, J=6Hz)
3.96 (4H, quartet, J=7Hz)

(2) A mixture of 1,3-dibromopropane (305 g) and triethylphosphonate (47.5 g) was stirred at 150°C for 30 minutes. The resultant mixture was concentrated under reduced pressure to give diethyl 3-bromopropylphosphonate (77.7 g) in the form of oily substance.

Infrared Absorption Spectrum (liquid film):
ν_{max} = 1270, 1240, 1060, 1030, 970 cm^{-1}
NMR Absorption Spectrum (neat):
Internal standard : TMS
δ(ppm)
1.33 (6H, t, J=7Hz)
4.08 (4H, quintet, J=7Hz)

(3) 65% Sodium hydride dispersion in mineral oil (16.3 g) was washed twice with dry petroleum ether (150 ml) and suspended in tetrahydrofuran (400 ml). To the suspension was added diethyl phosphonate (55.2 g) at -8- -10°C, whereafter the mixture was stirred at ambient temperature for 1.5 hours. To the mixture was added 1-bromo- 3-chloropropane (126.0 g), whereafter the reaction mixture was stirred for 4 hours at ambient temperature. The resultant mixture was mixed with ethanol (50 ml) to give precipitates. The precipitates were filtered off and then the filtrate was concentrated under reduced pressure to remove the solvent. The residue was distilled at 35- 40°C under reduced pressure (12 mmHg) to remove 1-bromo- 3-chloropropane. Subsequently, the residue was redistilled at 110 - 120°C under reduced pressure (4 mmHg) to give oily diethyl 3-chloropropyl phosphonate (52.9 g).
I.R. (film) ν max: 1270 (shoulder), 1240, 1160 cm^{-1}
NMR: δ (ppm) in $CDCl_3$; 1.36 (6H, t, J=7Hz),
1.6 - 2.5 (4H, m), 3.65 (2H, t, J=6Hz),
4.16 (4H, quintet, J=7Hz).

(4) A mixture of 1,5-dibromopentane (500 g.) and triethylphosphite (72.0 g.) was stirred at 160°C for 40 minutes and then excess 1,5-dibromopentane was distilled off under reduced pressure to give oily diethyl 5-bromopentylphosphonate (129.6 g.).

N.M.R.
δ(ppm) in $CDC\ell_3$: 1.32 (6H, t, J=7Hz)
1.42 - 2.05 (8H, m)
3.39 (2H, t, J=7Hz)
4.05 (4H, m)

(5) A mixture of 1-bromo-3-chloro -2-methylpropane (95 g.) and triethyl phosphite (61.4 g.) was heated to reflux for 5.5 hours with stirring and then excess 1-bromo-3-chloro-2-methylpropane was distilled off under reduced pressure to give oily diethyl 3-chloro-2 -methylpropylphosphonate (48.3 g.).

N.M.R.
δ(ppm) in $CDC\ell_3$: 1.18 (3H, d, J=6Hz)
1.31 (6H, t, J=6Hz)
1.48 - 2.52 (3H, m)
3.58 (2H, d, J=5Hz)
4.12 (4H, m)

(ii) For halogenation:

(1)-1 Di-tert-butyl cis-1-propenyl phosphonate (15.0 g.) was added to a solution of potassium tert-butoxide in tert.-butyl alcohol (K: 250 mg., tert.-C_4H_9OH: 150 ml.) and then the mixture was stirred for 6 hours at 55 - 60°C. The resultant mixture was concentrated under reduced pressure and the residue was shaken with a mixture of ethyl acetate (400 ml.) and ice-water (100 ml.). The ethyl acetate layer was separated, washed with water (50 ml.), dried over magnesium sulfate and evaporated to dryness under reduced pressure to give oily residue (13.34 g.), which was distilled under reduced pressure to give oily di-tert.-butyl trans-l -propenylphosphonate (12 g.), b.p. 78 - 80°C/2mmHg.
I.R. (liquid film)
νmax: 1630, 1260, 1170 cm^{-1}
N.M.R.
δ(ppm) in $CDC\ell_3$: 1.45 (18H, s)
1.80 (3H, m)
5.67 (1H, m)
6.80 (1H, m)

(1)-2 To a solution of di-tert.- butyl trans-l-propenyl phosphonate (12.0 g.) in carbon tetrachloride (120 ml.) were added basic aluminum oxide (24.0 g.), N-bromosuccinimide (10.95 g.) and then dibenzoyl peroxide (1.4 g.). The mixture was heated to reflux for an hour and then stirred for 30 minutes with ice-cooling. The resultant mixture was filtered and the filtrate was evaporated to dryness under reduced pressure to give oily di-tert.-butyl 3-bromo-trans -l-propenylphosphonate (17.2 g.).

I.R. (liquid film)
υmax: 1630, 1260, 1170 cm^{-1}
N.M.R.
δ(ppm) in $CDC\ell_3$: 1.51 (18H. s)
4.01 (2H, d, J=7Hz)
5.95 (1H, m)
6.77 (1H, m)

(2) To a solution of diethyl trans-l -propenylphosphonate (32.04 g.) in carbon tetrachloride (320 ml.) were added N-bromosuccinimide (41.65 g.) and dibenzoylperoxide (2.8 g.). The reaction mixture was heated to reflux for 1.5 hours and stirred for 30 minutes with ice-cooling. Insoluble materials were removed off by filtration and the filtrate was concentrated under reduced pressure to give an oily residue (63.09 g.), which was subjected to a column chromatography on silicagel and eluted with chloroform. The eluates were evaporated to dryness under reduced pressure to give an oily diethyl 3-bromo-trans- l-propenylphosphonate (27.04 g.).

I.R. (liquid film)
υmax: 1630, 1240, 1160 cm^{-1}

N.M.R.
δ(ppm) in $CDC\ell_3$: 1.32 (6H, t, J=7Hz)
3.9 - 4.3 (6H, m)
5.93 (1H, m)
6.81 (1H, m)

(3) To a solution of dimethyl cis-l- propenylphosphonate (6.10 g.) in carbon tetrachloride (60 ml.) was added N-bromosuccinimide (7.97 g.). The reaction mixture was heated to reflux for 2 hours and then cooled to ambient temperature to give precipitates, which were filtered off. The filtrates were concentrated under reduced pressure to give an oily residue, which was subjected to a column chromatography on silica gel and eluted with a mixture of chloroform and ethyl acetate (8:2) to give dimethyl 3-bromo trans-l-p propenylphosphonic acid (4.94 g,).

I.R. (liquid film)
υmax: 1630, 1250, 1190 cm^{-1}

N.M.R.
δ(ppm) in $CDC\ell_3$: 3.71 (6H, d, J=10Hz)
4.00 (2H, m)
5.88 (1H, m)
6.82 (1H, m)

(iii) For dehydrohalogenation:

(1)-1 To a solution of diethyl allylphosphonate (5.34 g.) in carbon tetrachloride (107 ml.) was added dropwise a solution of bromine (5.04 g.) in carbon tetrachloride (10 ml.) under ice-cooling in the course of 15 minutes. The reaction mixture was stirred at ambient temperature for 2 hours. After washing twice with 5% aqueous thiosulfate solution (100 ml.) and then with water (100 ml.), the resultant mixture was dried over magnesium sulfate and evaporated to dryness under reduced pressure to give oily diethyl 2,3-dibromopropyl phosphonate (9.74 g.).

I.R. (liquid film)
υmax: 1250 (broad), 1160 cm^{-1}

N.M.R.
δ(ppm) in $CDC\ell_3$: 1.32 (6H, t, J=7Hz)
2.00 - 3.12 (2H, m)
3.50 - 4.63 (7H, m)

(1)-2 To a solution of diethyl 2,3-dibromopropyl phosphonate (3.34 g.) in tert.-butanol (10 ml.) was added dropwise a solution of potassium tert.-butoxide (K: 430 mg., tert.-C_4H_9OH: 14 ml.) at ambient temperature in the course of 15 minutes. The reaction mixture was stirred at the same temperature for 30 minutes. The resultant mixture was concentrated under reduced pressure and then the residue was shaken with a mixture of ethyl acetate (50 ml.) and water (30 ml.). The ethyl acetate layer was separated, washed with water (30 ml.), dried over magnesium sulfate and evaporated to dryness under reduced pressure to give an oily mixture of isomeric diethyl 3-bromo-propenylphosphonates (2.13 g.). An aliquot (1.86 g.) of which was

fractionated by subjecting to a column chromatography on silica gel (developing solvent: chloroform) into two fractions (i.e. fraction A and fraction B). The fraction A was evaporated to dryness under reduced pressure to give oily diethyl 3-bromo-cis -l-propenylphosphonate (10 mg.). The fraction B was evaporated to dryness under reduced pressure to give oily mixture (1.65 g.) of diethyl 3-bromo-2-propenyl phosphonate and diethyl 3-bromo-trans-l -propenylphosphonate (molar ratio: ca 1:1).

The structures of these isomeric products were determined by N.M.R. spectra as follows:

N.M.R.

δ(ppm) in $CDC\ell_3$

(a) diethyl 3-bromo-cis -l-propenylphosphonate:

1.34 (6H, t, J=7Hz)
3.9 - 4.35 (4H, m)
4.47 (2H, m)
5.69 (1H, m)
6.65 (1H, m)

(b) diethyl 3-bromo-2- propenylphosphonate:

1.32 (6H, t, J=7Hz)
2.80 (2H, d, d, J=23 and 7Hz)
3.9 - 4.25 (4H, m)
6.1 - 6.5 (2H, m)

(c) diethyl 3-bromo-trans-l-propenylphosphonate;

1.32 (6H, t, J=7Hz)
3.9 - 4.25 (6H, m)
5.95 (1H, m)
6.80 (1H, m)

(iv) For Halogenation (II)

(1)-(a) 47% Aqueous hydrobromic acid (82.8 g) was added dropwise to diethyl 2,3-epoxypropyl phosphonate (77.6 g) under ice-cooling and with stirring over a five minutes interval. After the stirring was continued for an hour under ice-cooling and for 3 hours at ambient temperature, the reaction mixture was extracted with ethyl acetate (500 ml). The ethyl acetate layer was separated, washed three times with saturated aqueous sodium bicarbonate (200 ml and 100 ml x 2) and twice with saturated aqueous sodium chloride solution (100 ml x 2), dried over magnesium sulfate and evaporated to dryness to give oily diethyl 3-bromo-2-hydroxypropylphosphonate (94.7 g) I.R. (liquid film)

υ_{max}: 3350, 1230, 1160 cm^{-1}

N.M.R.

δ(ppm) in $CDCl_3$: 1.33 (6H, t, J=7Hz)
1.90 - 2.33 (2H, m)
3.49 (2H, d, d, J=1 and 4 Hz)
3.88 - 4.48 (5H, m)

(1)-(b) To a mixture of diethyl 3-bromo-2- hydroxypropyl phosphonate (82.5 g) and p-toluenesulfonic acid (1.03 g) was added dropwise 3,4-dihydro-2H- pyrane (250 g) under ice-cooling and with stirring. After the reaction mixture was stirred at the same temperature for 10 minutes and at ambient temperature for 1.5 hours, the dihydropyrane was removed off by evaporation under reduced pressure to give a residue, which was dissolved in ethyl acetate (500 ml). The ethyl acetate solution was washed with saturated aqueous sodium bicarbonate solution (100 ml) and with saturated aqueous sodium chloride solution (100 ml), dried over magnesium sulfate and evaporated to dryness under reduced pressure to give oily diethyl 3-bromo-2 -(tetrahydro-2H-pyran -2-yloxy)propylphosphonate (138 g).

I.R. (liquid film)

ν_{max}: 1240, 1190 cm^{-1}

N.M.R.

δ(ppm) in $CDCl_3$: 1.42 (6H, t, J=7Hz)
1.75 (6H. m)
2.00 - 2.56 (2H, m)
3.45 - 4.40 (9H, m)
4.86 (1H, m)

(2) To a solution of diethyl 2,3-epoxypropyl phosphonate (0.97 g) in dichloromethane (2 ml) was added dropwise trimethylbromosilane (3.06 g) under ice-cooling and with stirring. After the stirring was continued for 30 minutes under ice-cooling and for 1.5

hours at ambient temperature, the reaction mixture was concentrated under reduced pressure to give an oily residue, which was dissolved in water (8 ml) and washed three times with chloroform (5 ml x 3). The aqueous layer was separated, adjusted to pH 5 with conc. aqueous ammonia and evaporated to dryness under reduced pressure to give a residue, to which was added ethanol (20 ml). Insoluble materials were removed by filtration. The filtrate was allowed to stand for 3 hours at ambient temperature to precipitate crystals, which were collected by filtration and dried on phosphorus pentoxide to give crystalline monoammonium salt of 3-bromo2-hydroxypropyl phosphonic acid (560 mg).

MP: 119 - 124°C (dec.)

Suitable working examples of some preparations of the starting compound (V) are illustrated more specifically as follows

(i) O-Aralkylation

(1) A solution of isobutyl N-hydroxycarbamate (40 g) in absolute ethanol (400 ml) was added dropwise to a solution of sodium ethoxide in absolute ethanol (Na : 6.9g, absolute C_2H_5OH : 500ml) at around 25°C, with stirring. To the mixture was added dropwise p-methoxybenzyl bromide (60 g) for 30 minutes with stirring below 30°C. After continuation of stirring at the ambient temperature for additional 14 hours, the solvent was distilled off under reduced pressure. To the oily residue was added water (500 ml), extracted with ethyl ether (500 ml), washed with 0.1N-NaOH, water, dried over magnesium sulfate and evaporated to dryness under reduced pressure to give an oil(62 g).

The oil (62 g) was subjected to column chromatography on silica gel with an eluent (a mixture of 100 parts of chloroform and one part of methanol by volume). Fractions containing object compound was collected and concentrated under reduced pressure to give isobutyl N-(p-methoxybenzyloxy) carbamate (20.0 g) in the form of oily substance.

Infrared Absorption Spectrum (liquid film):

ν_{max} = 3290, 1725 cm^{-1}

NMR Absorption Spectrum ($CDC1_3$):

Internal standard : TMS

δ(ppm)

0.89 (6H, d, J = 7Hz)
1.92 (1H, m)
3.71 (3H, s)
3.88 (2H, d, J=7Hz)
4.74 (2H. s)
6.70~40. (4H, m)
7.86 (1H, s)

(ii) Acylation

(1) A solution of tosyl chloride (156.7 g) in pyridine (240 ml) was added dropwise to a solution of p-methoxybenzyloxyamine (102.3 g) in pyridine (210 ml) for 2.5 hours under cooling at 0~5°C and the mixture was stirred overnight at ambient temperature. The solvent was distilled off under reduced pressure and the residue was dissolved in ethyl acetate (1 ℓ). The insoluble substances were filtered off, and the filtrate was washed three times with 2N hydrochloric acid, twice with water, dried over magnesium sulfate and evaporated to dryness under reduced pressure to give crystalline product, which was recrystallized from a mixture of ethylacetate and petroleum ether to give N-(p-methoxybenzyloxy) -p-toluenesulfonamide (162.2 g) in the form of crystals.

MP : 109~111°C

(2) Hydroxylamine. hydrochloride (312.8 g) was dissolved in a solution of sodium hydroxide (558.0 g) in water (3.6 liters) under ice-cooling and with stirring. To the solution was added dropwise ethyl chloroformate (1025.4 g) over a 1.5 hours interval under ice-cooling and with stirring. After the stirring was continued for additional 15 minutes the reaction mixture was extracted twice with methyl isobutyl ketone (3 liters and 1.5 liters). The extract was washed with water (1.5 liters) and dried over magnesium sulfate, which was removed by filtration and washed with methylisobutyl ketone (0.9 liters). The washings were combined with the filtrate, as obtained in the above. To the mixture was added dropwise a solution of potassium hydroxide (265.5 g) in ethanol (1.13 liters) to precipitate crystals under ice-cooling (0 - 5°C) and with stirring over a 40 minutes interval. The stirring was continued for half an hour at the same temperature to give crystalline mono potassium salt of ethyl N-ethoxycarbonyloxycarbamate (758.0 g)

MP: 169.5 - 170°C (dec.)

Suitable examples of some preparations of the starting compound (VII) are illustrated more specifically as follows.(1) Butyraldehyde oxime (4.52 g.) was added to an ethanolic solution of sodium ethoxide [prepared from 1.17 g of sodium and 100 ml. of absolute ethanol] at 5 to 10°C. To the mixture was added diethyl 3-bromo- propylphosphonate (12.69g.) The reaction mixture was stirred at ambient temperature for 22 hours and then evaporated to dryness under reduced pressure. The residue was dissolved in water and washed with ethyl acetate (20 ml.) The aqueous layer was separated, saturated with sodium chloride and extracted five times with chloroform. The combined chloroform extracts were washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated to dryness under reduced pressure to give oily diethyl 3-butylidene aminopropyl phosphonate-N-oxide (7.1 g.).

N.M.R. : δ(ppm) in $CDC\ell_3$; 0.98 (3H, t, J=7Hz),
1.32 (6H, t, J=7Hz),
1.1 - 2.6 (8H, m),
3.8 - 4.3 (6H, m),
6.8 (1H, t, J=7Hz)

(2) Octanal oxime (20.67 g.) was dissolved in a methanolic solution of sodium methoxide [prepared from 2.3g of sodium and 100 ml. of absolute methanol] at 5 to 10°C. To the solution was added dropwise diethyl 3-bromopropyl phosphonate (25.9 g.), whereafter the reaction mixture was stirred at ambient temperature for 2 hours and then heated to reflux for 2 hours with stirring. The resultant mixture was evaporated to dryness under reduced pressure and the residue was dissolved in water. The aqueous solution was saturated with sodium chloride and extracted with chloroform. The chloroform extracts were dried over magnesium sulfate and evaporated to dryness under reduced pressure to give oily diethyl 3-octylidene aminopropyl phosphonate-N-oxide (38.9 g.).

N.M.R. : δ(ppm) in $CDC\ell_3$; 0.88 (3H, t, J=7Hz),
1.32 (6H, t, J=7Hz),
1.2 - 2.6 (16H, m),
3.8 - 4.3 (6H, m),
6.80 (1H, t, J=7Hz)

The following examples are given for illustrating this invention.

Examples for the Formation of C-P bond

(1) 50% Sodium hydride dispersion in mineral oil (5.7g) was washed with dry petroleum ether (100 ml) and suspended in dry benzene (400 ml). Dibutyl phosphonate (19.2g) was added dropwise to the suspension under reflux in the course of 30 minutes and then the mixture was refluxed with stirring for additional 3 hours. To the mixture, there was added dropwise a solution of N-(3-bromopropyl) -N-(p-methoxy benzyloxy)-p- toluenesulfonamide (38.4g) in dry benzene (140 ml) in the course of 40 minutes under reflux and the reaction mixture was refluxed with stirring for additional 5 hours. The resultant mixture was washed with water, dried over magnesium sulfate and concentrated under reduced pressure to give an oily residue (46g). The residue was subjected to column chromatography on silica gel with an eluent (a mixture of 20 parts of chloroform and one part of ethyl acetate by volume). The fractions containing the object compound were collected and concentrated under reduced pressure to give dibutyl 3-[N-(p-methoxy benzyloxy)-N- tosylamino] propyl phosphonate (29.5g) in the form of an oily substance.

Infrared Absorption Spectrum (liquid film) :
ν_{max} = 1620, 1600, 1370, 1360, 1260, 1170 cm^{-1}

NMR Absorption Spectrum ($CDC1_3$) :
δ *(ppm)*
0.92 (6H, t, J=7Hz)
1.05~2.00 (8H, m)
2.37 (3H, s)
2.94 (2H, m)
3.78 (3H, s)
4.02 (4H, quartet, J=6Hz)
5.04 (2H, s)
6.89 (2H, d, J=8Hz)
7.32 (4H, m)
7.74 (2H, d, J=8Hz)

(2) 50% Sodium hydride dispersion in mineral oil (3.87g) was washed twice with dry petroleum ether (100 ml) and suspended in dry benzene (250 ml). Dibutyl phosphonate (13.2g) was added dropwise to the suspension in the course of 15 minutes under reflux and

then the mixture was refluxed with stirring for additional 3 hours. To the mixture, there was added dropwise a solution of isobutyl N-(p-methoxy benzyloxy)-N-(3 -bromopropyl)carbamate (16.6g) in dry benzene (50 ml) in the course of 35 minutes under reflux and the reaction mixture was refluxed with stirring for additional 8 hours. The resultant mixture was washed with water, dried over magnesium sulfate and then concentrated under reduced pressure to give an oily residue (23.07g). The residue was subjected to column chromatography on silica gel with an eluent (a mixture of 100 parts of chloroform and one part of methanol by volume). The fractions containing the object compound were collected and concentrated under reduced pressure to give dibutyl 3-[N-isobutoxy carbonyl-N-(p-methoxybenzyloxy) amino]propyl phosphonate (15.6g) in the form of an oily substance.

Infrared Absorption Spectrum (liquid film) :

ν_{max} = 1720(shoulder), 1710, 1610, 1590, 1255, 1030 cm^{-1}

NMR Absorption Spectrum ($CDCl_3$) :

δ(ppm)
0.95 (12H, m)
1.2~2.1 (13H, m)
3.50 (2H, t, J=6Hz)
3.79 (3H, s)
3.95~4.23 (6H, m)
4.78 (2H, s)
6.90 (2H, d, J=8Hz)
7.33 (2H, d, J=8Hz)

(3) 50% Sodium hydride dispersion in mineral oil (12.2g) was washed with dry petroleum ether (100 ml) and suspended in dry benzene (600 ml). Dibutyl phosphonate (40.0g) was added dropwise to the suspension in the course of 30 minutes under reflux and then the mixture was refluxed with stirring for additional 3.5 hours. To the reaction mixture, there was added dropwise a solution of N-(3-bromopropyl) -N-benzyloxy-p- toluenesulfonamide (64.1g) in dry benzene (250 ml) under reflux in the course of an hour, and then the reaction mixture was refluxed with stirring for additional 5 hours. The resultant mixture was washed with water, dried over magnesium sulfate and concentrated to give an oily residue (77.0g). The residue was subjected to column chromatography on silica gel with an eluent (chloroform). The fractions containing the object compound were collected and concentrated under reduced pressure to give dibutyl 3-(N-benzyloxy-N -tosylamino) propylphosphonate (58.7g) in the form of an oily substance.

NMR Absorption Spectrum ($CDcl_3$) :

δ(ppm)
0.92 (3H, t, J=8Hz)
1.2~2.0 (16H, s)
2.38 (3H, s)
2.94 (2H, t, J=6Hz)
3.99 (4H, q, J=7Hz)
5.09 (2H, s)
7.2~7.5 (7H, m)
7.71 (2H, d, J=8Hz)

(4) 50% Sodium hydride dispersion in mineral oil (630 mg) was washed twice with dry petroleum ether (20 ml) and suspended in dry N,N-dimethyl formamide (20 ml). Diethyl phosphonate (1.52g) was added dropwise to the suspension at 80°C in the course of 5 minutes and then the mixture was stirred at the same temperature for 30 minutes. To the mixture, there was added N-(p-methoxybenzy loxy)-N-(3- chloropropyl)-p -toluene-sulfonamide (3.84 g) at 80°C for 5 minutes and then the reaction mixture was refluxed with stirring for 2.5 hours. The resultant mixture was concentrated under reduced pressure to give an oily residue. To the residue were added water (200 ml) and ethyl acetate (200 ml). The ethyl acetate layer was separated, dried over magnesium sulfate and then concentrated under reduced pressure to give diethyl 3-[N-(p-methoxy benzyloxy)-N)tosy lamino]propyl phosphonate (3.79g) in the form of an oily substance.

Infrared Absorption Spectrum (liquid film) :
ν_{max} = 1610, 1590, 1250 cm^{-1}
NMR Absorption Spectrum ($CDCl_3$) :
δ(ppm)
1.29 (6H, t, J=7Hz)
1.6~2.0 (4H, m)
2.34 (3H, s)
2.90 (2H, m)
3.75 (3H, s)
4.06 (4H, quintet, J=7Hz)
5.00 (2H, s)
6.85 (2H, d, J=8Hz)
7.28 (4H, m)
7.69 (2H, d, J=8Hz)

(5) 50% Sodium hydride dispersion in mineral oil (3.53g) was washed twice with dry petroleum ether (50 ml) and suspended in dry N,N-dimethylformamide (60 ml). Diethyl phosphonate (8.47g) was added dropwise to the suspension at 80°C in the course of 25 minutes and the mixture was stirred at the same temperature for additional 25 minutes. Subsequently, to the mixture was added N-(3-chloropropyl) -N-benzyloxy-p -toluene-sulfonamide (20g), and then the reaction mixture was refluxed with stirring for 15 minutes. The reaction mixture was cooled until 120°C and stirred at the same temperature for 2 hours. The resultant mixture was concentrated under reduced pressure to give a residual oil, which was dissolved in water (300 ml). The solution was extracted twice with ethyl acetate (400 ml). The combined ethyl acetate layer was dried over magnesium sulfate and concentrated under reduced pressure to give a residual oil (28.9g). The residual oil was subjected to column chromatography with an eluent (chloroform). Fractions containing the object compound were collected and concentrated under reduced pressure to give diethyl 3-(N-benzyloxy -N-tosylamino) propylphosphonate (25.5g) in the form of an oily substance.
Infrared Absorption Spectrum (liquid film) :
ν_{max} = 1590, 1350, 1240 cm^{-1}
NMR Absorption Spectrum ($CDCl_3$) :
δ(ppm)
1.28 (6H, t, J=7Hz)
1.6~2.0 (4H, m)
2.35 (3H, s)
2.89 (2H, m)
4.05 (4H, quintet, J=7Hz)
5.07 (2H, s)
7.2~7.4 (7H, m)
7.71 (2H, d, J= d, J=9Hz)

(6) A mixture of N-benzyloxy-N -(2-bromoethyl)-p- toluenesulfonamide (16.2 g.) and triethyl phosphite (21.0 g.) was stirred at 160°C for 10 hours and then cooled to ambient temperature. To the reaction mixture was added ethyl acetate and water. The ethyl acetate layer was separated, washed with water, dried over magnesium sulfate and concentrated under reduced pressure to give an oily residue (20.5 g.). A small volume of isopropyl ether was added to the residue to give crystals, which was separated by filtration and dried to give crystalline diethyl 2-(N-benzyloxy -N-tosylamino) ethylphosphonate (10.6 g.). The object compound (2.1 g.) was also recovered from the mother liquor by subjecting to a column chromatography on silicagel (developing solvent: chloroform)
M.p. 78 - 80°C.

N.M.R.
δ(ppm) in $CDC\ell_3$: 1.25 (6H, t, J=7Hz)
1.85 (2H, m)
2.36 (3H, s)
3.14 (2H, m)
4.01 (4H, m)
5.06 (2H, s)
7.14 (5H, s)
7.38, 7.80 } (4H, AB_q, J_{AB}=8Hz)

Example for Formation of C-N bond

(1) N-(p-methoxy benzyloxy)-p-toluene sulfonamide (9.21g) was added to a solution of sodium ethoxide in absolute ethanol (Na : 690 mg, absolute C_2H_5OH : 80 ml) at 70°C and the mixture was stirred at the same temperature for an hour. To the mixture was added dropwise diethyl 3-bromopropyl phosphonate (7.77g), whereafter the reaction mixture was refluxed with stirring for 6 hours. The resultant mixture was cooled to give precipitates, which were filtered off. The filtrate was concentrated under reduced pressure to give a residue. To the residue, there were added ethyl acetate (100 ml) and water (50 ml). The ethyl acetate layer was separated and washed twice with water (50 ml), dried over magnesium sulfate and then concentrated under reduced pressure to give an oily residue (13.85g). The residue was subjected to column chromatography on silica gel with an eluent (a mixture of 5 parts of chloroform and one part of methanol by volume). Fractions containing the object compound were collected and concentrated under reduced pressure to give diethyl 3-[N-(p-methoxybenzyloxy)-N-tosylamino] propylphosphonate (10.50g) in the form of an oily substance.

Infrared Absorption Spectrum (liquid film) :
ν_{max} = 1610, 1600, 1370, 1350, 1255, 1170 cm^{-1}

NMR Absorption Spectrum ($CDCl_3$) :
δ(ppm)
1.28 (6H, t, J=7Hz)
1.55~2.05 (4H, m)
2.37 (3H, s)
2.92 (2H, t, J=6Hz)
3.76 (3H, s)
4.07 (4H, quintet, J=7Hz)
5.01 (2H, s)
6.85 (2H, d, J=9Hz)
7.30 (4H, m)
7.71 (2H, d, J=9Hz)

(2) A solution of ethyl N-benzyloxy carbamate (7.80 g.) in absolute ethanol (5 ml.) was added dropwise to a solution of sodium ethoxide in absolute ethanol [Na: 920 mg., absolute C_2H_5OH: 100 ml.] at 70°C and the mixture was stirred at the same temperature for 30 minutes. To the mixture was added dropwise dibutyl 3-chloropropyl phosphonate (10.8 g.), whereafter the reaction mixture was refluxed with stirring for 22 hours. The resultant mixture was cooled to give precipitates, which were filtered off. The filtrate was concentrated under reduced pressure to give a residue. To the residue was added ethyl acetate (100 ml.) and water (50 ml.). The ethyl acetate layer was separated, dried over magnesium sulfate and then concentrated under reduced pressure to give an oily residue (16.6 g.). The residue was subjected to column chromatography on silica gel with an eluent (chloroform). Fractions containing the object compound were collected and concentrated under reduced pressure to give oily dibutyl 3-(N-benzyloxy-N- ethoxycarbonylamino)- propylphosphonate (7.33g.).

I.R. (film) ν_{max} : 1700, 1380, 1270, 1240, 1170 cm^{-1}
N.M.R.: δ(ppm) in $CDCl_3$;
0.90 (6H, t, J=7Hz)
1.2-2.1 (15H, m)
3.52 (2H, t, J=6Hz)
3.99 4H, quartet, J=7Hz)
4.20 (2H, quartet, J=7Hz)
4.83 (2H, s)
7.34 (5H, m)

(3) 50% Sodium hydride dispersion in mineral oil (580 mg.) was washed with dry petroleum ether (10 ml.) and suspended in dry N,N-dimethyl formamide (20 ml.). To the suspension was added N-benzyloxy -p-toluene sulfonamide (2.77 g.) at 70°C, whereafter the mixture was stirred at 70°C for 30 minutes. To the mixture, there was added dibutyl 3-chloropropylphosphonate (2.71 g.) at 74°C, whereafter the reaction mixture was stirred at 100°C for 30 minutes and refluxed with stirring for 1.5 hours. The reaction mixture was concentrated under reduced pressure. The oily residue was diluted with ethyl acetate and water. Ethyl acetate layer was separate. The aqueous layer was extracted with ethyl acetate. The combined ethyl acetate layer was dried over magnesium sulfate and concentrated under reduced pressure to give oily dibutyl 3-(N-benzyloxy -N-tosylamino) propylphosphonate (3.12 g.).

I.R. (film) ν_{max}: 1600, 1250, 1170 cm^{-1}
N.M.R.: δ(ppm) in $CDCl_3$;
0.91 (6H, t, J=7Hz)
1.0-2.0 (12H, m)
2.38 (3H, s)
2.90 (2H, m)
4.01 (4H, quartet, J=7Hz)
5.11 (2H, s)
7.15-7.50 (7H, m)
7.74 (2H, d, J=9Hz)

(4) 65% Sodium hydride dispersion in mineral oil (810 mg.) was washed twice with dry petroleum ether (50 ml.) and suspended in dry N,N-dimethyl formamide (20 ml.). To the suspension was added N-benzyloxy -p-toluenesulfonamide (5.54g.) at ambient temperature, whereafter the mixture was stirred at 40°C for 15 minutes. To the mixture was added diethyl 3-chloropropyl phosphonate (4.27g, whereafter the reaction mixture was stirred at 70°C for 2 hours and at 90°C for one hour. The resultant mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (80 ml.) and water (30 ml.). The ethyl acetate layer was separated, washed twice with water (20 ml.), dried over magnesium sulfate and concentrated under reduced pressure to give oily diethyl 3-(N-benzyloxy -N-tosylamino)propyl phosphonate (8.98 g.).
I.R. (film ν_{max} : 1590, 1350, 1240 cm^{-1}
N.M.R.: δ(ppm) in $CDCl_3$;
1.28 (6H, t, J=7Hz)
1.6 -2.0 (4H, m)
2.35 (3H, s)
2.89 (2H, m)
4.05 (4H, quintet, J=7Hz)
5.07 (2H, s)
7.2-7.4 (7H, m)
7.71 (2H, d, J=9Hz)

(5) Hydroxylamine hydrochloride (13.9 g.) was dissolved in hot methanol (70 ml.). To this solution was added a solution of sodium methoxide in absolute methanol [Na: 4.6 g., absolute CH_3OH:70 ml.] over a 15-minutes interval in an atmosphere of nitrogen, whereafter the mixture was stirred at ambient temperature for 30 minutes. The resulting sodium chloride was separated by filtration and washed with methanol (10 ml.). To the combined solution of the filtrate and washings was added 3-bromopropylphosphonic acid (4.06 g.) with stirring in an atmosphere of nitrogen, and the resultant mixture was then concentrated under reduced pressure at ambient temperature over 3 hours interval to give residue (10.4 g.), which was dissolved in water (5 ml.). The solution was passed through a column of anion exchange resin, Amberlite IRA400 (200 ml.) (trade name, maker: Rohm & Haas Co.). After the column was washed with water (1 ℓ), the object compound was eluted with 1N hydrochloric acid (500 ml.). Fractions containing the object compound were collected and concentrated under reduced pressure to give residue (4.01 g.), which was passed through a column of cation exchange resin, Amberlite IR120B (150 ml.) (trade name, maker: Rohm & Haas Co.). After the column was washed with water (1 ℓ), the object compound was eluted with 1N hydrochloric acid (500 ml.). Fractions containing the object compound were collected and concentrated under reduced pressure to give residue (2.48 g.), which was dissolved in water (5 ml.). The aqueous solution was adjusted to pH 4 with sodium bicarbonate, whereafter the mixture was allowed to stand overnight to give crystalline 3-(N-hydroxyamino) propylphosphonic acid (1.47 g.)
mp: 151-154°C (dec.).

(6) 50% Sodium hydride dispersion in mineral oil (810 mg) was washed with dry petroleum ether (10 ml) and suspended in dry N,N-dimethylformamide (15 ml). To this suspension was added dropwise a solution of methyl N-methoxy carbamate (1.47 g) in N,N-dimethyl formamide (3 ml) under ice-cooling. The mixture was stirred at the same temperature for 15 minutes and then at ambient temperature for an hour. To reaction mixture was added dropwise diethyl 3-bromopropyl phosphonate (3.63 g) and the mixture was stirred at ambient temperature for 45 minute and at 60°C for 45 minutes. Subsequently, the reaction mixture was concentrated under reduced pressure to give an oily residue, to which was added 3% hydroxhloric acid (40 ml). The resultant mixture was extracted five times with ethyl acetate (50 ml). The combined ethyl acetate layer was dried over magnesium sulfate and concentrated under reduced pressure to give oily diethyl 3-(N-methoxy -N-methoxycarbonylamino) propylphosphonate (4.12 g).

I.R. (liquid film)
ν_{max} : 1720, 1450, 1380, 1280, 1230, 1195, 1170, 1100, 1110, 965 cm^{-1}
N.M.R.
δ(ppm) in $CDC\ell_3$; 1.30 (6H, t, J=7Hz), 1.5 - 2.2 (4H, m), 3.55 (2H, t, J=6Hz), 3.62 (3H, s), 3.73 (3H, s), 4.08 (4H, quintet, J=7Hz)

(7) To a solution of diethyl 3-chloropropyl phosphonate (430.6 g) in dry N,N-dimethyl formamide (2.25 ℓ) was added potassium salt of ethyl N-ethoxycarbonyloxy carbamate (429.2 g). This mixture was stirred at 64 - 66°C for three hours. After the resulting potassium chloride was removed by filtration, the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (2.0 ℓ) and washed with water (4.0 ℓ). The aqueous layer was extracted twice with ethyl acetate (1.2 and 0.8 ℓ). The combined ethyl acetate layer was washed with saturated aqueous sodium chloride solution (1.5 ℓ), dried over magnesium sulfate and concentrated under reduced pressure to give oily diethyl 3-(N-ethoxycarbonyl -N-ethoxycarbonyl oxyamino)- propylphosphonate (643.7 g).
I.R. (liquid film)
ν_{max} : 1780, 1730, 1720(Sh) cm^{-1}
N.M.R.
δ(ppm) in $CDCl_3$; 1.1 - 1.5 (12H, m), 1.6 - 2.1 (4H, m), 3.74 (2H, t, J=6Hz), 3.95 - 4.45 (8H, m)

(8) To a solution of diethyl 5-bromopenty phosphonate (28.7 g.) in dry N,N-dimethylformamide (144 ml.) was added potassium salt of ethyl N-ethoxycarbonyl oxycarbamate (21.5 g.). This mixture was stirred at 30°C for an hour and then poured into ice water (600 ml.). The resultant mixture was extracted twice with ethyl acetate (200 ml. and 100 ml.). The combined ethyl acetate layer was washed four times with water (100 ml.) and dried over magnesium sulfate to give an oily diethyl 5-(N-ethoxycarbonyl -N-ethoxycarbonyl oxyamino)pentyl phosphonate (36.2 g.).
N.M.R.
δ(ppm) in $CDC\ell_3$; 1.14 - 1.48 (12H, m), 1.08 - 2.08 (8H, m), 3.64 (2H, t, J=6Hz), 3.88 - 4.46 (8H. m)

(9) To a solution of di-tert-butyl 3-bromoptrans-l-propenyl -phosphonate (17.1 g.) in dry N,N-dimethylformamide (55 ml.) was added potassium salt of ethyl N-ethoxycarbony loxycarbamate (11.03 g.). The reaction mixture was stirred for 10 minutes under ice-cooling and for 1.5 hours at ambient temperature. The reaction mixture was poured into ice water (400 ml.) and then the resultant mixture was extracted three times with ethyl acetate (300 ml., 200 ml. and 100 ml.). The combined ethyl acetate layer was washed three times with water (100 ml.), dried over magnesium sulfate and then concentrated under reduced pressure to give an oily residue (20.23 g.). The residue was subjected to column chromatography on silica gel (200 g.) [developing solvent : a mixture of chloroform and ethyl acetate (4:1)]. The fractions containing the object compound were collected and concentrated under reduced pressure to give an oily di-tert-butyl 3-(N-ethoxycarbonyl -N-ethoxycarbonyloxy -amino)-trans-l -propenylphosphonate (8.84 g.).
I.R. (liquid film)
ν_{max} : 1790, 1730 (broad), 1640, 1250 (broad), 1170 cm^{-1}
N.M.R.
δ(ppm) in $CDC\ell_3$: 1.20 - 1.40 (6H, m), 1.46 (18H, s), 4.10 - 4.45 (6H, m), 5.92 (1H, m), 6.54 (1H, m)

(10) To a solution of dimethyl 3-bromo-trans -l-propenylphosphonate (5.34 g.) in N,N-dimethylformamide (25 ml.) was added potassium salt of ethyl N-ethoxy-carbonyloxycarbamate (5.01 g.). After the reaction mixture was stirred for 10 minutes under ice-cooling and for 50 minutes at ambient temperature, the mixture was

poured into ice water (250 ml.). The resultant mixture was extracted three times with ethyl acetate (200 ml. and 100 ml. x 2). The combined ethyl acetate layer was washed with water (100 ml.), dried over magnesium sulfate and then concentrated under reduced pressure to give an oily residue (4.72 g.). The residue was subjected to a column chromatography on silica gel (30 g.) (developing solvent: chloroform) to give oily dimethyl 3-(N-ethoxycarbonyl -N-ethoxycarbony loxyamino)-trans-l -propenylphosphonate (4.07 g.).

I.R. (liquid film)

ν_{max} : 1790, 1720, 1640, 1250 (broad) cm^{-1}

N.M.R.

δ(ppm) in $CDC\ell_3$: 1.15 - 1.45 (6H, m),
3.72 (6H, d, J=12Hz)
4.0 - 4.5 (6H, m)
5.94 (1H, m)
6.85 (1H, m)

(11) A solution of diethyl 3-bromo-trans -l-propenylphosphonate (23.83 g.) in N,N-dimethylformamide (50 ml.) was added dropwise to a suspension of ethyl N-ethoxycarbony loxycarbamate (19.94 g.) in N,N-dimethylformamide (100 ml.) at -25 ~ -30°C in the course of 20 minutes. The reaction mixture was stirred at -20 - -30°C for an hour and at -5 ~ -10°C for an hour. Subsequently, the resultant mixture was poured into a mixture of water (1 liter) and ethyl acetate (0.7 ℓ). The ethyl acetate later was separated and the aqueous layer was extracted twice with ethyl acetate (300 ml.). The combined ethyl acetate layer was washed with water (300 ml.), dried over magnesium sulfate and concentrated under reduced pressure to give an oily residue (28.89 g.), which was subjected to a column chromatography on silica gel [Developing solvent : a mixture of chloroform and ethyl acetate (4:1)]. The eluate was concentrated under reduced pressure to give oily diethyl 3-(N-ethoxycarbonyl -N-ethoxycarbonyloxy -amino)-trans -l-propenylphosphonate (13.80 g.).

I.R. (liquid film)

ν_{max} : 1795, 1730, 1640, 1210 (broad), 1170 cm^{-1}

N.M.R.

δ(ppm) in $CDC\ell_3$: 1.10 - 1.45 (12H, m)
3.83 4.50 (10H, m)
5.95 (1H, m)
6.74 (1H, m)

(12) A mixture of diethyl 3-chloro-2-methylpropylphosphonate (22.8 g.), potassium salt of ethyl N-ethoxycarbonyloxycarbamate (21.5 g.) and dry N,N-dimethylformamide (114 ml.) was stirred at 80 - 85°C for 3 hours and then concentrated under reduced pressure to give an oily residue, to which was added a mixture of water (100 ml.) and ethyl acetate (100 ml.). The ethyl acetate layer was separated and the resultant aqueous layer was saturated with sodium chloride and extracted again with ethyl acetate (50 ml.). The combined ethyl acetate layer was washed with aqueous solution saturated with sodium chloride, dried over magnesium sulfate and concentrated under reduced pressure to give oily diethyl 3-(N-ethoxycarbonyl -N-ethoxycarbonyloxyamino)-2- methylpropylphosphonate (30.2 g.)

N.M.R.

δ(ppm) in $CDC\ell_3$: 1.03 - 1.53 (15H, m)
1.46 - 2.53 (3H, m)
3.58 (2H, d, J=6Hz)
3.83 - 4.50 (8H, m)

(13) To a solution of hydroxylamine hydrochloride (55.6 g.) in water (100 ml.) were added solution of sodium hydroxide (32.0 g.) in water (75 ml.) under ice-cooling and then methanol (75 ml.). To this solution was added dropwise diethyl 3-bromopropylphosphonate (25.5 g.), whereafter the mixture was warmed at 40 - 45°C for 3 hours with stirring. The methanol was distilled off under reduced pressure. The resultant aqueous solution was adjusted to pH 8 with sodium bicarbonate, washed three times with benzene which were discarded (once with 150 ml. and twice with 100 ml. portions) and then extracted with three 150 ml. portions of chloroform. The chloroform extracts were combined, dried over magnesium sulfate and evaporated to dryness under reduced pressure to give oily diethyl 3-(N-hydroxyamino) propylphosphonate (13.05 g.).

I.R.. (liquid film)
ν_{max} : 3350 (broad), 1240, 1170 cm^{-1}
N.M.R.
δ ppm in $CDCl_3$; 1.33 (6H, t, J=7Hz)
1.5 - 2.2 (4H, m)
2.90 (2H, t, J=7Hz)
4.13 (4H, quintet, J=7Hz)
5.94 (2H, broad s)

(14) To a solution of diethyl 3-bromo-2- (tetrahydro-2H-pyran-2 -yloxy)propylphosphonate (134.4 g.) in N,N-dimethylformamide (880 ml.) was added potassium salt of ethyl N-ethoxycarbonyloxy carbamate (88.45 g.) under ice-cooling, and the mixture was stirred at ambient temperature for half an hour, and then for additional 2.4 hours at 50 to 60°C.

The solvent was distilled off under reduced pressure.

The residue was dissolved in water (1300 ml.) and then extracted twice with ethyl acetate (1000 ml. and 800 ml.). The combined extracts were washed twice with a saturated aqueous sodium chloride solution (500 ml. and 300 ml.), dried over magnesium sulfate and evaporated to dryness under reduced pressure to give an oily residue (143.2 g.), which was subjected to column chromatography on silica gel (700 g.) and fractionated by elution with a mixture of chloroform and ethyl acetate (the ratio was gradually changed from 9 : 1 to 1 : 1 v/v respectively) and then ethyl acetate. The fractions containing an object compound were combined and evaporated to dryness under reduced pressure to give oily diethyl 3-(N-ethoxycarbonyl -N-ethoxycarbonyl oxyamino)-2-(tetrahydro -2H-pyran-2 -yloxy)propylphosphonate (62.6 g.).

I.R. (liquid film)
ν_{max} : 1780, 1730, 1220, 1170 cm^{-1}
N.M.R.
δ ppm in $CDCl_3$; 1.28 - 1.57 (12H, m)
1.72 (6H, m)
2.00 to 2.60 (2H, m)
3.45 to 4.58 (13H, m)
4.88 (1H, m)

Additionally diethyl 3-(N-ethoxycarbonyl -N-hydroxyamino)- 2-(tetrahydro-2H-pyran -2-yloxy)propylphosphonate (21.8 g.) was obtained from the later fractions of ethyl acetate eluates.

I.R. (liquid film)
ν_{max} : 3200, 1780, 1730, 1230, 1170 cm^{-1}
N.M.R.
δ ppm in $CDCl_3$; 1.18 - 1.52 (9H, m)
1.68 (6H, m)
1.90 - 2.68 (2H, m)
3.42 - 4.58 (11H, m)
4.83 (1H, m)

(15) A mixture of diethyl 3-(N-ethoxycarbonyl -N-ethoxycarbonyl -oxyamino)-2-(tetrahydro -2H-pyran-2-yloxy) propylphosphonate (54.0 g.), ethanol (100 ml.) and 0.1N hydrochloric acid (100 ml.) was stirred for 4 hours at ambient temperature. After the reaction was completed, the ethanol was distilled off from the reaction mixture under reduced pressure to give an aqueous solution, which was extracted three times with ethyl acetate (200 ml. once and 50 ml. twice). The combined extracts were washed with a saturated sodium chloride aqueous solution, dried over magnesium sulfate, and evaporated to dryness under reduced pressure to give oily diethyl 3-(N-ethoxycarbonyl-N-ethoxycarbonyloxyamino) -2-hydroxypropylphosphonate (39.25 g.).

I.R. (liquid film)
ν_{max} : 3350, 1780, 1720, 1220, 1020 cm^{-1}
N.M.R.
δ ppm in $CDCl_3$: 1.1 - 1.5 (12H, m)
1.90, 2.20 (2H, d, d, J=6Hz, 18Hz)
3.4 - 3.8 (2H, m)
3.8 - 4.5 (9H, m)

Example for Formation of hydroxyamino function

(1) A mixture of diethyl 3-(N-butylideneamino)propylphosphonate-N-oxide (6.5 g), acetic

acid (20 ml) and conc. hydrochloric acid (20 ml) was refluxed with stirring for 5 hours. The resultant solution was concentrated under reduced pressure to give a residue, which was dissolved in water, and washed with ethyl acetate. After treatment with activated charcoal, the aqueous layer was concentrated under reduced pressure. The resulting residue was dissolved in a small volume of ethanol, and insoluble materials were removed by filtration. The filtrate was concentrated under reduced pressure to give a residue, which was dissolved in water (8 ml). The solution was adjusted to pH 4.0 with sodium bicarbonate and concentrated under reduced pressure to give an oil (4.5 g), which was dissolved in water (8 ml) and allowed to stand overnight at 5°C. The resulting crystals were separated by filtration and washed with a small volume of 50% aqueous ethanol to give crystalline 3-(N-hydroxyamino) propylphosphonic acid (0.48 g). Mp 161 - 168°C (dec.)

(2) A mixture of diethyl 3-(N-octylideneamino)-propylphosphonate-N-oxide (16.7 g), acetic acid (45 ml) and conc. hydrochloric acid (45 ml) was refluxed with stirring for 6.5 hours. The resultant mixture was concentrated under reduced pressure to give a residue, which was dissolved in a small volume of water. The aqueous solution was washed with ethyl acetate, treated with activated charcoal and concentrated under reduced pressure to give a residue, which was dissolved in a small volume of ethanol. After insoluble materials were removed by filtration, the filtrate was evaporated to dryness and the residue was dissolved in a small amount of water. This solution was passed through a column packed with anion exchange resin Amberlite IR 400 (OH-type) (trade name, made by Rohm & Haas Co.) The object compound was eluted with 1N hydrochloric acid. The eluate was concentrated under reduced pressure to give an oil (4.5 g), which was passed through a column packed with cation exchange resin, Amberlite IR 120B (H-type) (trade name, made by Rohm & Haas Co.) and then the object compound was eluted with 1N hydrochloric acid. The eluate was concentrated under reduced pressure to give an oil (3.0 g), which was dissolved in water (4 ml). The aqueous solution was adjusted to pH 4.0 with sodium bicarbonate and allowed to stand overnight at 5°C to give crystals, which were separated by filtration and dried to give crystalline 3-(N-hydroxyamino) propylphosphonic acid (1.0 g). The crystals were recrystalized from water (4 ml) to give purified 3-(N-hydroxyamino)propylphosphonic acid (0.42 g). Mp 159 - 162°C (dec.)

Example for Hydrolysis (I)

(1) A mixture of dimethyl 3-(N-ethoxycarbonyl -N-ethoxy -carbonyloxyamino)-trans -l-propenylphosphonate (3.70 g.) and trimethylbromosilane (8.71 g.) was stirred for 30 minutes under ice-cooling and for 30 minutes at ambient temperature. Subsequently, the reaction mixture was concentrated under reduced pressure to give a residue. To the residue was added water (25 ml.). After the mixture was stirred for an hour at ambient temperature, the mixture was washed three times with chloroform (10 ml.), and then concentrated under reduced pressure to give oily 3-(N-ethoxycarbonyl -N-ethoxycarbonyloxyamino)-trans-l -propenylphosphonic acid (2.80 g.). Furthermore, the combined chloroform layer was extracted with water (20 ml.). The aqueous layer was washed twice with chloroform (5 ml.) and concentrated under reduced pressure to recover the same object compound (0.43 g.).

I.R. (liquid film)

ν_{max} : 1780, 1710 (broad), 1640, 1220 (broad) cm^{-1}

N.M.R.

δ (ppm) in D_2O : 1.2 - 1.4 (6H, m)
4.04 - 4.46 (6H, m)
6.03 (1H, m)
6.55 (1H, m)

(2) Trimethylbromosilane (21.18 g.) was added to diethyl 3-(N-ethoxycarbonyl -N-ethoxycarbony loxyamino)-trans -l-propenyl phosphonate (12.2 g.) under ice-cooling. The mixture was stirred at ambient temperature for 3 hours and then concentrated under reduced pressure to give a residue, which was dissolved in water (30 ml.). The solution was stirred at ambient temperature for 30 minutes and then washed three times with chloroform (10 ml.). The aqueous layer was separated and concentrated under reduced pressure to give oily 3-(N-ethoxycarbonyl-N -ethoxycarbonyloxyamino) -trans-l-propenyl phosphonate (5.90 g.). Furthermore, the same compound (3.58 g.) was recovered from the combined chloroform layer by extracting it with water, washing the aqueous extract with chloroform and concentrating it under reduced pressure.

I.R. (liquid film)

ν_{max} : 1780, 1710 (broad), 1640, 1220 (broad) cm^{-1}

N.M.R.

δ ppm) in D_2O : 1.2 - 1.4 (6H, m)
4.04 - 4.46 (6H, m)
6.03 (1H, m)
6.55 (1H, m)

(3) A mixture of diethyl 3-(N-hydroxyamino) propylphosphonate (12.9 g.), acetic acid (65 ml.) and 1N hydrochloric acid (130 ml.) was heated to reflux with stirring for 8 hours and then was concentrated under reduced pressure to remove off acetic acid. The concentrate was decolorized by treating with an activated charcoal and evaporated to dryness under reduced pressure to give an oily residue (9.5 g.), which was dissolved in water (30 ml.) and adjusted to pH 4 with sodium bicarbonate (ca. 4.2 g.) to give crystals of 3-(N-hydroxyamino)- propylphosphonic acid (4.80 g.), m.p. 160 - 163.5°C (decomp.). An additional crystals of the same object compound (0.91 g.) was recovered from the mother liquor after standing overnight at ambient temperature (m.p. 159 - 163°C (decomp.)). The I.R. and N.M.R. spectra of these crystals were superimposable with those of the authentic specimen (m.p. 160 - 166°C (decomp.)).

(4) To a solution of diethyl 3-(N-ethoxycarbonyl-N -ethoxycarbonyloxyamino) -2-(tetrahydro-2H -pyran-2-yloxy) propylphosphonate (5.01 g.) in methylene chloride (10 ml.), was added dropwise trimethylbromosilane (6.73 g.) with stirring under ice-cooling. The mixture was stirred for an hour under ice-cooling and for additional 2 hours at ambient temperature and evaporated under reduced pressure to remove off the solvent and unreacted excess trimethylbromosilane. The residue was dissolved in water (50 ml.), stirred for an hour at ambient temperature and washed twice with chloroform (20 ml. and 10 ml. portions). The combined chloroform washings were extracted with water (30 ml.). The aqueous extract was washed once again with chloroform (5 ml.) and combined with the above-remained aqueous solution and then evaporated to dryness under reduced pressure to give a tarry residue. This residue was dissolved in water (40 ml.) treated with an activated charcoal (300 mg.) and evaporated to dryness under reduced pressure to give oily 3-(N-ethoxycarbonyl -N-hydroxyamino) -2-hydroxypropylphosphonic acid (2.6 g.).

N.M.R.
δ ppm in D_2O ; 1.37 (3H, t, J = 7Hz)
1.98 - 2.62 (2H, m)
3.40 - 4.00 (2H, m)
4.15 - 4.55 (3H, m)

(5) Trimethylbromosilane (122 g.) was added dropwise to a solution of diethyl 3-(N-ethoxycarbonyl -N-ethoxycarbonyloxyamino) -2-(tetrahydro-2H-pyran -2-yloxy)propylphosphonate (79.4 g.) in methylene chloride (160 ml.) under ice-cooling with stirring over a period of 15 minutes. The mixture was further stirred for an hour at 0 - 5°C and for additional 2.5 hours at ambient temperature, and then evaporated under reduced pressure. The oily residue was dissolved in water (500 ml.) stirred at ambient temperature for an hour, and then washed twice with chloroform (200 and 100 ml. portions) to remove off bis-(trimethylsilyl) ether. The combined chloroform washings were back extracted once with water (50 ml.). The combined aqueous layers were evaporated under reduced pressure. The dark brown oily residue was dissolved in water (300 ml.) washed twice with chloroform (each 150 ml. portion) and ethyl acetate (100 ml.) successively, treated with activated charcoal (2.5 g.), and evaporated under reduced pressure. The oily residue was dissolved in 1N hydrochloric acid (750 ml.) treated with activated charcoal (2.5 g.) and then heated to reflux for 13.5 hours. The mixture was evaporated under reduced pressure. The oily residue was dissolved in a mixture of water (50 ml.) and methanol (100 ml.) adjusted to pH about 4 with propylene oxide, and diluted with ethanol (300 ml.). The oily precipitates were collected by decantation, and dissolved in water (60 ml.). This aqueous solution was diluted with methanol (120 ml.) under heating at 60°C, and then allowed to stand overnight at ambient temperature. The precipitates were collected by filtration, washed twice with 80% aqueous methanol (each 20 ml. portion) and methanol (20 ml.), then dried on phosphorus pentoxide to give 2-hydroxy-3-(N-hydroxyamino)propylphosphonic acid (10.60 g.). M.p. 153 - 155°C

I.R. (Nujol) υ_{max}: 3450, 3600 - 2200, 1610, 1580, 1200, 1110, 1050, 910 cm^{-1}

N.M.R.
δ ppm in D_2O : 1.75, 2.08 (2H, d, d, J = 7Hz, 18Hz)
3.0 - 3.7 (2H, m)
4.0 - 4.5 (1H, m)

(6) To a solution of diethyl 3-(N-ethoxycarbonyl -N-ethoxycarbonyloxyamino) -2-hydroxypropylphosphonate (24.0 g.) in methylene chloride (50 ml.) was added dropwise trimethylbromosilane (41 ml.) under ice-cooling, whereafter the mixture was stirred for half an hour at the same temperature and then for additional 2.5 hours at ambient temperature. After the reaction was completed, the chloroform and the excess of the trimethylbromosilane was distilled off from the reaction mixture under reduced pressure to give a residue, which

was dissolved in water (125 ml.) and stirred for an hour at an hour at ambient temperature. This aqueous solution was washed three times with chloroform (each 30 ml. portion) and evaporated to dryness under reduced pressure to give a residue, which was dissolved in 1N hydrochloric acid (240 ml.) and heated to reflux for 15 hours. The resultant aqueous solution was evaporated to dryness under reduced pressure to give a residue, which was dissolved in water (60 ml.), decolorized with activated charcoal (500 mg.) and evaporated to dryness under reduced pressure. The residue thus obtained was dissolved in a mixture of water (20 ml.) and methanol (40 ml.), and adjusted to pH 3 - 4 with propylene oxide (about 25 ml.) to precipitate oily materials. Furthermore, to this solution was added ethanol (80 ml.) and allowed to stand for a while in order to precipitate said materials completely, and these materials were collected by decantationand dissolved in water (20 ml.). The insoluble materials were removed by filtration, and to the filtrate was added methanol (35 ml.) at 50 - 60°C. The resultant solution was allowed to stand for 3.5 hours at ambient temperature, and precipitating crystals were collected by filtration, washed twice with methanol (10 ml.) and dried on phosphorus pentoxide to give 2-hydroxy-3- (N-hydroxyamino)propylphosphonic acid (5.9 g.).

This object compound was identified by comparing its I.R. and N.M.R. spectra with those of the object compound of the above Example (5).

Examples for Hydrolysis (II)

(1) A mixture of diethyl 3-[N-(p-methoxybenzyloxy) -N-tosylamino] propylphosphonate (3.0g), 6N hydrochloric acid (25 ml) and acetic acid (25 ml) was refluxed with stirring for 12 hours. The resultant mixture was concentrated under reduced pressure to give a brownish oily residue. The residue was washed with ethyl ether (100 ml), and then water (100 ml) was added thereto with stirring. Insoluble materials were filtered off from the mixture, whereafter the filtrate was washed with ethyl ether, and then treated with an activated charcoal. The aqueous solution was concentrated under reduced pressure to give a faint yellowish oily residue. The residue was allowed to stand overnight in desiccator under reduced pressure to give crystals. The crystals were washed with ethyl ether to give p-toluene sulfonic acid salt of 3-(N-hydroxyamino) propylphosphonic acid (1.50g) in the form of fiant yellowish crystals. MP: 129~135°C

(2) A mixture of dibutyl 3-[N-(p-methoxybenzyloxy) -N-tosylamino] propylphosphonate (28.4g), 6N hydrochloric acid (280 ml) and acetic acid (280 ml) was refluxed with stirring for 20 hours. The resultant mixture was concentrated under reduced pressure to give a residue, and then water was added thereto. The mixture was treated with an activated charcoal, whereafter the mixture was concentrated under reduced pressure to give an oily residue. The oily residue was washed with ether and dried under reduced pressure. The solid was washed with acetonitrile and ethyl ether to give p-toluene-sulfonic acid salt of 3-(N-hydroxyamino) propylphosphonic acid (12.4g) in the form of crystals. MP: 129~135°C

A solution of p-toluenesulfonic acid salt of 3-(N-hydroxyamino) propylphosphonic acid (12.0g), obtained above, in water (100 ml) was passed through a column packed with a cation exchange resin, Amberlite IR 120B (trade name, made by Rohm & Haas Co.; H^+ type). The column was washed with water (800 ml) and then elution was conducted with 1N hydrochloric acid (800 ml). The eluate was concentrated under reduced pressure to remove completely water. The residue thus obtained, was pulverized with acetonitrile (300 ml) to give a pwder, which was washed twice with ethyl ether (50 ml) to give hydrochloric acid salt of 3-(N-hydroxyamino) propylphosphonic acid (4.30 g) in the form of powder.

NMR Absorption Spectrum (DMSO-d_6)

δ(ppm)
1.4~2.2 (4H, m)
3.16 (2H, m)

(3) A mixture of diethyl 3-(N-benzyloxy -N-tosylamino)- propylphosphonate (13.2g), conc. hydrochloric acid (130 ml) and acetic acid (130 ml) was refluxed with stirring for 45 hours. The resultant mixture was concentrated under reduced pressure to give a residue and then water and an activated charcoal was added thereto, whereafter the mixture was filtered. The filtrate was concentrated under reduced pressure, and the resultant residual oil (8.59 g) was dissolved in water (25 ml). To the solution were added pyridine (2.08 g) and ethanol (5 ml), and then the mixture was allowed to stand overnight at 4°C to give 3-(N-hydroxyamino)propylphosphonic acid (2.30g) in the form of crystals. MP : 160~166°C (dec.).

(4) A mixture of dibutyl 3-[N-isobutoxycarbonyl -N-(p-methoxybenzyloxy) amino]propylphosphonate (6.04 g), conc. hydrochloric acid (60 ml) and acetic acid (60 ml) was refluxed

with stirring for 21 hours. The resultant mixture was concentrated under reduced pressure, and to the residue was added water. The mixture was concentrated under reduced pressure to give a residue, which was washed with acetonitrile and then dissolved in water (10 ml). To the solution were added pyridine (800 ml) and ethanol (4 ml), and then the mixture was allowed to stand overnight at 4°C to give 3-(N-hydroxyamino) propylphosphonic acid (1.02g) in the form of crystals. MP: 160~166°C (dec.).

(5) A solution of dibutyl 3-(N-benzyloxy -N-ethoxycarbonyl-amino) propylphosphonate (6.72 g.) in acetic acid (70 ml.) and conc. hydrochloric acid (70 ml.) was refluxed with stirring for 48 hours. The reaction mixture was concentrated under reduced pressure to give an oily residue, to which there was added water (30 ml.). The solution was washed with ethyl acetate (20 ml.), treated with activated charcoal and then concentrated under reduced pressure to give an oily residue (2.60 g.). The residue was dissolved in water (5 ml.). To the solution was added pyridine (1.08 g.) and ethanol (2 ml.). The mixture was allowed to stand overnight at ambient temperature to give crystalline 3-(N-hydroxyamino) propylphosphonic acid (1.12 g.).

N.M.R.: δ(ppm) in D_2O;
1.3-2.4 (4H, m)
3.37 (2H, t)

(6) A mixture of diethyl 3-(N-methoxy-N-methoxy -carbonylamino) propylphosphonate (4.0 g), acetic acid (20 ml) and conc. hydrochloric acid (20 ml) was refluxed for 15 hours. The resultant mixture was concentrated under reduced pressure to give a residue, which was dissolved in ethanol (15 ml). The solution was neutralized with pyridine to give crystals, which were separated by filtration, washed with a small volume of ethanol and dried to give crystalline 3-(N-methoxyamino) propylphosphonic acid (1.52 g).

Mp 167 - 169°C (dec).
I.R. (Nujol)
ν_{max} : 3400 - 2000, 1630, 1545, 1235, 1125, 1050, 980, 925, 905 cm_0^1
N.M.R.
δ(ppm) in D_2O; 1.3 - 2.3 (4H, m),
3.42 (2H, t, J=7Hz)
3.90 (3H, s)

(7) A solution of diethyl 3-(N-ethoxycarbonyl -N-ethoxycarbonyl -oxyamino) propylphosphonate (146.0 g) in conc. hydrochloric acid (1020 ml) was refluxed for 9 hours. After concentration of the reaction mixture under reduced pressure, the residue was dissolved in water (200 ml) and treated with activated charcoal (6 g). The activated charcoal was removed by filtration and the filtrate was concentrated under reduced pressure and the resulting oil (86.7 g) was dissolved in water (160 ml).
After the solution was adjusted to pH 4.0 with 30% aqueous ammonia under ice-cooling, ethanol (80 ml) was added to the solution to give crystals which were separated by filtration and washed with ethanol (80 ml) to give crystalline 3-(N-hydroxyamino) propylphosphonic acid (37.78 g).
The mother liquor and the ethanol washings were combined and then allowed to stand overnight to give the same crystalline object compound (6.07 g). Mp 162-164°C (dec.)

I.R. (Nujol)
ν_{max} : 1640, 1595, 1240, 1220, 1190 cm^{-1}
N.M.R.
δ (ppm) in D_2O ; 1.3 - 2.35 (4H, m),
3.36 (2H, t, J=7Hz)

(8) A mixture of diethyl 5-(N-ethoxycarbonyl -N-ethoxycarbonyl -oxyamino) pentylphosphonate (90.0 g.) and conc. hydrochloric acid (630 ml.) was refluxed for 14 hours and concentrated under reduced pressure to give a residue, which was dissolved in water (200 ml.). The aqueous solution was washed with ethyl acetate, treated with activated charcoal and then concentrated under reduced pressure to give an oily residue (53.7 g.). The residue was dissolved in a mixture of water and methanol (1:2). The solution was adjusted to pH 4.0 with 28% aqueous ammonia under ice-cooling to give precipitates, which were separated by filtration, washed with methanol and dried to give crude crystals. The crystals were dissolved in 20-fold volume of water under heating, treated with activated charcoal and then cooled to ambient temperature. To the solution was added ethanol (100 ml.) and then allowed to stand overnight at 4°C to give crystals, which were separated by filtration and dried to give crystalline 5-(N-hydroxyamino)pentylphosphonic acid (18.8 g.). M.p. 184 - 185.5°C (dec.).

N.M.R.
δ(ppm) in D_2O : 1.20 - 2.02 (8H, m)
3.30 (2H, t, J=7Hz)

(9) To a solution of diethyl 2-(N-benzyloxy-N -tosylamino) -ethylphosphonate (12.5 g.) in acetic acid (65 ml.) was added conc. hydrochloric acid (130 ml.). The mixture was refluxed for 42 hours at 140°C, concentrated under reduced pressure to give a residue, which was dissolved in water (60 ml.). To the aqueous solution was added ethyl acetate (60 ml.). The aqueous layer was separated, washed with ethyl acetate, treated with activated charcoal and concentrated under reduced pressure to give an oily residue (8.9 g.), which was dissolved in ethanol (50 ml.) and adjusted to pH 4.0 with pyridine to give crystals. The crystals were separated by filtration, washed with ethanol and dried to give crystalline 2-(N-hydroxyamino) ethylphosphonic acid (3.5 g.), which was recrystallized from a mixture of water and ethanol (2:1) to give crystals of the same compound (2.4 g.). M.p. 173 - 173.5°C (dec.).
N.M.R.
δ(ppm) in D_2O : 2.04 (2H, m),
3.60 (2H, m)

(10) A mixture of di-tert-butyl 3-(N-ethoxycarbonyl-N-ethoxy-carbonyloxyamino)-trans-l- propenylphosphonate (8.60 g.) and 1N hydrochloric acid (250 ml.) was refluxed for 15 hours. The resultant mixture was concentrated under reduced pressure to give a residue, which was dissolved in water (100 ml.) and treated with activated charcoal. The solution was concentrated under reduced pressure to give a residue (4 g.), which was dissolved in water (10 ml.) and adjusted to pH 4 with 1N aqueous sodium hydroxide solution. The aqueous solution was passed through a column of anion exchange resin, Amberlite IRA-400 (trade name, made by Rhom & Haas Co.) (OH form). The object compound was eluted from the resin with 1N hydrochloric acid and then the eluate was concentrated under reduced pressure to give an oily residue (3.4 g.), which was dissolved in a mixture of water (0.5 ml.) and ethanol (20 ml.). The solution was adjusted to pH 4 with pyridine and concentrated under reduced pressure to give a residue, which was pulverized with methanol to give powder (1 g.). The powder was dissolved in water (0.5 ml.). To the aqueous solution was added methanol to give precipitates which were separated by filtration and dried to give powdery 3-(N-hydroxyamino)- trans-l-propenyl phosphonic acid (280 mg.). Furthermore, the same object compound (120 mg.) was recovered from the mother liquor.
I.R. (Nujol)
ν_{max} : 1630, 1260 cm^{-1}
N.M.R.
δ(ppm) in D_2O : 3.99 (2H, d.d. J=5 and 1Hz)
6.05 - 6.65 (2H, m)

(11) A mixture of 3-(N-ethoxycarbonyl -N-ethoxycarbonyloxyamino) -trans-l-propenyl-phosphonic acid (8.53 g.) and 1N hydrochloric acid (250 ml.) was refluxed for 16 hours. The resultant mixture was concentrated under reduced pressure to give a residue, which was dissolved in water (30 ml.). The aqueous solution was treated with activated charcoal (0.5 g.) and concentrated under reduced pressure to give an oily residue (5.85 g.), which was dissolved in water (10 ml.). The aqueous solution was passed through a column of anion exchange resin, Amberlite IRA 400 (100 ml.). The column was washed with water (600 ml.) and the object compound was eluted with 1N hydrochloric acid (300 ml.). The eluate was concentrated under reduced pressure to give an oily residue (3.9 g.), to which were added ethanol (10 ml.) and water (2 ml.). The mixture was adjusted to pH 4 - 4.5 with pyridine and then to the mixture was added ethanol (30 ml.). The supernatant was removed by decantation to give residue, which was pulverized with ethanol (30 ml.) to give powdery 3-(N-hydroxyamino) -trans-l- propenylphosphonic acid (2.38 g.).
I.R. (Nujol)
ν_{max} : 1630, 1260 cm^{-1}
N.M.R.
δ(ppm) in D_2O : 3.99 (2H, d,d, J=5 and 1Hz)
6.05 - 6.65 (2H, m)

(12) A mixture of diethyl 3-(N-ethoxycarbonyl -N-ethoxycarbonyloxyamino) -2-methylpropylphosphonate (28.3 g.). and conc. hydrochloric acid (280 ml.) was refluxed for 18 hours and then concentrated under reduced pressure to give an oily residue. To the residue was added a mixture of water (100 ml.) and ethyl acetate (100 ml.). From the resultant mixture, the aqueous layer was separated, treated with activated charcoal and

concentrated under reduced pressure to give an oily residue. The residue was dissolved in a mixture of methanol (30 ml.) and water (15 ml.). The solution was adjusted to pH 4.0 with aqueous ammonia under ice-cooling and concentrated under reduced pressure to give a residue, which was passed through a column of anion exchange resin, Amberlite IRA-400 (OH form). The column was washed with water and then the object compound was eluted with 1N hydrochloric acid. The eluate was concentrated under reduced pressure to give oily hydrochloric acid salt of 3-(N-hydroxyamino) -2-methylpropylphosphonic acid (9.6 g.).

N.M.R.

δ(ppm) in D_2O : 1.22 (3H, d, J=6Hz)
1.58 - 2.58 (3H, m)
3.32 (2H, d, J=6Hz)

(13) A solution of sodium hydroxide (14.0 g.) in water (175 ml.) was heated to reflux for a while under bubbling with nitrogen gas. To this solution was added diethyl 3-(N-ethoxycarbonyl -N-ethoxycarbonyloxyamino) propylphosphonate (24.8 g.), and the mixture was heated to reflux for 1.5 hours with stirring under nitrogen atmosphere. After cooling, the reaction mixture was adjusted to pH 4.0 with 10% hydrochloric acid and then concentrated under reduced pressure to about half of the original volume. The aqueous concentrate was adjusted to pH 1.0 with 10% hydrochloric acid, washed with three 50 ml. portions of n-butanol, which were discarded, and adjusted to pH 4.0 with 20% aqueous sodium hydroxide solution and then evaporated under reduced pressure. The residue was dissolved in ethanol (50 ml.) and evaporated to dryness under reduced pressure to remove off a residual water as thoroughly as possible. The solid residue were dissolved in hot methanol (120 ml.), and insoluble solid (sodium chloride) was filtered off and the filtrate evaporated to dryness under reduced pressure. The crystalline residue thus obtained was treated with ethanol (100 ml.) and collected by filtration to give monoethyl 3-(N-hydroxyamino) propylphosphonate (6.5 g.).

N.M.R.

δppm in D_2O ; 1.22 (3H, t, J=7Hz)
1.48 - 2.20 (4H, m)
3.37 (2H, t, J=6Hz)
3.89 (2H, quintet)

(14) A solution of 3-(N-ethoxycarbonyl -N-hydroxyamino)-2 -hydroxypropylphosphonic acid (2.4 g.) in 1N hydrochloric acid (100 ml.) was heated to reflux for 14 hours. The reaction mixture was evaporated to dryness under reduced pressure to give a residue, to which was added water (20 ml.), washed twice with chloroform (each 10 ml. portion) and decolorized with activated charcoal (200 mg.). The activated charcoal was filtered off and the filtrate was evaporated to dryness under reduced pressure to give a dark reddish oil, to which was added water (3 ml) and adjusted to pH 4.0 with 28% aqueous ammonia. This aqueous solution was diluted with methanol and allowed to stand at ambient temperature, and then the precipitating crystals were collected by filtration to give 2-hydroxy-3 -(N-hydroxyamino) propylphosphonic acid (0.62 g.).

This object compound was identified by comparing its I.R. and N.M.R. spectra with those of the object compound of Example (5) in Hydrolysis (I).

Examples for N-Acylation

(1) Acetic anhydride (4.51g) was added to a suspension of 3-(N-hydroxyamino) propylphosphonic acid (3.80g) in water (20 ml) at an ambient temperature, while stirring. After the stirring was continued for 1.5 hours, the resultant mixture was adjusted to pH 2.5 with 1N aqueous sodium hydroxide solution and then concentrated under reduced pressure. To the residual oil was added water (40 ml), and then concentrated under reduced pressure. This operation was repeated once again. The residual oil was washed twice with ethyl ether (60 ml), and then dissolved in ethanol (5 ml). To the solution, there was added ethyl ether (50 ml) to reprecipitate the oil. The upper layer was removed by decantation. This operation was repeated once again. The oil thus obtained, was dissolved in water (50 ml), adjusted to pH 6.5 and then concentrated under reduced pressure to give a foamy residue. n-Butanol was added to the foamy residue and concentrated under reduced pressure to remove completely water. The resultant residual oil was pulverized with isopropanol and then the obtained powder was washed with isopropanol and ethyl ether, respectively and then dried to give a crude powder (5.58 g). The crude powder was recrystallized from a mixture of methanol and acetone to give monosodium salt of 3-(N-acetyl -N-hydroxyamino) propylphosphonic acid (3.75g).
MP: 187~188°C(dec.)

(2) p-Toluenesulfonic acid salt of 3-(N-hydroxyamino) -propylphosphonic acid (980 mg) was dissolved in a mixture of water (12 ml), 1N aqueous potassium hydroxide solution (12

ml) and acetone (20 ml). To the solution was added dropwise a solution of benzoyl chloride (1.70 g) in dry acetone (12 ml) under ice-cooling, with stirring. During the period, the solution was adjusted to pH 7.5-9 with 1N aqueous potassium hydroxide solution. The resultant mixture was adjusted to pH 10 and stirred for an hour, whereafter the mixture was adjusted to pH 7 and then acetone was distilled off under reduced pressure. The resultant residue was adjusted to pH 4 with 10% hydrochloric acid and washed with ethyl ether. The aqueous layer was adjusted to pH 1.6 with 10% hydrochloric-acid, and then water was added thereto to give 150 ml of a solution. The solution was passed through a column of activated charcoal. The column was washed with water, and then elution was conducted with 70% aqueous acetone. The eluate was concentrated under reduced pressure to give a residual oil (960 mg). This purification operation using a column of an activated charcoal was repeated once again to give a residual oil (460 mg). The oil was dissolved in water (30 ml) and adjusted to pH 6.5 with 1N aqueous sodium hydroxide solution. The solution was concentrated under reduced pressure and then the obtained residue was pulverized with ethanol to give monosodium salt of 3-(N-benzoyl-N -hydroxyamino) propylphosphonic acid in the form of powder.

NMR Absorption Spectrum (D_2O) :

δ(ppm)

1.8~2.1 (4H, m)

3.77 (2H, t, J=6Hz)

7.57 (5H, s)

(3) Thienylacetyl chloride (1350 mg) was added dropwise to a solution of 3-(N-hydroxyamino) propylphosphonic acid (755 mg) and sodium bicarbonate (1.26 g) in a mixture of water (15 ml) and methanol (10 ml) under ice-cooling with stirring for 1.5 hours. During the period, the reaction mixture was adjusted to pH 7-8 with 5% aqueous sodium bicarbonate solution. The reaction mixture was adjusted to pH 10 and stirred under ice-cooling for additional 45 minutes. The resultant mixture was adjusted to pH 7 with 10% hydrochloric acid and methanol was distilled off under reduced pressure. The residue thus obtained, was adjusted to pH 2 with 10% hydrochloric acid, washed twice with ethyl ether (30 ml) and then extracted three times with n-butanol (30 ml). The combined n-butanol layer was dried under reduced pressure to give 3-(N-hydroxy -N-thienylacetylamino) -propylphosphonic acid (960 mg) in the form of powder. The powder was crystallized from a mixture of ethanol and ethyl ether to give 3-(N-hydroxy -N-thienylacetylamino) propylphosphonic acid (200 mg) in the form of colorless needles. Mp: 128~131°C (dec.)

(4) A solution of N-benzyloxycarbonyl aminoacetyl chloride (2,85 g) in ethyl ether (5 ml) was added dropwise to a solution of 3-(N-hydroxyamino) propylphosphonic acid (985 mg) and sodium bicarbonate (1.51 g) in a mixture of water (20 ml) and methanol (20 ml) with stirring under ice-cooling. During the period, the reaction mixture was adjusted to pH 7-8 with 5% aqueous sodium bicarbonate solution. The stirring was continued for an hour, whereafter the mixture was adjusted to pH 10 with 1N aqueous sodium hydroxide solution and stirred at the same temperature for 45 minutes. The resultant mixture was adjusted to pH 7 and methanol was distilled off under reduced pressure. The resultant aqueous solution was adjusted to pH 2 with 10% hydrochloric acid and washed with ethyl acetate (30 ml), whereafter the solution was adjusted to pH 1 with 10% hydrochloric acid and then extracted twice with n-butanol (30 ml). The combined n-butanol layer was concentrated under reduced pressure to give a residue, which was crystallized from ether to give 3-[N-(N-benzyloxycarbonylamino acetyl)- N-hydroxyamino] propylphosphonic acid (720 mg) in the form of crystals. MP: 101~105°C

The obtained 3-[N-N-benzyloxycarbonyl aminoacetyl) -N-hydroxyamino] propylphosphonic acid was hydrolyzed to give 3-(N-aminoacetyl -N-hydroxyamino) propylphosphonic acid in the following manner.

48% Hydrogen bromide-acetic acid (1 ml) was added under ice-cooling to a solutionof 3-[N-(N-benzyloxycarbonyl aminoacetyl) -N-hydroxyamino] propylphosphonic acid (200 mg) in acetic acid (1 ml) and the reaction mixture was stirred at an ambient temperature for an hour. To the resultant mixture was added dry ethyl ether (20 ml) to precipitate an oil. The oil was separated, washed twice with dry ethyl ether (10 ml) and then dissolved in water (0.5 ml). The solution was adjusted to pH 4 with pyridine and ethanol (5 ml) was added thereto to give precipitates. The upper layer was removed by decantation and the precipitates was pulverized with ethyl ether (10 ml) to give 3-[N-aminoacetyl -N-hydroxyamino) propylphosphonic acid (40 mg) in the form of powder.

Infrared Absorption Spectrum (Nujol) :
ν_{max} = 3400~2600, 1650, 1270, 1220, 1110, 1030, 900 cm^{-1}
NMR Absorption Spectrum (D_2O) :

δ(ppm)
1.6~2.2 (4H, m)
3.67 (2H, t, J=5Hz)
4.05 (2H, s)

(5) Formic acid (20 ml.) was added dropwise to acetic anhydride (40 ml.) at 0-5°C in the course of 15 minutes with stirring. After stirring was continued at the same temperature for 10 minutes and then at 45-50°C for 15 minutes, the mixture was cooled down to 0-5°C. To this cooled mixture was added dropwise a solution of 3-(N-hydroxyamino) propylphosphonic acid (32.8 g.) in formic acid (60 ml.) at the same temperature in the course of 20 minutes, stirred for additional 45 minutes at ambient temperature, and then the resultant mixture was concentrated under reduced pressure. The residue was dissolved in ethanol (300 ml.), treated with activated charcoal (6 g.) and then filtered. The filtrate was diluted with ethanol (200 ml.) and treated with 28% aqueous ammonia (28 ml.) with stirring under ice-cooling to give an oily precipitate. The precipitate was separated by decantation and dissolved in water (120 ml.). The aqueous solution was treated with activated charcoal (4 g.), and filtered. To the aqueous filtrate was added ethanol (800 ml.) at 80°C and allowed to stand overnight at ambient temperature to give crystalline monoammonium salt of 3-(N-formyl -N-hydroxyamino) propylphosphonic acid (30.55 g.), mp 158-160.5°C (dec.) The same monoammonium salt (4.35 g.) was recovered additionally from the mother liquor, by concentrating it to about 100ml under reduced pressure mixing with ethanol (300 ml.) and allowing to stand at ambient temperature for 2 hours.

(6) To a cooled mixture of formic acid (2 ml.) and acetic anhydride (4 ml.) at 0 - 5°C, which was prepared in the same manner as above, was added dropwise 3-(N-hydroxyamino) propyl phosphonic acid (3.28 g.), and stirred at ambient temperature for an hour. The resultant mixture was concentrated under reduced pressure. The oily residue was washed with ether (50 ml. x 3) and then dissolved in water (60 ml.). The aqueous solution was adjusted to pH 4.8 with 1N aqueous sodium hydroxide solution and concentrated under reduced pressure. The residue was dissolved in methanol (50 ml.) and was added ethanol (10 ml.) at 60°C, to give an oily precipitate, which was removed off by decantation. The alcoholic solution was treated with ethanol (50 ml.) to give solid precipitates, which was collected by filtration, washed with ethanol and dried to give monosodium salt of 3-(N-formyl -N-hydroxyamino) -propylphosphonic acid as an powder (3.52 g.). The powder was further purified by reprecipitation in the following manner. A solution of this powder in methanol (80 ml.) was diluted with ethanol (100 ml.) at ambient temperature with stirring. Stirring was continued overnight at ambient temperature to give precipitates, which was filtered, washed with ethanol and then dried to give a purified monosodium salt of 3-(N-formyl -N-hydroxyamino) propylphosphonic acid (2.50 g.).
I.R. (nujol ν_{max} : 3600-2200, 1675, 1510, 1270, 1230, 1165, 1015, 985, 920, 885 cm^{-1}
N.M.R.: δ(ppm) in D_2O;
1.2-2.2 (4H, m)
3.62 (2H, t, J=6Hz)
7.98 (s) 1H
8.33 (s)

(7) To a cooled mixture of formic acid (1 ml.) and acetic anhydride (2 ml.) at 0-5°C, which was prepared in the same manner as aforementioned, was added dropwise 3-(N-hydroxyamino) -propylphosphonic acid (1.64 g.), stirred at ambient temperature for an hour, and then concentrated under reduced pressure. The residue was dissolved in 1N aqueous potassium hydroxide solution (10 ml.) and evaporated to dryness under reduced pressure. The residue became to crystallize after standing at ambient temperature for 3 hours, which was treated with methanol collected by filtration (1.13 g.) and recrystallized from 20% aqueous ethanol to give crystalline potassium salt of 3-(N-formyl -N-hydroxyamino) propylphosphonic acid (0.73 g.), mp. 202-204°C (dec.).
I.R. (nujol) ν_{max} : 2700-2200, 1655, 1560, 1310, 1260, 1220, 1190, 1155, 1125, 1000, 940, 890 cm^{-1}

N.M.R.: δ(ppm) in D_2O;
1.25-2.3 (4H, m)
3.65 (2H, t, J=6Hz)
8.00 (s)
8.35 (s)

(8) To a solution of 3-(N-hydroxyamino) propylphosphonic acid (2.46 g.) in a mixture of water (15 ml.) and acetone (15 ml.) was added dropwise butyric anhydride (4.75 g.) in the course of 15 minutes with stirring at ambient temperature. After stirring was continued at the same temperature for additional one hour, the resultant mixture was concentrated under reduced pressure. The oily residue was dissolved in 1N aqueous sodium hydroxide solution (15 ml.) and evaporated to dryness under reduced pressure. The residue was washed with ether (50 ml. x 3) by decantation, dissolved in ethanol (70 ml.), heated to reflux for 2 hours, and then evaporated to dryness under reduced pressure. The resultant residue was triturated with ether and filtered to give a powder (2.50 g.), which was treated with hot (60°C) acetone (60 ml.). Insoluble materials were collected by filtration, washed with a small amount of acetone and dried to give a solid monosodium salt of 3-(N-butyryl -N-hydroxyamino)-propylphosphonic acid (690 mg.), which was recrystallized from isopropanol to give needles, mp: 182-187°C (dec.).

(9) A mixture of benzoyloxyacetic acid (5.4 g.) and thionyl chloride (50 ml.) was stirred at 70-80°C for an hour and then excess thionyl chloride was distilled off under reduced pressure to give benzoyloxyacetyl chloride. A solution of benzoyloxy acetylchloride obtained above in acetone (10 ml.) was added dropwise to a solution of 3-(N-hydroxyamino) propylphosphonic acid (1.64 g.) in a mixture of water (16 ml.) and acetone (20 ml.) over 30 minutes interval with stirring under ice-cooling and maintaining carefully the pH at around 7-8, together with by adding dropwise a 5% aqueous sodium bicarbonate solution and stirring was continued for additional 30 minutes.

After acetone was distilled off from the reaction mixture under reduced pressure, the residual solution was adjusted at around pH 11-12 and stirred for an hour under maintaining the pH at around 11-12 with 1N aqueous sodium hydroxide solution. The resultant mixture was acidified to about pH 2 with 10% hydrochloric acid and washed out twice with ethyl acetate. The aqueous layer was taken up, adjusted to about pH 1.5-2 and subjected to column chromatography on activated charcoal. After the column was washed with a small portion of water, the object compound was eluted with 70% (V/V) aqueous acetone. The fractions containing the object compound was collected, adjusted to pH 5 with 1N aqueous sodium hydroxide solution and concentrated under reduced pressure to give monosodium salt of 3-(N-hydroxyacetyl -N-hydroxyamino) propylphosphonic acid (300 mg.) as a powder.

I.R. (nujol ν_{max} : 3600-2200, 1640, 1280, 1225, 1130, 1040, 900 cm^{-1}

N.M.R.: δ(ppm) in D_2O;
1.32-2.2 (4H, m)
3.73 (2H, t, J=8Hz)
4.47 (2H, s)

(10) Chloroacetyl chloride (4.52 g.) was added dropwise to a solution of 3-(N-hydroxyamino) propylphosphonic acid (2.46 g.) in a mixture of water (15 ml.) and acetone (15 ml.) over a 20 minutes-interval with stirring under ice-cooling and maintaining the pH at around 7-8 by adding 5% aqueous sodium bicarbonate solution. After stirring for further hour, the reaction mixture was adjusted to pH 9 with 1N aqueous sodium hydroxide solution and stirred at ambient temperature for 35 minutes. After acetone was distilled off under reduced pressure, the aqueous solution was acidified to pH 1.8 with 10% hydrochloric acid and evaporated to dryness under reduced pressure. The residue was dissolved in ethanol (40 ml.) and heated for 10 minutes at 60°C. The insoluble substance was separated out and the ethanolic layer was allowed to stand overnight at ambient temperature to give crystalline 3-(N-chloroacetyl -N-hydroxyamino) propylphosphonic acid (1.85 g.), mp: 163-165°C (dec.).

(11) A mixture of 3-(N-hydroxyamino) propylphosphonic acid (1.64 g.) in 1N aqueous sodium hydroxide solution (10 ml.) and S-methylisothiourea sulfate (1.40 g.) in water (5 ml.) was heated to reflux for 1.5 hours and allowed to stand overnight at ambient temperature to give crystalline precipitates, which was collected by filtration and washed with water and then with ethanol to give 3-(1-hydroxyguanidino) propylphosphonic acid (690 mg.), mp: 244-247°C (dec.).

(12) Formic acid (1 ml) was added dropwise to acetic anhydride (2 ml), while stirring and ice-cooling. The mixture was stirred for an hour at ambient temperature. Subsequently, to the mixture was added 3-(N-methoxyamino) -propylphosphonic acid (680 mg). The reaction mixture was stirred for 45 minutes and then concentrated under reduced pressure. The residue thus obtained was dissolved in 1N aqueous sodium hydroxide solution (4 ml) and then the solution was concentrated under reduced pressure to give a residue, which was dissolved in ethanol (50 ml). The solution was concentrated under reduced pressure to give a residue, which was pulverized with acetone to give powdery monosodium salt of 3-(N-formyl -N-methoxyamino) propylphosphonic acid (680 mg).

I.R. (Nujol)
ν_{max} : 3600 - 2300, 1660, 1280, 1230, 1050, 890 cm^{-1}

N.M.R.
δ(ppm) in D_2O; 1.3 - 2.3 (4H, m),
3.70 (2H, t, J=6Hz),
3.72 (3H, s),
8.00 (s)) 1H
8.42 (s)

(13) To a mixture of 3-(N-hydroxyamino) propylphosphonic acid (1.64 g), water (16 ml) and acetone (16 ml) was added dropwise a solution of ethoxalyl chloride (2.75 g) in acetone (10 ml) under ice-cooling in the course of 45 minutes, while stirring. During this period, pH of the reaction mixture was kept at 7-8 with 5% aqueous sodium bicarbonate solution. The stirring was continued for an additional hour, and then acetone was evaporated under reduced pressure. The residue thus obtained was adjusted to pH 1.8 - 2.0 with 10% hydrochloric acid and subjected to a column chromatography using activated charcoal. The object compound was eluted with 70% aqueous acetone. After acetone was evaporated under reduced pressure, the resulting solution was adjusted to pH 5.2 with 1N aqueous sodium hydroxide solution and concentrated under reduced pressure to give a residue, which was pulverized with acetone to give powdery monosodium salt of 3-(N-ethoxalyl -N-hydroxyamino) propylphosphonic acid.

I.R. (Nujol)
ν_{max} : 3600 - 2500, 1730, 1640, 1300, 1250, 1130, 1010 cm^{-1}

N.M.R.
δ(ppm) in D_2O : 1.32 (3H, t, J=7Hz),
1.5 - 2.3 (4H, m),
3.75 (2H, t, J=6Hz),
4.48 (2H, quartet, J=7Hz)

(14) A mixture of 3-(N-hydroxyamino) propylphosphonic acid (820 mg), bis(trimethylsilyl) acetamide (5.0 g), triethylamine (1.01 g) and dichloromethane (40 ml) was stirred at ambient temperature for 2.5 hours. The reaction mixture was cooled to 0 - 5°C and mesyl chloride (1.15 g) was added dropwise with stirring. The reaction mixture was stirred for 1.25 hours and then concentrated under reduced pressure to give a residue, which was dissolved in water (50 ml). The solution was subjected to a column chromatography using activated charcoal. After the column was washed with water, the object compound was eluted with 70% aqueous acetone. The eluate was collected and evaporated to dryness to give powdery 3-(N-hydroxy-N-mesylamino) -propylphosphonic acid (320 mg). This powder was dissolved in ethanol (20 ml). To the solution was added conc. aqueous ammonia (0.4 ml) to give precipitates, which were separated by filtration and dried to give crystalline monoammonium salt of 3-(N-hydroxy -N-mesylamino) -propylphosphonic acid (220 mg). Mp 103 - 105°C (dec).

I.R. (Nujol)
ν_{max}: 3600 - 2200, 1330, 1320, 1150, 1040, 1010, 960, 930, 890 cm^{-1}

N.M.R.
δ(ppm) in D_2O: 1.4 - 2.2 (4H, m),
3.10 (3H, s),
3.28 (2H, t, J=6Hz)

(15) A mixture of 3-(N-hydroxyamino) propylphosphonic acid (1.64 g), bis(trimethylsilyl) acetamide (10.0 g) and dichloromethane (32 ml) was stirred for 3 hours at ambient temperature. To this mixture was added dropwise a solution of 2-acetoxy-4-chlorobenzoyl chloride

(2.3 g) in dichloromethane (10 ml with stirring under ice-cooling. The reaction mixture was stirred at the same temperature for 30 minutes and at ambient temperature for 1.5 hours. The mixture was concentrated under reduced pressure to give a residue, which was dissolved in ethyl acetate (80 ml). The solution was washed with cold 5% hydrochloric acid (30 ml). The washings was extracted three times with ethyl acetate (30 ml). The combined ethyl acetate layer was washed with saturated aqueous sodium chloride solution (10 ml), dried over magnesium sulfate and evaporated to dryness to give a crude powder (4.35 g) of 3-[N-(2-acetoxy-4-chloro benzoyl) -N-hydroxyamino] propylphosphonic acid. This crude powder (1 g) was dissolved in a mixture of ethanol (30 ml) and conc. aqueous ammonia (8 ml). The solution was stirred at ambient temperature for 4 hours and then concentrated under reduced pressure to give a residue, which was dissolved in a small volume of ethanol. To the solution was added ether to give precipitates, which were separated by filtration and dried to give powdery monoammonium salt of 3-[N-(4-chloro -2-hydroxy benzoyl) -N-hydroxyamino] propylphosphonic acid (430 mg).

I.R. (Nujol)
ν_{max} : 3600 - 2200, 1600, 1280, 1110, 1030, 900, 820 cm^{-1}

N.M.R.
δ(ppm) in D_2O; 1.4 - 2.2 (4H, m), 3.72 (2H, t, J=6Hz), 6.8 - 7.2 (3H, m)

(16) A mixture of 3-(N-hydroxyamino) propylphosphonic acid (1.64 g), bis(trimethylsilyl) acetamide (10 g) and dichloromethane (30 ml) was stirred at ambient temperature for 3 hours and cooled to 0 - 5°C. To the mixture was added methyl isothiocyanate (800 mg) under ice-cooling. The reaction mixture was stirred at the same temperature for an hour and concentrated under reduced pressure to give a residue. To this residue was added water (50 ml) and stirred at ambient temperature for 30 minutes. After the remaining dichloromethane was removed by evaporation under reduced pressure, an additional 50 ml of water was added. The aqueous solution was subjected to a column chromatography using activated charcoal. The column was washed with water (650 ml) and then the object compound was eluted with 70% aqueous acetone. The eluate was concentrated under reduced pressure to give crystals, which were separated by filtration, washed with ethanol and dried to give crystalline 3-[N-hydroxy -N-[(N-methyl) thiocarbamoy amino] propylphosphonic acid (320 mg). Further, the ethanol washing was concentrated under reduced pressure to give a residue which was pulvelized to give the same object compound (450 mg). Mp 190 - 194°C (dec.).

I.R. (Nujol)
ν_{max} : 3300, 3200 - 2300, 1560, 1350, 1285, 1175, 1020, 1010, 905 cm^{-1}

N.M.R.
δ(ppm) in D_2O: 1.3 - 2.3 (4H, m), 3.05 (3H, s), 4.10 (2H, t, J=6Hz)

(17) A mixture of 3-(N-hydroxyamino) propylphosphonic acid (1.64 g), dichloromethane (30 ml) and bis(trimethylsilyl) acetamide (10 g) was stirred at ambient temperature for 3 hours. The mixture was cooled to 0 - 5°C and phenyl isocyanate (1.80 g) was added thereto. The reaction mixture was stirred at the same temperature for an hour and at ambient temperature for 3 hours and then allowed to stand overnight. The resultant mixture was concentrated under reduced pressure. To the residue was added water (60 ml), and then the mixture was stirred at ambient temperature for 3 hours. Insoluble materials were removed by filtration and the filtrate was washed twice with ethyl acetate (50 ml). To the aqueous layer was added an additional 90 ml of water, whereafter the aqueous solution was subjected to a column chromatography using activated charcoal. The object compound was eluted with 70% aqueous acetone. The eluate was evaporated to dryness under reduced pressure, whereafter the resulting crystals were washed with acetone and dried to give crystalline 3-(N-hydroxy -N-phenylcarbamoylamino) propylphosphonic acid (1.13 g). Mp 126 - 130°C (dec.)

I.R. (Nujol)
ν_{max}: 3370, 3300-2200, 1610, 1590, 1550, 1285, 1230, 1200, 1075, 995, 940 cm^{-1}

N.M.R.
δ(ppm) in D_2O; 1.6 - 2.2 (4H, m), 3.69 (2H, t, J=7Hz), 7.43 (5H, s)

(18) A solution of methyl chlorocarbonate (3 g) in acetone (10 ml) was added dropwise to a mixture of 3-(N-hydroxyamino) propylphosphonic acid (1.64 g), water (16 ml) and acetone (16 ml) in the course of 30 minutes under ice-cooling, while stirring. During this period, pH of the mixture was kept at around 7 - 8 with 5% aqueous sodium bicarbonate solution. The stirring was continued at the same temperature for an additional hour, and then acetone was evaporated under reduced pressure. The resulting aqueous solution was adjusted to pH 2 with 10% hydrochloric acid and then subjected to a column chromatography using activated charcoal. The object compound was eluted with 70% aqueous acetone. After removal of acetone by evaporation under reduced pressure, the resulting aqueous solution was adjusted to pH 5.0 with 1N aqueous sodium hydroxide solution and then concentrated under reduced pressure. The residue was dissolved in methanol (40 ml) and refluxed for 4 hours. The methanol solution was evaporated to dryness to give powdery sodium salt of 3-(N-hydroxy -N-methoxycarbonylamino) propylphosphonic acid (320 mg).

I.R. (Nujol)
ν_{max} : 3600 - 2200, 1700, 1265, 1170, 1060, 900, 820 cm^{-1}

N.M.R.
δ(ppm) in D_2O; 1.4 - 2.1 (4H, m)
3.63 (2H, t, J = 6Hz)
3.76 (3H, s)

(19) A mixture of 3-(N-hydroxyamino) propylphosphonic acid (1.64 g), potassium isocyanate (2.43 g) and water (17 ml) was stirred at ambient temperature for 3 hours, while maintaining the pH at around 5-7 with 3N hydrochloric acid. The reaction mixture was adjusted to pH 9 with 1N aqueous sodium hydroxide solution and then stirred at ambient temperature for 20 minutes. The resultant mixture was adjusted to pH 1.8 with 3N hydrochloric acid and concentrated under reduced pressure. The residue was extracted with methanol and the extract was concentrated under reduced pressure to give crude 3-(N-carbamoyl-N -hydroxyamino) propylphosphonic acid (2.50 g). A part (1 g) of the object compound was dissolved in water (5 ml), and the solution was passed through a column of nonionic adsorption resin Diaion HP 20 (trade name, made by Mitsubishi Chemical Industries). The object compound was eluted with water. The fractions containing the object compound was collected and evaporated to dryness to give powdery 3-(N-carbamoyl-N -hydroxyamino)-propylphosphonic acid (410 mg).

N.M.R.
δ(ppm) in D_2O; 1.4 - 2.1 (4H, m),
3.53 (2H, t, J = 6Hz)

(20) To a stirring mixture of 3-(N-hydroxyamino) -propylphosphonic acid (1.64 g), water (12 ml) and acetone (12 ml) was added a solution of succinic anhydride (2.5 g) in acetone (10 ml). The mixture was stirred at ambient temperature for 3 hours, whereafter succinic anhydride (1.5 g) was added thereto and the mixture was stirred for an hour. After concentration of the reaction mixture under reduced pressure, the resulting residue was washed three times with acetone (50 ml) and treated with a column of activated charcoal. The object compound was eluted with 70% aqueous acetone. The eluate was concentrated under reduced pressure to give a residue (720 mg), which was dissolved in 1N aqueous sodium hydroxide solution (2.8 ml). The solution was evaporated to dryness to give a residue, which was pulverized with ethanol to give powdery 3-[N-3-carboxy -propionyl)-N- hydroxyamino] propylphosphonic acid (650 mg).

I.R. (Nujol)
ν_{max} : 3600 - 2400, 1710, 1620, 1250, 1140, 1030, 890 cm^{-1}

N.M.R.
δ(ppm) in D_2O- 1.4 - 2.2 (4H, m), 2.5 - 2.9
(4H, m), 3.73 (2H, t, J = 7Hz)

(21) Formic acid (4.5 ml) was added dropwise to acetic anhydride (9.4 ml) at 15 - 20°C in the course of 3 minutes with stirring. After stirring was continued at the same temperature for 30 minutes, 3-(N-hydroxyamino) propylphosphonic acid (7.75 g) was added, and the mixture was stirred at the same temperature for 1.5 hours. To the resultant mixture was added benzene (100 ml), whereafter the mixture was stirred for 10 minutes to precipitate an oil. The oil was separated by decantation, washed twice with benzene (50 ml) and then dissolved in water (25 ml). To this aqueous solution was added calcium carbonate (2.37 g) at 15 - 20°C, while stirring. After the resultant aqueous solution was treated with activated charcoal, the filtrate was triturated with methanol (300 ml) at 0 - 5°C to give precipitates. After stirred for

30 minutes, the precipitates was collected by decantation and dissolved in water (25 ml). A small volume of insoluble materials was removed by filtration, whereafter, to the filtrate was added dropwise methanol (300 ml) with stirring at 0 - 5°C to give precipitates. After the stirring was continued for an hour, the precipitates was collected by filtration, washed with methanol (20 ml) and dried over phosphorus pentoxide under reduced pressure to give powdery calcium bis[3-(N-formyl -N-hydroxyamino) propylphosphonate] (3.72 g).

I.R. (Nujol)
ν_{max} : 3600 - 2200, 1660, 1230, 1190, 1100, 1050, 920 cm^{-1}

N.M.R.
δ(ppm) in D_2O; 1.3 - 2.4 (4H, m)
3.70 (2H, t, J=6Hz),
8.00 (s)
} 1H
8.40 (s)

(22) Formic acid (1.67 g.) was added to acetic anhydride (1.86 g.) at ambient temperature with stirring. The stirring was continued at ambient temperature for 30 minutes, and then to the mixture was added a solution of 3-(N-hydroxyamino) -trans-l- propenylphosphonic acid (2.14 g.) in formic acid (7 ml.). The reaction mixture was stirred at ambient temperature for 1.5 hours and concentrated under reduced pressure to give a residue, to which was added methanol (20 ml.). Insoluble materials were removed by filtration and to the filtrate was added a methanol solution (3 ml.) of potassium hydroxide (780 mg.) to give crystals. The crystals were separated by filtration and dried to give crystalline monopotassium salt of 3-(N-formyl-N- hydroxyamino)-trans-l -propenylphosphonic acid (0.76 g.). The same object compound (0.73 g.) was recovered from the mother liquor. M.p. 178 - 180°C (dec.).

I.R. (Nujol)
ν_{max} = 1665, 1250 cm^{-1}

N.M.R.
δ(ppm) in D_2O : 4.30 (2H, m)
6.01 (1H, m)
6.38 (1H, m)
8.02 (s)
} 1H
8.38 (s)

(23) Formic acid (2 ml.) was added dropwise to acetic anhydride (2.45 ml.) at ambient temperature with stirring. After the stirring was continued at the same temperature for 30 minutes, 3-(N-hydroxyamino) propylphosphonic acid (3.10 g.) was added to the mixture. The reaction mixture was stirred at ambient temperature for an hour and then concentrated under reduced pressure to give an oily residue, which was dissolved in water (25 ml.). To the aqueous solution was added dropwise a solution of diacetic acid salts of N,N′∂ dibenzylethylenediamine (3.60 g.) in water (15 ml.) under ice-cooling and with stirring. The resultant mixture was concentrated under reduced pressure to give an oily residue, which was dissolved in water (30 ml.). The aqueous solution was concentrated under reduced pressure to give an oily residue, which was dissolved in water (30 ml.). The aqueous solution was concentrated under reduced pressure to give an oily residue, which was crystallized with a mixture of methanol (30 ml.) and ethanol (40 ml.). The crystals were separated by filtration, washed with ethanol (20 ml.) and then dried to give crystals (3.34 g.). The same crystals (1.00 g.) were recovered from the filtrate and the washings by concentrating them under reduced pressure to a volume of 40 ml. and allowing the concentrate to stand overnight at 4°C. A part (3 g.) of the combined crystals, as obtained above, was recrystallized from a mixture of water and ethanol (1:6) (40 ml.) to give N,N′-dibenzylethylenediamine bis[3-(N-formyl-N -hydroxyamino) propylphosphonate] (2.60 g.) in the form of needles. M.p. 155 - 157°C (dec.)

I.R. (Nujol)
ν_{max} : 3400 - 2200, 1665, 1220, 1110, 1020, 925 cm^{-1}

N.M.R.
δ(ppm) in D_2O : 1.3 - 2.1 (4H, m)
3.53 (2H, s)
3.55 (2H, t, J=6Hz)
4.30 (2H, s)
7.53 (5H, s)
7.90 (s)
} 1H
8.28 (s)

(24) Formic acid (1.19 g.) was added dropwise to acetic anhydride (1.33 g.) at ambient temperature with stirring. After the stirring was continued at the same temperature for 30 minutes, 5-(N-hydroxyamino) pentylphosphonic acid (1.83 g.) was added to the mixture. The reaction mixture was stirred at ambient temperature for an hour and 45 minutes, and then concentrated under reduced pressure to give an oily residue. The residue was dissolved in ethanol (30 ml) and to the solution was added dropwise conc. aqueous ammonia (2 ml.) to give crystals. After the mixture containing crystals was stirred at ambient temperature for an hour, the crystals were separated by filtration and dried to give crystalline monoammonium salt of 5-(N-forml-N -hydroxyamino) pentylphosphonic acid (2.10 g.). A part (1.8 g.) of the crystals was dissolved in water (6 ml.) to give insoluble materials, which were removed by filtration and washed with water. The filtrate and the washings were combined and ethanol (30 ml.) was added thereto under heating at 60°C to give purified crystals (1.62 g) of the same compound as mentioned above. M.p. 170 - 175°C (dec.).

I.R. (Nujol)
ν_{max} : 3600 - 2200, 1635, 1190, 1100, 1045, 1015, 945 cm^{-1}

N.M.R.
δ(ppm) in D_2O : 1.1 - 2.0 (8H, m)
3.55 (2H, t, J=6Hz)
7.95 (s) } 1H
8.30 (s)

(25) Formic acid (1.5 ml.) was added dropwise to acetic anhydride (530 mg.) at ambient temperature with stirring. The stirring was continued at the same temperature for 30 minutes, and then to the mixture were added 2-(N-hydroxyamino) ethylphosphonic acid (564 mg.). The reaction mixture was stirred at ambient temperature for 2 hours and concentrated under reduced pressure to give an oily residue. The residue was dissolved in methanol (10 ml.) to give a small volume of insoluble materials, which were removed by filtration. To the filtrate was added dropwise a solution of potassium hydroxide in methanol (2 ml.). The mixture was stirred for 30 minutes to give crystals, which were separated by filtration and washed twice with methanol (5 ml.) to give crystalline monopotassium salt of 2-(N-formyl-N -hydroxyamino) ethylphosphonic acid (630 mg.). M.p. 201 - 203°C (dec.)

I.R. (Nujol)
ν_{max} : 3600 - 2200, 1650, 1280, 1250, 1230, 1160, 1100, 1020, 920, 880, 795 cm^{-1}

N.M.R.
δ(ppm) in D_2O : 1.7 - 2.4 (2H, m)
3.6 - 4.2 (2H, m)
8.00 (s) } 1H
8.31 (s)

(26) Formic acid (2.0 ml.) was added dropwise to acetic anhydride (2.45 g.) at ambient temperature with stirring. After the stirring was continued at the same temperature for 30 minutes, 3-(N-hydroxyamino) propylphosphonic acid (3.10 g.) was added to the mixture. The reaction mixture was stirred for an hour and concentrated under reduced pressure to give a residue, which was dissolved in water (25 ml.). To the aqueous solution was added ethylenediamine (0.60 g.). The mixture was concentrated under reduced pressure to give a residue, which was dissolved in water. The aqueous solution was concentrated under reduced pressure to give a residue, and to the residue was added ethanol (30 ml.) to give crystals. The crystals were separated by filtration and washed twice with ethanol (10 ml.) to give crystalline ethylendiamine bis[3-(N-formyl-N- hydroxyamino) propylphosphonate] (3.95 g.), a part (3 g.) of which was recrystallized from 90% aqueous methanol to give needles (1 g.) of the same object compound. M.p. 112 - 118°C.

I.R. (Nujol)
ν_{max} = 3600 - 2200, 1630, 1200, 1120, 1010, 910 cm^{-1}

N.M.R.
δ(ppm) in D_2O : 1.3 - 2.1 (4H, m)
3.36 (2H, s)
3.62 (2H, t, J=6Hz)
7.96 (s) } 1H
8.32 (s)

(27) Formic acid (1.0 ml.) was added dropwise to acetic anhydride (1.2 ml.) at ambient temperature with stirring. The stirring was continued at the same temperature for 30 minutes and then 3-(N-hydroxyamino) propylphosphonic acid (1.51 g.) was added to the mixture. The reaction mixture was stirred at ambient temperature for 1.5 hours and concentrated under reduced pressure to give an oily residue, which was dissolved in ethanol (20 ml.). To the aqueous solution was added ethanolamine (0.61 g.) to precipitate an oil, which was separated by decantation and crystallized with ethanol (20 ml.) to give crystals. The crystals were separated by filtration, washed with ethanol and dried to give crystalline monoethanolamine salt of 3-(N-formyl-N- hydroxyamino) propylphosphonic acid (1.75 g.), a part (1.5 g.) of which was recrystallized from 90% aqueous ethanol to give the purified object compound (1.15 g). M.p. 139 - 142°C.

I.R. (Nujol)

ν_{max} : 3600 - 2200, 3190, 1660, 1190, 1100, 1035, 1020, 925, 880 cm^{-1}

N.M.R.

δ(ppm) in D_2O : 1.3 - 2.1 (4H, m)
3.10 (2H, t, J=5Hz)
3.60 (2H, t, J=6Hz)
3.80 (2H, t, J=5Hz)
7.96 (s) } 1H
8.32 (s)

(28) To a suspension of 2-(N-hydroxyamino) ethylphosphonic acid (564 mg.) in water (3 ml.) was added dropwise acetic anhydride (820 mg.) at ambient temperature. The reaction mixture was stirred at the same temperature and concentrated under reduced pressure to give an oily residue. The residue was dissolved in water (5 ml.) and the aqueous solution was concentrated under reduced pressure to give a residue. This operation was repeated twice. Subsequently, the residue obtained was dissolved in 1N aqueous sodium hydroxide solution (4 ml.). The aqueous solution was concentrated under reduced pressure to give precipitates, which were pulverized with ethanol to give crude powder. The crude powder was dissolved in water (10 ml.) and the aqueous solution was heated at 100 - 110°C for an hour and concentrated under reduced pressure to give precipitates, which were pulverized with ethanol to give crystalline monosodium salt of 2-(N-acetyl-N -hydroxyamin) ethylphosphonic acid (380 mg.). M.p. 185 - 192°C (dec.)

I.R. (Nujol)

ν_{max} : 3600 - 2200, 1620, 1230, 1160, 1040, 940, 890, 810 cm^{-1}

N.M.R.

δ(ppm) in D_2O : 1.6 - 2.3 (2H, m)
2.12 (3H, s)
3.5 - 4.1 (2H, m)

(29) Formic acid (2.0 g.) was added to acetic anhydride (3.5 g.) under ice-cooling with stirring. The mixture was stirred at ambient temperature for 30 minutes and added, under ice-cooling, to a solution of hydrochloric acid salt of 3-(N-hydroxyamino)-2 -methylpropylphosphonic acid (4.7 g.) in water (10 ml.) which was adjusted to pH 4.0 with aqueous potassium hydroxide solution. The reaction mixture was stirred at ambient temperature for 30 minutes and then concentrated under reduced pressure to give a residue, which was dissolved in water (20 ml.). To the solution was added dropwise a solution of potassium hydroxide (1.3 g.) in water (10 ml.). The mixture was concentrated under reduced pressure to give a residue, which was dissolved in water (20 ml.) and then the solution was concentrated under reduced pressure to give a residue. The residue was subjected to a column chromatography on cellulose (volume of cellulose: 600 ml., developing solvent: 70% aqueous isopropylalcohol). The eluate was concentrated under reduced pressure to give an oily residue, which was crystallized from a mixture of methanol and ethanol (1:10) to give crystalline monopotassium salt of 3-)N-formyl-N -hydroxyamino)-2 -methylpropylphosphonic acid (0.95 g.). M.p. 128 - 131°C (dec.)

N.M.R.

1.04 (3H, d, J=6Hz)
1.60 (2H, m)
2.26 (1H, m)
3.50 (2H, d, J=6Hz)
8.00 (s) } 1H
8.39 (s)

(30) A solution of monosodium salt of 3-(N-ethoxyalyl-N -hydroxyamino) propylphosphonic acid (277 mg) in a mixture of water (3 ml) and 1N aqueous sodium hydroxide solution (2 ml) was stirred at ambient temperature for 4 hours. The reaction mixture was neutralized with 1N hydrochloric acid (1 ml) and evaporated to dryness under reduced pressure. The residue was extracted with methanol (25 ml). The extract was evaporated to dryness under reduced pressure to give powdery disodium salt of 3-(N-hydroxy -N-oxaloamino) propylphosphonic acid (250 mg).

I.R. (Nujol)
ν_{max} : 3600 - 2100, 1620, 1280, 1225, 1150, 1030, 900 cm^{-1}

N.M.R.
δ(ppm) in D_2O; 1.30 - 2.30 (4H, m), 3.72 (2H, t, J=7Hz)

(31) Formic acid (300 mg.) was added dropwise to acetic anhydride (330 mg.) with stirring and the mixture was stirred for half an hour. To this solution were added 2-hydroxy-3 -(N-hydroxyamino) propylphosphonic acid (430 mg.) and then formic acid (0.5 ml.), and the mixture was stirred for 1.5 hours at ambient temperature and then evaporated to dryness under reduced pressure. The oily residue was dissolved in methanol (10 ml.) and adjusted to pH 6 - 7 with conc. aqueous ammonium hydroxide solution to give oily precipitates which was collected by decantation and pulverized by triturating with methanol to give monoammonium salt of 3-(N-formyl-N -hydroxyamino)- 2-hydroxypropylphosphonic acid (80 mg.).

I.R. (Nujol)
ν_{max} : 3700 - 2200, 1620, 1160, 1000 cm^{-1}

N.M.R.
δppm in D_2O; 1.72, 1.92 (2H, d, d, J=6Hz, 17Hz)
3.4 - 3.8 (2H, m)
4.2 (1H, m)
7.90 (s) } 1H
8.32 (s) }

(32) An oily 3-(N-formyl-N- hydroxyamino) propylphosphonic acid (12.05 g.), which was prepared by the reaction of 3-(N-hydroxyamino) propylphosphonic acid (15.5 g.), acetic anhydride (12.3 g.) and formic acid (9.8 ml.) conducted in substantially the same manner as that of Example (31), was dissolved in water (80 ml.) and treated with magnesium hydroxide (5.83 g.) for 15 minutes under ice-cooling with stirring.

The mixture was filtered and about half of the filtrate was evaporated to dryness under reduced pressure. The oily residue was pulverized by triturating with ethanol (60 ml.) to give magnesium salt of 3-(N-formyl-N -hydroxyamino)propyl phosphonic acid (12.05 g.), m.p. > 250°C.

I.R. (Nujol)
ν_{max} : 3700 - 2300, 1660, 1100, 1005 cm^{-1}

(33) Monoethyl 3-(N-formyl-N -hydroxyamino) propylphosphonate (0.86 g.) was obtained by reacting monoethyl 3-(N-hydroxyamino) propylphosphonate (0.92 g.) with a mixture of acetic anhydride (0.66 g.) and formic acid (0.60 g.) in substantially the same manner as that of Example (31) for 2 hours, evaporating to dryness under reduced pressure and crystallization from ethanol.

N.M.R.
δppm in D_2O : 1.30 (3H, t, J=7Hz)
1.47 - 2.30 (4H, m)
3.65 (2H, t, J=6Hz)
4.08 (2H, m)
7.99 (s) } 1H
8.30 (s) }

(34) 3-(N-Hydroxyamino) propylphosphonic acid (31.0 g.) was added to a mixture of acetic anhydride (24.6 ml.) and formic acid (19.6 ml.), which was prepared in the same manner as that of Example (31), and stirred for 1 hour at ambient temperature. The reaction mixture was stirred for 20 minutes by adding benzene (400 ml.) to give oily precipitates which were collected by decantation and washed with benzene (200 ml.) by decantation. The oily product was dissolved in water (120 ml.), treated with calcium oxide (11.2 g.) for 15 minutes under ice-cooling and filtered. The filtrate was carefully adjusted to pH 7 with 20% aqueous

sodium hydroxide solution under ice-cooling and allowed to stand overnight at ambient temperature to give crystals of monocalcium salt of 3-(N-formyl-N -hydroxyamino) propylphosphonic acid (34.6 g.), m.p. > 250°.

I.R. (Nujol)

ν_{max} : 3700 - 2500, 1650, 1320, 1265, 1220, 1145, 1060, 980, 895 cm^{-1}

An additional crystal of the same mono calcium salt (9.6 g.) was recovered from the mother liquor by condensing to about half of its original volume.

(35) An oily 3-(N-formyl-N -hydroxyamino) propylphosphonic acid was obtained from 3-(N-hydroxyamino) propylphosphonic acid (9.30 g.) and a mixture of acetic anhydride (7.4 ml.) and formic acid (6.0 ml.) in substantially the same manner as that of Example (34). This oil was dissolved in water (70 ml.) to form a clear solution (81 ml.), of which an aliquot (27 ml.) was mixted with a solution of arginine (3.48 g.) in water (30 ml.) and evaporated to dryness under reduced pressure. The residue was triturated with ethanol (50 ml.) to give solid arginine salt of 3-(N-formyl-N -hydroxyamino)- propylphosphonic acid (6.76 g.).

I.R. (Nujol)

ν_{max} : 3700 - 2200, 1640, 1160, 1030 cm^{-1}

(36) To a mixture of 3-(N-hydroxyamino) propylphosphonic acid (0.775 g.), sodium bicarbonate (0.84 g.), water (5 ml.) and acetone (5 ml.) was added dropwise a solution of methoxyacetyl chloride (1.05 g.) in anhydrous acetone (5 ml.) with stirring under ice-cooling. The reaction mixture was stirred for 30 minutes at the same temperature, adjusted to pH 9.0 with 1N aqueous sodium hydroxide solution and then stirred for 1 hour at ambient temperature. After adjusting to pH 3.0 with 10% hydrochloric acid, the mixture was evaporated to dryness under reduced pressure. The oily residue was washed twice with ethyl acetate (each 10 ml. portion) by decantation and dissolved in water (50 ml.). The aqueous solution was adjusted to pH 15 with 10% hydrochloric acid and passed through a column packed with activated charcoal (50 ml.). The column was washed with 70% aqueous acetone, and the effluent and washings were combined and evaporated to dryness under reduced pressure. The oily residue was dissolved in small amount of water, adjusted to pH 5.0 with 1N aqueous sodium hydroxide solution and evaporated to dryness to give monosodium salt of 3-(N-hydroxy-N- methoxyacetylamino) propylphosphonic acid (0.4 g.).

N.M.R.

δppm in D_2O : 1.36 - 2.08 (4H, m)
3.40 (3H, s)
3.64 (2H, t, J = 6Hz)
4.36 (2H, s)

(37) To a solution of diethyl 3-(N-hydroxyamino) propylphosphonate (2.80 g.) in chloroform (30 ml.) was added dropwise a mixture of acetic anhydride (2.04 g.) and formic acid (1.38 g.), which was prepared in the same manner as that of Example (31), under ice-cooling with stirring. The reaction mixture was stirred for half an hour at 0 - 5°C and for additional an hour at ambient temperature, and then evaporated to dryness under reduced pressure to give an oily residue, which was dissolved in a mixture of methanol (15 ml.) and water (5 ml.), adjusted to pH 8 with 1N aqueous sodium hydroxide solution and stirred for 1.5 hours at ambient temperature. The methanol was distilled off from this solution under reduced pressure to give an aqueous solution, which was adjusted to pH 5 with 10% hydrochloric acid and extracted with chloroform (once with 30 ml. portion and three times with 10 ml. portions). These combined extracts were dried over magnesium sulfate and evaporated to dryness under reduced pressure to give crude diethyl 3-N-formyl-N -hydroxyamino) propylphosphonate (2.89 g.), which was passed through a column packed with silica gel (60 g.). The column was eluted with a mixture of chloroform and methanol (25:1 by volume), and the fractions containing an object compound were collected and evaporated to dryness under reduced pressure to give the same pure object compound (1.71 g.).

I.R. (liquid film)

ν_{max} : 3500 (broad), 1620, 1200, 1030 cm^{-1}

N.M.R.

δppm in $CDC\ell_3$: 1.36 (6H, t, J = 7Hz)
1.5 - 2.4 (4H, m)
3.72 (2H, t, J = 6Hz)
4.15 (4H, m)
7.30 (s)) 1H
7.95 (s)

(38) A solution of phenoxyacetyl chloride (3.4 g.) in dried acetone (10 ml.) was added dropwise to a solution of 3-(N-hydroxyamino) propylphosphonic acid (1.51 g.) in mixture of 1N aqueous sodium hydroxide solution (30 ml.) and acetone (20 ml.) under ice-cooling in the course of 10 minutes, and the mixture was stirred for an hour at the same temperature, and then adjusted to pH 10 with 1N aqueous sodium hydroxide solution. The acetone was distilled off from the reaction mixture, and the remaining aqueous solution was adjusted to pH 2.0 with 10% hydrochloric acid, washed with ethyl ether, and then adjusted to pH 1.0 with 10% hydrochloric acid and saturated with sodium chloride. This solution was extracted twice with ethyl acetate (each 100 ml. portion) insoluble materials (0.2 g.) produced at this stage were collected by filtration] and the combined extracts were dried over magnesium sulfate and evaporated to dryness under reduced pressure to give 3-(N-hydroxy-N -phenoxyacetylamino) propylphosphonic acid (0.1 g.). Insoluble materials produced above were identified with the same object compound.

Total yield was 0.3 g.

N.M.R.

δppm in CD_3OD : 1.37 - 2.40 (4H, m),
3.74 (2H, t, J=6Hz)
4.90 (2H, s)
6.73 - 7.54 (5H, m)

(39) To N,N-dimethylformamide (0.80 g.) was added thionyl chloride (1.80 g.), and the mixture was stirred for half an hour at 50°C and then the unreacted thionyl chloride was removed. To the residue was added a small amount of methylene chloride and evaporated to dryness under reduced pressure. To the residue thus obtained were added methylene chloride (50 ml.) and crotonic acid (0.86 g.) at -30°C and the mixture was stirred for half an hour at the same temperature. To this solution was added a solution of 3-(N-hydroxyamino) propylphosphonic acid (1.55 g.) and N,O-bis(trimethylsilyl) acetamide (10 g.) in methylene chloride (30 ml.) at -40°C. After the mixture was stirred for half an hour at the same temperature, the temperature was gradually elevated to 0°C and the mixture was stirred for 2 hours. The reaction mixture was evaporated to dryness under reduced pressure to give a residue, which was dissolved in water (30 ml.), washed twice with ethyl acetate (each 30 ml. portion) and evaporated to dryness under reduced pressure. The resultant oily residue was washed with ethyl acetate, dissolved in ethanol (15 ml.) and then adjusted to pH 4.0 with an ethanolic potassium hydroxide to precipitate crystals. These crystals were collected by filtration, washed with a small amount of ethanol and dried to give monopotassium salt of 3-(N-crotonoyl -N-hydroxyamino) propylphosphonic acid (0.91 g.).

N.M.R.

δppm in D_2O : 1.26 - 2.30 (4H, m)
1.88 (3H, d, J=6Hz)
3.74 (2H, t, J=6Hz)
6.24 - 7.20 (2H, m)

(40) Monoammonium salt of 3-[N-hydroxy-N-(2 -phenylglycolloyl) amino]propylphosphonic acid was obtained by reacting 3-(N-hydroxyamino) propylphosphonic acid with 2-phenylglycollic acid, N,N-dimethylformamide and thionyl chloride, in substantially the same manner as that of Example (39) and then by treating the resultant compound with 28% aqueous ammonia.

N.M.R.

δppm in D_2O : 1.40 - 2.14 (4H, m)
3.68 (2H, t, J=6Hz)
5.70 (1H, s)
7.46 (5H, s)

(41) To a suspension of 2-(2,2-dichloroacetoxyimino) -2-phenylacetic acid (3.06 g.) in methylene chloride (20 ml.) was added phosphorus pentoxide (2.28 g.) under ice-cooling, and the mixture was stirred for 20 minutes at the same temperature and then evaporated to dryness under reduced pressure to give a residue, which was dissolved in methylene chloride (10 ml.). This solution was added dropwise to a solution of 3-(N-hydroxyamino) propylphosphonic acid (1.55 g.) and N,O-bis(trimethylsilyl) acetamide (10 g.) in methylene chloride (30 ml.) at -30 to 40°C in the course of 5 minutes, whereafter the mixture was stirred for half an hour at the same temperature and for additional an hour at 0°C. The reaction mixture was evaporated to dryness under reduced pressure to give an oily residue, which was dissolved in water (30 ml.), stirred for 20 minutes, saturated with sodium chloride, and extracted five times with ethyl acetate (each 20 ml.) and three times with n-butanol (each 30 ml.). These extracts were evaporated to dryness under reduced pressure to give an oily residue (4.5 g.),

which was dissolved in water (40 ml.). This aqueous solution was passed through a column packed with activated charcoal (100 ml.), and elution was conducted with water and then 30% aqueous acetone. The fractions containing an object compound were collected and evaporated to dryness under reduced pressure to give an oil (1.4 g.), which was dissolved in methanol and adjusted to pH 7 with 28% aqueous ammonia. The precipitates were collected by filtration and dried to give monoammonium salt of 3-[N-hydroxy-N-(2- hydroxyimino-2-phenylacetyl)amino] -propylphosphonic acid (1.30 g.).

N.M.R.

δppm in D_2O : 1.07 - 2.03 (4H, m)
3.54 (t, J=6Hz)) 2H
3.88 (t, J=6Hz)
7.55 (5H, s)

(42) 3-[N-Hydroxy-N-[2-(1H-tetrazol-l-yl) acetyl]amino] propylphosphonic acid (1.75 g.) was obtained by reacting 3-(N-hydroxyamino) propylphosphonic acid (1.55 g.) with 2-(1H-tetrazol-l-yl) acetyl chloride (2.22 g.) in methylene chloride (30 ml.) in substantially the same manner as that of Example (41). M.p. 157 - 159°C.

N.M.R.

δppm in D_2O : 1.47 - 2.36 (4H, m)
3.78 (2H, t, J=6Hz)
5.72 (2H, s)
9.30 (1H, s)

(43) Monoammonium salt of 3-(N-hydroxy-N -nicotinoylamino) propylphosphonic acid (1.3 g.) was obtained by reacting 3-(N-hydroxyamino) propylphosphonic acid (0.775 g.) with nicotinoyl chloride (1.23 g.) in methylene chloride (15 ml.) in substantially the same manner as that of Example (41), and by passing the resultant compound through a column packed with anion-exchange resin Amberlite IR-45 (Trademark, maker; Rohm & Haas Co.) (20 ml.) and eluting with 1N aqueous ammonia.

N.M.R.

δppm in D_2O : 1.37 - 2.40 (4H, m)
3.84 (2H, t, J=6Hz)
7.62 (1H, d, d, J=8Hz, 5Hz)
8.14 (1H, double t; J=7Hz, 1Hz)
8.46 - 9.10 (2H, m)

(44)

(a) 3-(N-Hydroxy-N-phenylglyoxyloylamino) propylphosphonic acid was obtained by reacting 3-(N-hydroxyamino) propylphosphonic acid (1.55 g.) with phenylglyoxyloyl chloride (1.72 g.) in methylene chloride (40 ML.) in substantially the same manner as that of Example (41).

This compound was dissolved in ethanol (13 ml.), adjusted to pH 7.0 with 28% aqueous ammonia under ice-cooling and allowed to stand to give monoammonium salt of the same object compound (1.94 g.).

N.M.R.

δppm in D_2O : 1.36 - 2.08 (4H, m)
3.88 (2H, t, J=6Hz)
7.36 - 8.08 (5H, m)

(b) To a solution of monoammonium salt of 3-(N-hydroxy-N- phenylglyoxyloylamino) propylphosphonic acid (0.32 g.) in water (9 ml.) was added sodium borohydride (0.04 g.) under ice-cooling, whereafter the mixture was stirred for an hour at ambient temperature. The reaction mixture was adjusted to pH 1.0 with 10% hydrochloric acid and then evaporated to dryness under reduced pressure. To the resultant residue was added ethanol (7 ml.) and the insoluble materials were removed by filtration. The filtrate was evaporated to dryness under reduced pressure and the remaining oily residue was dissolved in ethanol (10 ml.), adjusted to pH 7.0 with 28% aqueous ammonia solution and then evaporated to dryness under reduced pressure to give oily monoammonium salt of 3-[N-hydroxy-N-(2-phenylglycolloyl) amino]propylphosphonic acid (0.29 g.).

N.M.R.

δppm in D_2O : 1.40 - 2.14 (4H, m)
3.68 (2H, t, J=6Hz)
5.70 (1H, s)
7.46 (5H, s)

(45) To a suspension of 2-hydroxy-3-(N- hydroxyamino)- propylphosphonic acid (855 mg.) in water (4 ml.) was added acetic anhydride (1.02 g.) under ice-cooling, and the reaction mixture was stirred for 15 minutes at the same temperature. The reaction mixture was evaporated to dryness under reduced pressure to give a residue, which was dissolved in water (3 ml.) and adjusted to pH 10 with 28% aqueous ammonia, whereafter the aqueous solution was stirred for 3 hours at ambient temperature. This aqueous solution was adjusted to pH 2 with 1N hydrochloric acid and passed through a column of activated charcoal (50 ml.). The column was washed with water, and then elution was conducted with 80% aqueous acetone (200 ml.) to give an oily residue (400 mg.), which was dissolved in methanol (5 ml.). To this methanolic solution were added sodium hydroxide (80 mg.) in methanol (3 ml.), and then ethanol to give powder. This powder was collected by filtration and dried to give mono-sodium salt of 3-(N-acetyl-N -hydroxyamino)-2 -hydroxypropylphosphonic acid (230 mg.).

I.R. (Nujol
ν_{max} : 1630, 1140 cm^{-1}
N.M.R.
δppm in D_2O : 1.88 (2H, d, d, J = 6Hz, 18Hz)
2.16 (3H, s)
3.65 - 3.90 (2H, m)
4.30 (1H, m)

(46) To a suspension of 3-(N-hydroxyamino)-trans -l-propenylphosphonic acid (1.53 g.) in water (7 ml.) was added dropwise acetic anhydride (2.04 g.), and the mixture was stirred for half an hour at ambient temperature, and evaporated to dryness under reduced pressure to give a residue, to which were added water (20 ml.) and then 1N aqueous potassium hydroxide solution (10 ml.) under ice-cooling. The mixture was heated for an hour at 100°C and evaporated to dryness under reduced pressure to give a pale brown oil (1.68 g.), to which were added methanol (7 ml.) and acetone (2 ml.). Insoluble materials were filtered off and the filtrate was adjusted to pH 1 with 1N hydrochloric acid, passed through a column packed with activated charcoal (50 ml.). The column was washed with water (200 ml.) and eluted with 80% aqueous acetone (70 ml.). The effluent was adjusted to pH 5.6 with 1N aqueous potassium hydroxide solution and evaporated to dryness under reduced pressure, and an oily residue was powdered with a mixture of ethanol and acetone to give monopotassium salt of 3-(N-acetyl-N-hydroxyamino)-trans -l-propenylphosphonic acid (0.40 g.).

I.R. (Nujol)
ν_{max} : 1650, 1620 (shoulder), 1140 cm^{-1}
N.M.R.
δppm in D_2O : 2.13 (3H, s)
4.35 (2H, m)
5.70 - 6.60 (2H, m)

(47) To an aqueous solution (45 ml.) of potassium alum (9.17 g.) was added mono sodium salt of 3-(N-formyl-N- hydroxyamino) propylphosphonic acid (3.08 g.) with stirring, and the solution was adjusted to pH 6 - 7 with 10% aqueous sodium hydroxide solution and then stirred for 2 hours at ambient temperature. The precipitating materials were collected by filtration, washed twice with water (each 10 ml.) and dried to give aluminum salt of 3-(N-formyl-N -hydroxyamino) propylphosphonic acid (2.28 g.)

I.R. (Nujol)
ν_{max} : 3700 - 2300, 1640, 1100, 920

(48) (a) Preparation of the starting compound :
1) Pulverized potassium carbonate (160 g.) was added to a solution of ethyl 2-hydroxyiminoacetoacetate (a mixture of syn and anti isomers) (152 g.) in acetone (500 ml.). Dimethyl sulfate (130 g.) was dropwise added thereto with stirring over 1 hour at 45 to 50°C and the mixture was stirred for 2 hours. An insoluble material was filtered off and the filtrate was concentrated under reduced pressure. The filtered insoluble material was dissolved in water (500 ml.) and this solution was added to the residue. The mixture was extracted twice with ethyl acetate (300 ml.). The extract was washed twice with water (200 ml.) and with a saturated sodium chloride aqueous solution (200 ml.) and dried over magnesium sulfate. The solvent was distilled off under reduced pressure and the residue was distilled under reduced pressure to give colorless oil of ethyl 2-methoxyiminoacetoacetate (a mixture of syn and anti isomers) (145.3 g.), bp 55 to 64°C C/O.5 mm Hg.

I.R. (Film): 1745, 1695, 1600 cm^{-1}
N.M.R. ($CDC\ell_3$, δ)
ppm 4.33 (4H, q, J=8Hz)
4.08 (3H, s)
3.95 (3H, s)
2.40 (3H, s)
1.63 (3H, s)
1.33 (6H, t, J=8Hz)

2) Sulfuryl chloride (235 ml.) was dropwise added over 20 minutes with stirring and ice-cooling to a solution of ethyl 2-methoxyiminoacetoacetate (syn isomer) (500 g.) in acetic acid (500 ml.), and the mixture was stirred overnight under cooling with water. Nitrogen gas was introduced to the reaction mixture for 2 hours, and the resulting mixture was poured into water (2.5 ℓ.) After extracting with methylene chloride (500 ml.) and twice with methylene chloride (200 ml.), the extracts were combined. The combined extracts were washed with a saturated aqueous solution of sodium chloride, and adjusted to pH 6.5 by adding water (800 ml.) and sodium bicarbonate. Methylene chloride layer was separated, washed with an aqueous solution of sodium chloride and dried over magnesium sulfate. The solvent was distilled off to give ethyl 2-methoxyimino-4- chloroacetoacetate (syn isomer) (559 g.)
I.R. (Film): 1735, 1705 cm^{-1}

3) Ethyl 2-methoxyimino-4- chloroacetoacetate (syn isomer) (50 g.) was added over 3 minutes with stirring at ambient temperature to a solution of thiourea (18.4 g.) and sodium acetate (19.8 g.) in a mixture of methanol (250 ml.) and water (250 ml.). After stirring for 35 minutes at 40 to 45°C, the reaction mixture was cooled with ice and adjusted to pH 6.3 with a saturated aqueous solution of sodium bicarbonate. After stirring for 30 minutes at the same temperature, precipitates were collected by filtration, washed with water (200 ml.) and then with diisopropyl ether (100 ml.), and dried to give colorless crystals of ethyl 2-methoxyimino-2- (2-amino-1,3-thiazol-4-yl) acetate (syn isomer) 37.8 g.), mp 161 to 162°C.
I.R. (Nujol): 3400, 3300, 3150, 1725, 1630, 1559 cm^{-1}
N.M.R. ($CDC\ell_3$, δ)
ppm 6.72 (1H, s)
5.91 (2H, broad s)
4.38 (2H, q, J=7Hz)
4.03 (3H, s)
1.38 (3H, t, J=7Hz)

4) A mixture of acetic anhydride (6.1 g.) and formic acid (2.8 g.) was stirred for 2 hours at 50°C. The resulting mixture was cooled and ethyl 2-methoxyimino-2- (2-amino-1,3-thiazol-4-yl) acetate (syn isomer) (4.6 g.) was added thereto at 15°C. After the mixture was stirred for 3.5 hours at ambient temperature, cooled water (100 ml.) was added thereto. The resulting mixture was extracted with ethyl acetate (200 ml.). The extract was washed with water and then with a saturated aqueous solution of sodium bicarbonate until the washing was changed to weakly alkaline solution. The extract was further washed with a saturated aqueous solution of sodium chloride and dried over magnesium sulfate. The solvent was distilled off and the residue was washed with diisopropyl ether, collected by filtration and dried to give ethyl 2-methoxyimino -2-(2-formamido-1,3 thiazol-4-yl)-acetate (syn isomer) 4.22 g.), mp 122 to 124°C (dec.).
I.R. (Nujol): 3150, 1728, 1700 cm^{-1}
N.M.R. ($CDC\ell_3$, δ)
ppm 12.58 (1H, broad s)
8.95 (1H, s)
7.17 (1H, s)
4.42 (2H, q, J=8Hz)
4.00 (3H, s)
1.37 (3H, t, J=8Hz)

5) A solution of sodium hydroxide (1.6 g.) in water (30 ml.) was dropwise added over 5 minutes with stirring and ice-cooling to a suspension of ethyl 2-methoxyimino-2- (2-formamido-1,3- thiazol-4-yl)acetate (syn isomer) (5.14 g.) in water (60 ml.), and the resulting mixture was stirred for 1.5 hours at 10 to 20°C. The reaction mixture was adjusted to pH 7 with 10% hydrochloric acid and washed twice with ethyl acetate (100 ml.). To the aqueous layer was added ethyl acetate (200 ml.), and the resulting mixture was adjusted to pH 1 with

10% hydrochloric acid and extracted with the ethyl acetate. The aqueous layer was further extracted with ethyl acetate (100 ml.). Both ethyl acetate extracts were combined, washed with a sodium chloride aqueous solution (100 ml.) and dried over magnesium sulfate. The solvent was distilled off to give 2-methoxyimino-2- (2-formamido-1,3- thiazol-4-yl) acetic acid (syn isomer) (1.85 g.), mp 152°C (dec.), which was recrystallized from ethyl acetate to give a pure compound, mp 167°C (dec.).

I.R. Nujol): 3200, 2800 - 2100, 1950, 1600 cm^{-1}

N.M.R. (d_6-DMSO, δ)

ppm 8.60 (1H, s)
7.62 (1H, s)
3.98 (1H, s)

(b) Preparation of the object compound :

Hydrochloric acid salt of 3-[N-{2-(2-amino- 1,3-thiazol-4-yl) -2-methoxyiminoacetyl}-N -hydroxyamino]propylphosphonic acid (3.0 g) was obtained by reacting 3-(N-hydroxyamino) propylphosphonic acid (1.40 g) with 2-methoxyimino-2-(2- formamido-1,3-thiazol- 4-yl)acetic acid (syn isomer) (2.29 g), N,N-dimethylformamide (0.80 g) and phosphorus oxychloride (1.69 g) in substantially the same manner as that of Example (39) and then hydrolyzing the resultant material with hydrochloric acid (2ml).

N.M.R.

δppm in D_2O : 1.7 - 2.1 (4H, m)
3.7 - 3.9 (2H,
4.04 (3H, s)
7.04 (1H, s)

Example for O-Acylation

(1) A solution of benzoyl chloride (700 mg) in dry acetone (6 ml) was added dropwise to a solution of sodium salt of 3-(N-formyl-N- hydroxyamino) propylphosphonic acid (820 mg) in a mixture of water (15 ml) and acetone (15 ml) under ice-cooling, while stirring. During this period, pH of the mixture was kept at around 7.5 - 7.7 with 1N aqueous sodium hydroxide solution. The stirring was continued at the same temperature for 10 minutes and then acetone was evaporated under reduced pressure. The resulting aqueous solution was adjusted to pH 3.5 with 1N hydrochloric acid and ether (40 ml) was added thereto. After removal of the precipitated impurities, the aqueous layer was adjusted to pH 1.6 with 1N hydrochloric acid and extracted three times with ethyl acetate (50 ml, 20 ml x 2). The combined ethyl acetate layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated to dryness to give crystals, which were washed with ether to give crystalline 3-(N-benzoyloxy -N-formylamino) propylphosphonic acid (620 mg). Mp 149 - 153°C (dec.)

I.R. (Nujol)

ν_{max} : 3400 - 2100, 1765, 1630, 1250,
1135, 1035, 1010, 980 cm^{-1}

N.M.R.

δ(ppm) in CD_3OD ; 1.6 - 2.4 (4H, m),
3.92 (2H, t, J=6Hz),
7.94 - 8.3 (5H, m),
8.35 (1H, s)

(2) Monosodium salt of 3-(N-formyl-N- hydroxyamino) propylphosphonic acid (2.05 g.) was dissolved in a mixture of 1N aqueous sodium hydroxide solution (20 ml.), water (10 ml.) and acetone (10 ml.). To the solution was added dropwise a solution of p-chlorobenzoyl chloride (2.10 g.) in dry acetone (5 ml.) at 0-5°C with stirring. After the stirring was continued at the same temperature for 30 minutes, ethyl acetate (40 ml.) was added to the reaction mixture and then the resultant mixture was adjusted to pH 1 with 10% hydrochloric acid. The ethyl acetate layer was separated and then the aqueous layer was extracted again with ethyl acetate (20 ml.). The combined ethyl acetate layer was washed with aqueous sodium chloride solution, dried over magnesium sulfate and concentrated under reduced pressure to give an oily residue, which was crystallized with ethyl ether (40 ml.) to give crystals. The crystals were separated by filtration, washed twice with ethylether (10 ml.) to give crystalline 3-[N-(p-chlorobenzoyloxy) -N-formylamino]propyl phosphonic acid (2.71 g.).

M.p. 133 - 136°C (dec.)

I.R. (Nujol)

ν_{max} : 3600 - 2400, 1770, 1650, 1240,
1200, 1090, 1010, 970 cm^{-1}

N.M.R.
δ(ppm) in DC_3OD : 1.5 - 2.3 (4H, m)
3.90 (2H, t, J=6Hz)
7.50, 8.08 (4H, AB_q, J_{AB}=15Hz)
8.33 (1H, s)

(3) To a solution of monosodium salt of 3-(N-formyl-N- hydroxyamino) propylphosphonic acid (2.05 g.) in a mixture of 1N aqueous sodium hydroxide solution (20 ml.) and acetone (10 ml.) was added dropwise a solution of n-butyryl chloride (1.56 g.) in acetone (7 ml.) at 0-5°C with stirring. After the stirring was continued at the same temperature for 30 minutes, the reaction mixture was concentrated under reduced pressure to give a formy residue. To the residue was added ethanol (50 ml.) to give insoluble materials, which were removed by filtration. The filtrate was concentrated under reduced pressure to give a residue, which was pulverized with acetone, (30 ml.) to give powdery monosodium salt of 3-(N-formyl-N-n-butyryloxyamino) propylphosphonic acid (980 mg.).

I.R. (Nujol)
ν_{max} : 3600 - 2200, 1795, 1690, 1160, 1070, 910, 895 cm^{-1}

N.M.R.
δ(ppm) in D_2O : 1.00 (3H, t, J=7Hz)
1.4 - 2.1 (6H, m)
2.58 (2H, t, J=7Hz)
3.76 (2H, t, J=6Hz)
8.20 (1H, s)

Example for Esterification
(1) Diazomethane in ethyl ether was added dropwise to a solution of 3-(N-acetyl-N-hydroxyamino) propylphosphonic acid (600 mg) in methanol (20 ml) under ice-cooling until yellow color of diazomethane in the reaction mixture didn't disappear. The solvent was distilled off from the solution under reduced pressure. The obtained residue was subjected to column chromatography on silica gel with an eluent (a mixture of 19 parts of chloroform and one part of methanol by volume). The fractions containing the object compound were collected and concentrated under reduced pressure to give a residual oil (350 mg). This purification operation was repeated once again to give dimethyl 3-(N-acetyl-N- hydroxyamino) propylphosphonate (260 mg).

Infrared Absorption Spectrum (liquid film) :
ν_{max} = 2600~3600, 1640, 1230, 1030 cm^{-1}
NMR Absorption Spectrum ($CDCl_3$) :
δ(ppm)
1.6~2.2 (4H, m)
2.13 (3H, s)
3.66 (1H, t, J=6Hz)
3.70 (6H, d, J=10Hz)
9.65 (1H, broad s)

(2) To a solution of monosodium salt of 3-(N-formyl- N-hydroxyamino) propylphosphonic acid (2.05 g.) in a mixture of water (10 ml.) and methanol (50 ml.) was added dropwise a solution of diazomethane in ethyl ether under ice-cooling with stirring until the above phosphonic acid was not detected by a thin-layer chromatography on silica gel. After the reaction was completed, the reaction mixture was concentrated under reduced pressure to give a formyl residue. To the residue was added ethanol (50 ml.) to give insoluble materials, which were removed by filtration. The ethanolic solution was concentrated under reduced pressure to give a residue, which was pulverized with acetone to give crude powder (1.47 g.). The powder was dissolved in methanol (10 ml.) and to the solution was added isopropyl alcohol (40 ml.) to give precipitates. The mixture was stirred for 6 hours at ambient temperature, and the precipitates were separated by filtration and washed twice with isopropyl alcohol (5 ml.) to give powdery monosodium salt of methyl 3-(N-formyl-N -hydroxyamino)- propylphosphonate (470 mg.). The object compound (330 mg.) was also recovered from the filtrate and washings by concentrating them to a volume of 10 ml.

I.R. (Nujol)
ν_{max} : 3600 - 2200, 1660, 1230, 1190, 1040, 880 cm^{-1}

N.M.R.
δ(ppm) in D_2O : 1.2 - 2.2 (4H, m)
3.58 (3H, d, J=10Hz)
3.75 (2H, t, J=6Hz)
7.97 (s)) 1H
8.30 (s)

(3) Dimethyl 3-(N-formyl-N- hydroxyamino)-2 -hydroxypropyl-phosphonate (170 mg) was obtained by reacting 3-(N-formyl-N- hydroxyamino)-2 -hydroxypropylphosphonic acid (200 mg) with diazomethane in substantially the same manner as that of Example (1).
N.M.R.
δppm in $CDCl_3$
2.17 (2H, d, d, J=6 and 18Hz)
2.20 (3H, s)
3.81 (6H, d, J=11Hz)
3.6 - 3.9 (2H, m)
4.35 (1H, m)

Formation of C-S bond
(1) A mixture of 3-[N-(2-chloroacetyl) -N-hydroxyamino]propyl phosphonic acid (232 mg), water (2 ml, D, L-cysteine hydrochloride (176 mg) was adjusted to pH 8 with 1N aqueous sodium hydroxide solution and stirred at ambient temperature for 5 hours. The reaction mixture was adjusted to pH 3 with 1N hydrochloric acid, and ethanol (5 ml) was added. This mixture was allowed to stand overnight in a refrigerator (4°C) to give crystals, which were separated by filtration, washed with ethanol and then dried to give crystalline 3-[N- 2-amino-2 -carboxyethylthio)acetyl -N-hydroxyamino] propylphosphonic acid (240 mg). Mp 167 - 169.5°C (dec.).
I.R. (Nujol)
ν_{max} : 3600 - 2000, 1635, 1600, 1580, 1220, 1170, 1030, 960 cm^{-1}
N.M.R.
δ(ppm) in D_2O; 1.4 - 2.1 (4H, m),
3.1 - 3.3 (2H, m),
3.64 (4H, broad s),
4.02 (1H, t, J=6Hz)

Example for Fermentation
(1) Culture medium (100 ml) containing 2% of starch, 1% of cottonseed meal and 1% of dried yeast was poured into each of five 500 ml. Sakaguchi-flasks and sterilized at 120°C for 20 minutes. A loopful of slant culture of *Streptomyces rubellomurinus* FERM receipt No. 3563 (ATCC No. 31215) was inoculated to each of the medium and cultured at 30°C for two days. The resultant culture was inoculated to a medium (20 ℓ) containing 5% of soluble starch, 0.5% of cottonseed meal, 2.5% of gluten meal, 0.5% of dried yeast, 1% of $MgSO_4 \cdot 4H_2O$, 1% of KH_2PO_4 and 0.7% of Na_2HPO_4, $12H_2O$ in 30 ℓ.Jar-fermenter which had been sterilized at 120°C for 20 minutes in advance, and cultured at 30°C for 3 days.

After the culture was completed, diatomaceous earth (400 g) was added to the culture broth and the mixture was filtered. The filtrate (20 ℓ) was concentrated under reduced pressure to a volume of one liter. To the concentrate was added methanol (4 ℓ), and the mixture was stirred to give precipitates, the precipitates were removed by filtration and the filtrate was concentrated to a volume of one liter. The resultant concentrate was passed through a column of an activated charcoal. The passed-through solution was adjusted to pH 2.0 with a cation exchange resin, Duolite C-20 (trade mark, made by Diamond Shamrock Chemical Co.) (H^+ type; 500 ml) and passed through a column of Duolite A6 (trade mark, made by Diamond Shamrock Chemical Co.) (OH^- type) (500 ml). Subsequently, elution was carried out with 0.1N aqueous sodium hydroxide solution (1500 ml). The eluate was adjusted to pH 2.0 with Duolite C-20 (H^+ type) and then passed through a column of an activated charcoal. The object compound was eluted with 70% aqueous acetone (1 ℓ). Fractions containing the object compound were collected and concentrated under reduced pressure. The residue thus obtained, was adjusted to pH 6.5 with 6N aqueous sodium hydroxide solution and subjected to column chromatography on cellulose (300 ml) with an eluent (80% aqueous propanol). Fractions containing the object compound were collected and dried under reduced pressure to give a white powder (600 mg). The powder was dissolved in a small volume of methanol under heating, and then a small volume of acetone was added to the solution. The mixture was allowed to stand overnight at 4°C to give crystals, which was

filtered and dried to give monosodium salt of FR-900098(300 mg) in the form of colorless crystals.

(2) An aqueous medium containing 2% of potato starch, 1% of gluten meal, 1% of dried yeast and 1% of corn steep liquor was adjusted to pH 7.0 with 6N aqueous sodium hydroxide solution. Then, each 100 ml of the medium was poured into six of 500 ml. Erlenmeyer flasks, respectively and sterilized at 120°C for 20 minutes. To each of the medium was inoculated a loopful of slant culture of *Streptomyces lavendulae* ATCC 31279 and the organism was grown on a rotary shaker at 30°C for 3 days.

On the other hand, an aqueous medium (20 liters) containing 3% of methyl oleate, 1% of cottonseed meal, 1% of wheat germ, 0.5% of dried yeast, 0.5% of corn steep liquor, 1% of potassium biphosphate, 1% of secondary sodium phosphate was poured into 30 liters, jar-fermenter and sterilized at 120°C for 30 minutes. To the medium was added whole volume of the cultured broth, as obtained above and then the organism was grown at 30°C for 3 days. During the culture period, the fermentation was conducted by stirring the broth with a propeller equipment in a ratio of 250 r.p.m., passing sterile air through the broth in a ratio of 20 liters/broth/minute and maintaining the internal atmospheric pressure of the fermenter at 0.5 (kg/cm^2).

After completion of the culture, the cultured broth was filtered with an aid of diatomaceous earth (2 kg). The filtrate (15) liters) was adjusted to pH 2.0 with 1N hydrochloric acid and passed through a column of activated charcoal (5 liters). After the column was washed with water, elution was carried out with 70% aqueous acetone (4 liters). The eluate was concentrated to a volume of one liter, adjusted to pH 2 with 6N hydrochloric acid and then passed through a column of an anion exchange resin, Duolite A-6 (OH-type) (trade name, Diamond Shamrock Chemical Co.) (500 ml). After the column was washed with water, elution was carried out with 0.1N aqueous sodium hydroxide solution (1.5 liters). The eluate was passed through a column of cation exchange resin, Duolite C-20 (H^+ type) (trade name, Diamond Shamrock Chemical Co.). After the column was washed with water, elution was carried out with 60% aqueous acetone (500 ml). The eluate was concentrated under reduced pressure to give an oily residue, which was subjected to a column chromatography on cellulose (300 ml) (developing solvent: 80% aqueous acetonitrile). The fractions containing the object compound were collected and concentrated under reduced pressure to give an oily residue, which was adjusted to pH 7.0 with 1N aqueous potassium hydroxide solution and subjected to a column chromatography on cellulose (300 ml) (developing solvent: 60% aqueous propanol). Fractions containing the object compound were collected and concentrated under reduced pressure to give an oily residue, which was dissolved in ethanol (2 ml). To the solution were added acetone (20 ml) and diethyl ether (200 ml) to give precipitates, which was separated by filtration and dried to give crude powder (150 mg). The powder was dissolved in water (150 ml), and the solution was adjusted to pH 7 and passed through a column of activated charcoal (100 ml). The passed solution was concentrated under reduced pressure to give an oily residue, which was subjected to a column chromatography on cellulose (200 ml) (developing solvent: 65% aqueous propanol). The fractions containing the object compound was collected and concentrated under reduced pressure to give an oily residue, which was dissolved in methanol (1 ml). The solution was warmed at 50°C, and to the solution was added acetone (10 ml). The mixture was allowed to stand overnight at 4°C to give crystals, which was collected by filtration and dried to give monopotassium salt of FR-31705 (5 mg) in the form of needles.

(3) Each 100 ml of an aqueous medium containing 1% of potato starch, 1% of glycerol, 1% of cottonseed meal and 1% of dried yeast was poured into ten of 500 ml. Erlenmeyer flasks and sterilized at 120°C for 20 minutes. Each one loopful of slant culture of *Streptomyces lavendulae* ATCC 31279 was inoculated into the medium, respectively and the organism was grown on a rotary shaker at 30°C for 3 days.

On the other hand, 80 liters of an aqueous medium containing 3% of methyl oleate, 1% of cottonseed meal, 1% of wheat germ, 0.5% of corn steep liquor, 0.5% of dried yeast, 1% of potassium biphosphate and 1% of secondary sodium phosphate was poured into 100 liters jar-fermenter and sterilized at 120°C for 30 minutes. Whole volume of the cultured broth, as obtained above, was inoculated into the medium and the organism was grown at 30°C for 72 hours. During the culture period, the fermentation was conducted by stirring the broth with a propeller equipment in a ratio of 130 r.p.m., passing sterile air through the broth in a ratio of 80 liters/broth/minute and maintaining the internal atmospheric pressure of the fermenter at 1 (kg/cm^2.

After completion of the culture, the cultured broth was filtered with an aid of diatomaceous earth (5 kg). The filtrate (70 liters) was adjusted to pH 2 with 6NHC1 and then treated with activated charcoal (20 liters). Elution was carried out with 20% aqueous acetone. Acetone

was removed from the eluate under reduced pressure. The resultant aqueous solution was adjusted to pH 2 with cation exchange resin, Duolite C-20 (H^+ type) and then passed through a column of anion exchange resin, Duolite A-6 (OH- type). Elution was carried out with 0.2N aqueous ammonia. The eluate was adjusted to pH 6 and lyophilized to give crude powder (100 g), which was dissolved in water (3 liters). The solution was adjusted to pH 2 with 6N hydrochloric acid and treated with activated charcoal (6 liters). Elution was carried out with 0.03N aqueous ammonia. The eluate containing the object compound and concentrated under reduced pressure to a volume of one liter. The concentrate was adjusted to pH 2, further concentrated under reduced pressure and then subjected to a column chromatography on cellulose (one liter). The column was washed with acetone (one liter). Then, elution was carried out with 97% aqueous acetone to provide the eluate containing FR-31705 and the same was carried out with 95% aqueous acetone to provide the eluate containing FR-900136. The eluate containing FR-900136 was neutralized with 1N aqueous sodium hydroxide solution and concentrated under reduced pressure to give a residue, which was pulvelized with a mixture of acetone and diethylether to give monosodium salt of FR-900136 (50 mg) as powder.

(4) Ten of 500ml. Erlenmeyer flasks containing 100 ml of an aqueous medium containing 1% of potato starch, 1% of glycerol, 1% of cottonseed meal and 1% of dried yeast was sterilized at 120°C for 20 minutes. To each of the flasks was inoculated a loopful of slant culture of *Streptomyces rubellomurinus* subsp. *indigoferus* ATCC 31304, whereafter the organism was grown on a rotary shaker at 30°C for 3 days.

On the other hand, an aqueous medium (70 liters) containing 2% of soluble starch, 0.25% of corn steep liquor, 0.25% of dried yeast, 0.5% of cottonseed meal, 0.5% of wheat germ, 0.5% of KH_2PO_4, 0.5% of $Na_2HPO_4.12H_2O$ and 0.000125% of $COC1_2.12H_2O$ was poured into 100 liters.jar-fermenter and sterilized at 120°C for 30 minutes. To the medium was added whole volume of the cultured broth, as obtained above and then the organism was grown at 30°C for 3 days. During the culture period, the fermentation was conducted by stirring the broth with a propeller equipment in a ratio of 300 r.p.m., passing sterile air through the broth in a ratio of 70 liters/broth/minute and maintaining internal atmospheric pressure of the fermenter at 0.5 (kg/cm^2)

After completion of the culture, the cultured broth was adjusted to pH 2.8 with 6N hydrochloric acid to give precipitates, which were removed off by filtration. The filtrate was passed through a column of activated charcoal (10 liters). Then, elution was carried out with 70% aqueous acetone (20 liters). The eluate was concentrated under reduced pressure to give residue, to which water was added to give an aqueous solution (15 liters). The aqueous solution was passed through a column of DEAE-Sephadex, (H^+) type (8 liters) (trade name, made by Pharmacia A.B.) which was in advance treated with 1/100 M phosphate buffer solution (pH 6.0). Then, elution was carried out with 0.3 M aqueous sodium chloride solution (10 liters). The eluate was adjusted to pH 3.3 with 6N hydrochloric acid and then passed through a column of activated charcoal (2 liters). Water was added to the passed solution so that the total volume became 30 liters. The resultant aqueous solution was adjusted to pH 2.8 with 6N hydrochloric acid and then passed through a column of activated charcoal (7 liters). Then, elution was conducted with 70% aqueous acetone. The active fractions were collected, adjusted to pH 6.0 with 6N aqueous sodium hydroxide solution and concentrated under reduced pressure to a volume of 100 ml. The concentrate was subjected to a column chromatography on cellulose. (1 liter). The column was developed with 75% aqueous propanol (2 liters) to give fraction (A) and then developed with 70% aqueous propanol (2 liters) to give fraction (B).

The fraction (A) was concentrated under reduced pressure to a volume of 40 ml and the resultant concentrate was passed through a column of Sephadex G-15 (1 liter) (trade name, made by Pharmacia A.B.) and then subjected to a column chromatography on cellulose. The column was developed with 80% aqueous propanol. The active fractions were collected and concentrated under reduced pressure to give a residue, which was lyophilized to give monosodium salt of FR-900098 (300 mg) as white powder.

The fraction (B), as obtained above, was concentrated under reduced pressure to a volume of 60 ml and the resultant concentrate was passed through a column of Sephadex G-15 (1 liter) and then subjected to a column chromatography on cellulose. The column was developed with 75% aqueous propanol. The active fractions were collected and evaporated to dryness to give white powder of monosodium salt of FR-33289 (600 mg)

Examples for the antimicrobial composition

(i) Preparation for injection

(1) The required quantities of sterile antibiotic, monosodium salt of 3-(N-acetyl-N-hydroxyamino) propylphosphonic acid were distributed into vials, thereby containing 500

mg. of the active ingredient. The vials were sealed hermetically to exclude bacteria. Whenever the vials are required for use, 2 ml. of a sterile distilled water for injection is added to the vial and the vial is subjected to administration.

In substantially the same manner as described in the above example (1), there was prepared an injection preparation of an antibiotic as illustrated in the following Example (2) to (4).

(2) Monoammonium salt of 3-(N-formyl-N -hydroxyamino)- propylphosphonic acid (250 mg.) was used as the active ingredient for injection.

(3) Monopotassium salt of 3-(N-formyl-N -hydroxyamino)- trans-l- propenylphosphonic acid (250 mg.) was used as the active ingredient for injection.

(4) Monosodium salt of 3-(N-acetyl -N-hydroxyamino)-2 -hydroxypropylphosphonic acid (500 mg.) was used as the active ingredient for injection.

(5) Monopotassium salt of 3-(N-formyl-N -hydroxyamino)-2 -hydroxypropyl phosphonic acid (250 mg.) was used as be active ingredient for injection.

(ii) Preparation for tablet

(1) A suitable formulation of a tablet consists of the following mixture.

hydroxyamino)propylphosphonic acid	200 mg.
Mannitol	400 mg.
Starch	50 mg.
Magnesium stearate	10 mg.

(iii) Preparation for capsule

Monopotassium salt of 3-(N-formyl-N hydroxyamino)propylphosphonic acid	300 mg.
Magnesium stearate	15 mg.

The above ingredients were mixed and then inserted into a hard gelatin capsule in a conventional manner.

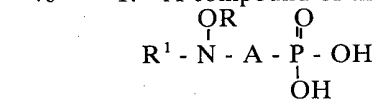
(iv) Preparation for oily suspension

Monosodium salt of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid	200 mg.
Lanette wax SX (trade name)	50 mg.
Soft paraffin	100 mg.
Brilliant blue FCF	25 mg.

The above ingredients were mixed with liquid paraffin so as to be totally 3 g. to give an infusion preparation.

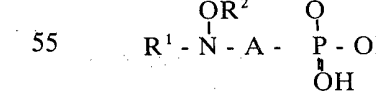
WHAT WE CLAIM IS:-

1. A compound of the formula:



wherein R^1 is hydrogen or acyl
R^2 is hydrogen, lower alkyl, ar(lower) alkyl wherein the aryl moiety may be substituted or acyl, and
A is lower alkylene, lower alkenylene or
hydroxy(lower) alkylene,
or the esters at the phosphono group thereof or the pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, which is the compound of the formula:



wherein R^1 is acyl,
R^2 is hydrogen, and
A is lower alkylene, lower alkenylene or hydroxy(lower) alkylene,
or the pharmaceutically acceptable salts thereof.

3. A compound according to claim 2, wherein the compound is the inorganic salt thereof.

4. A compound according to claim 3, wherein the inorganic salt is a salt selected from the group of sodium salt, potassium salt, calcium salt, magnesium salt and ammonium salt.

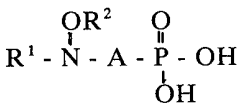
5. A compound according to claim 2, wherein the compound is the organic salt thereof.
6. A compound according to claim 5, wherein the compound is a salt selected from the group of ethanolamine salt, ethylenediamine salt, N,N'-dibenzylethylene diamine salt and arginine salt.
7. A compound according to claim 2, wherein A is lower alkylene.
8. A compound according to claim 2, wherein R^1 is lower alkanoyl, and A is lower alkylene.
9. A compound according to claim 8, wherein R^1 is formyl or acetyl, and A is trimethylene.
10. A compound according to claim 9, wherein the salt is the sodium, potassium, calcium, magnesium, ammonium, ethanolamine, ethylenediamine, N,N'-dibenzylethylenediamine or arginine salt.
11. A compound according to claim 9, which is 3-(N-formyl-N-hydroxyamino) propylphosphonic acid.
12. A compound according to claim 10, which is the sodium, calcium, magnesium, ammonium, ethanolamine, ethylene diamine, N,N'-dibenzylethylenediamine or arginine salt of 3-(N-formyl-N -hydroxyamino) propylphosphonic acid.
13. A compound according to claim 9, which is 3-(N-acetyl-N- hydroxyamino) propylphosphonic acid.
14. A compound according to claim 10, which is the sodium salt of 3-(N-acetyl-N-hydroxyamino) propylphosphonic acid.
15. A compound according to claim 2, wherein A is lower alkenylene.
16. A compound according to claim 2, wherein R^1 is lower alkanoyl, and A is lower alkenylene.
17. A compound according to claim 16, wherein R^1 is formyl or acetyl, and A is propenylene.
18. A compound according to claim 17, wherein the salt is the sodium or potassium salt.
19. A compound according to claim 17, which is 3-(N-formyl-N- hydroxyamino) -trans-l-propenylphosphonic acid.
20. A compound according to claim 18, which is the sodium or potassium salt of 3-(N-formyl-N- hydroxyamino)- trans-l- propenylphosphonic acid.
21. A compound according to claim 17, which is 3-(N-acetyl- N-hydroxyamino) -trans-l-propenylphosphonic acid.
22. A compound according to claim 18, wherein the potassium salt of 3-(N-acetyl-N -hydroxyamino)-trans -l-propenylphosphonic acid.
23. A compound according to claim 2, wherein A is hydroxy(lower) alkylene.
24. A compound according to claim 2, wherein R^1 is lower alkanoyl, and A is hydroxy(lower) alkylene.
25. A compound according to claim 24, wherein R^1 is formyl or acetyl, and A is hydroxytrimethylene.
26. A compound according to claim 25, wherein the salt is the sodium or ammonium salt.
27. A compound according to claim 25, which is 3-(N-formyl-N - hydroxyamino)-2-hydroxypropylphosphonic acid.
28. A compound according to claim 26, which is the sodium or ammonium salt of 3-(N-formyl-N- hydroxyamino)-2- hydroxypropylphosphonic acid.
29. A compound according to claim 25, which is 3-(N- acetyl-N- hydroxyamino)-2-hydroxypropylphosphonic acid.
30. A compound according to claim 26, which is the sodium salt of 3-(N-acetyl-N-hydroxyamino)-2 -hydroxypropylphosphonic acid.
31. A compound according to claim 1, wherein R^1 is hydrogen.
32. A compound according to claim 1, wherein R^1 and R^2 are each hydrogen.
33. A compound according to claims 31 or 32, wherein A is lower alkylene.
34. A compound according to claim 33, which is (N-hydroxyamino) (lower) alkylphosphonic acid.
35. A compound according to claim 33, wherein A is trimethylene.
36. A compound according to claim 34, which is 3-(N-hydroxyamino) propylphosphonic acid.
37. A compound according to claims 31 or 32, wherein A is lower alkenylene.
38. A compound according to claim 37, which is (N-hydroxyamino) (lower) alkenylphosphonic acid.
39. A compound according to claim 37, wherein A is propenylene.
40. A compound according to claim 39, which is 3-(N-hydroxyamino) -trans-l-propenyl phosphonic acid.
41. A compound according to claims 31 or 32, wherein A is hydroxy (lower) alkylene.
42. A compound according to claim 41, which is (N-hydroxyamino)- hydroxy

(lower)alkylphosphonic acid.

43. A compound according to claim 41, wherein A is hydroxytrimethylene.

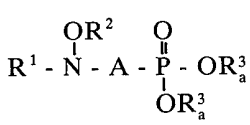
44. A compound according to claim 43, which is 2-hydroxy-3- (N-hydroxyamino) propylphosphonic acid.

45. A compound according to claim 1, which is the ester at the phosphono group of the compound of the formula:



wherein R^1, R^2 and A are as defined in the claim 1.

46. A compound according to claim 45, which is the compound of the formula:



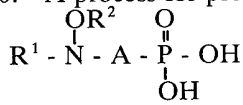
wherein R^1, R^2 and A are as defined in the claim 45, and R^3_a is a residue of the ester.

47. A compound according to claim 46, wherein R^3_a is lower alkyl, ar(lower)alkyl aryl or a residue of a silyl compound, each of which may have possible substituent.

48. A compound according to claim 46, wherein R^1 is lower alkanoyl, and A is lower alkylene, lower alkenylene or hydroxy(lower) alkylene.

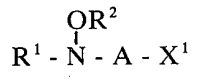
49. A compound according to claim 48, wherein R^1 is formyl or acetyl, and A is trimethylene, propenylene or hydroxytrimethylene.

50. A process for preparing a compound of the general formula:

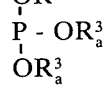


wherein R^1 is hydrogen or acyl, R^2 is hydrogen, lower alkyl, ar(lower)alkyl or acyl, and A is lower alklene, lower alkenylene, or hydroxy(lower) alkylene, or the esters at the phosphono group thereof or the pharmaceutically acceptable salts thereof which comprises,

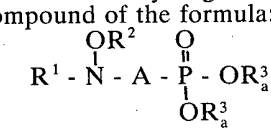
a) reacting a compound of the formula:



wherein R^1, R^2, and A are each as defined above, and X^1 is an acid residue, with a compound of the formula:

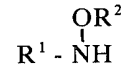


wherein R^3 is hydrogen or a residue of the ester, and R^3_a is a residue of the ester, to give a compound of the formula:

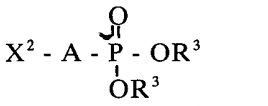


wherein R^1, R^2, A and R^3_a are each as defined above; or

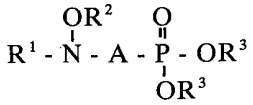
b) reacting a compound of the formula:



wherein R^1 and R^2 are each as defined above, with a compound of the formula:

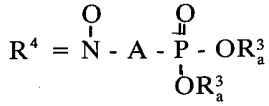


wherein R^3 and A are each as defined above, and X^2 is an acid residue, to give a compound of the formula:

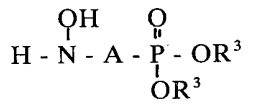


wherein R^1, R^2, R^3 and A are each as defined above; or

c) hydrolyzing a compound of the formula:

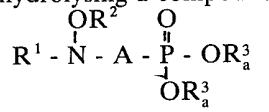


wherein R^3_a and A are each as defined above and R^4 is alkylidene, to give a compound of the formula:

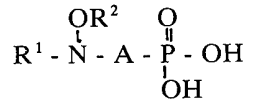


wherein R^3 and A are each as defined above; or

d) hydrolysing a compound of the formula:

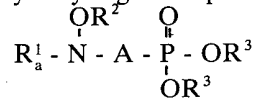


wherein R^1, R^2, R^3_a and A are each as defined above, to give a compound of the formula:

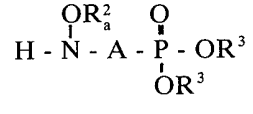


wherein R^1, R^2 and A are each as defined above; or

e) hydrolyzing a compound of the formula:

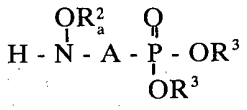


wherein R^2, R^3 and A are each as defined above, and R^1_a is acyl, to give a compound of the formula:

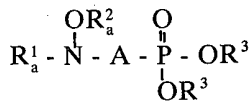


wherein R^3 and A are each as defined above, and R^2_a is hydrogen or lower alkyl; or

f) reacting a compound of the formula:

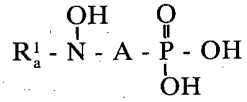


wherein R^2_a, R^3 and A are each as defined above with an acylating agent, to give a compound of the formula:

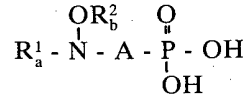


wherein R^1_a, R^2_a, R^3 and A are each as defined above; or

g) reacting a compound of the formula:

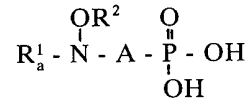


wherein R^1_a and A are each as defined above, with an acylating agent, to give a compound of the formula:

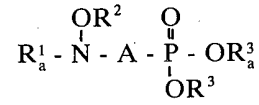


wherein R^1_a and A are each as defined above and R^2_b is an acyl group; or

h) reacting a compound of the formula:

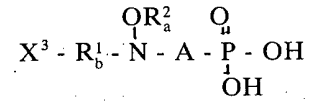


wherein R^1_a, R^2 and A are each as defined above, or the salt thereof or the reactive derivative at the phosphono group thereof, with an esterifying agent, to give a compound of the formula:



wherein R^1_a, R^2, R^3, R^3_a and A are each as defined above; or

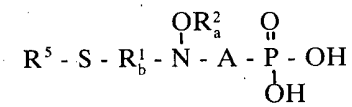
i) reacting a compound of the formula:



wherein R^2_a and A are each as defined above R^1_b is l-oxoalkylene, and X^3 is an acid residue, with a compound of the formula:

$$R^5 - SH$$

wherein R^5 is lower alkyl, to give a compound of the formula:



wherein R^1_b, R^2_a, R^5 and A are each as defined above;

j) culturing a 3-(N-acetyl-N-hydroxyamino) propylphosphonic acid producing strain belonging to the genus *Streptomyces* in an aqueous nutrient medium under aerobic conditions until substantial antibiotic activity is imparted to said medium to give the antibiotic, 3-(N-acetyl-N-hydroxyamino) propylphosphonic acid.

k) culturing a 3-(N-formyl-N -hydroxyamino) propylphosphonic acid producing strain belonging to the genus *Streptomyces* in an aqueous nutrient medium under aerobic conditions until substantial antibiotic activity is imparted to said medium to give the antibiotic, 3-(N-formyl-N- hydroxyamino) propylphosphonic acid.

l) culturing a 3-(N-formyl-N -hydroxyamino) trans-l- propenylphosphonic acid producing strain belonging to the genus *Streptomyces* in an aqueous nutrient medium under aerobic conditions until substantial antibiotic activity is imparted to said medium to give the antibiotic, 3-(N-formyl- N-hydroxyamino)trans -l-propenylphosphonic acid.

m) culturing a 3-(N-acetyl-N- hydroxyamino)-2- hydroxypropyl phosphonic acid producing strain belonging to the genus *Streptomyces* in an aqueous nutrient medium under aerobic conditions until substantial antibiotic activity is imparted to said medium to give the antibiotic, 3-(N-acetyl-N -hydroxyamino)-2- hydroxypropylphosphonic acid.

51. A process according to claim 50, wherein in subparagraph j) the strain of *Streptomyces* is *Streptomyces rubellomurinus.*

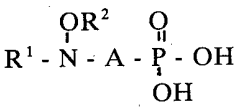
52. A process according to claim 51, wherein the strain of *Streptomyces* is *Streptomyces rubellomurinus* subsp. *indigoferus.*

53. A process according to claim 50, wherein in subparagraph k) the strain of *Streptomyces* is *Streptomyces lavendulae.*

54. A process according to claim 50, wherein in subparagraph l) the strain of *Streptomyces* is *Streptomyces lavendulae.*

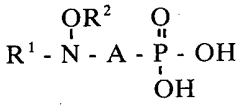
55. A process according to claim 50, wherein in subparagraph m) the strain of *Streptomyces* is *Streptomyces rubellomurinus* subsp. *indigoferus*.

56. A pharmaceutical composition which comprises, as an effective ingredient, one or more of the compounds of the formula:



wherein R^1 is hydrogen or acyl, R^2 is hydrogen, lower alkyl, ar(lower) alkyl or acyl, and A is lower alkylene, lower alkenylene or hydroxy(lower) alkylene, or the esters or the pharmaceutically acceptable salts thereof with a pharmaceutically acceptable carrier.

57. A pharmaceutical composition according to claim 56, which comprises, as an active ingredient, one or more of the compounds of the formula:



wherein R^1 is acyl, R^2 is hydrogen, and A is lower alkylene, lower alkenylene or hydroxy (lower)alkylene, or the pharmaceutically acceptable salts thereof.

58. A pharmaceutical composition according to claim 57, wherein R^1 is lower alkanoyl, and A is lower alkylene, lower alkenylene or hydroxy(lower) alkylene.

59. A pharmaceutical composition according to claim 58, wherein R^1 is formyl or acetyl, and A is trimethylene, propenylene or hydroxytrimethylene.

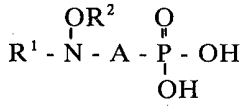
60. A method of treating an infectious disease in non-human animals caused by a pathogenic microorganism with the use of the composition of claim 56.

61. A method of treating an infectious disease in non-human animals caused by a pathogenic microorganism with the use of the composition of claim 57.

62. A method of treating an infectious disease in non-human animals caused by a pathogenic microorganism with the use of the composition of claim 58.

63. A method of treating an infectious disease in non-human animals by a pathogenic microorganism with the use of the composition of claim 59.

64. A use of the compound of the formula:



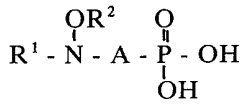
wherein R^1 is hydrogen or acyl, R^2 is hydrogen, lower alkyl ar(lower)alkyl or acyl, and A is lower alkylene, lower alkenylene or hydroxy(lower) alkylene, or the esters at the phosphono group thereof or the pharmaceutically acceptable salts thereof for the treatment of an infectious disease in non-human animals caused by a pathogenic microorganism.

65. A use of the compound according to claim 64, wherein R^1 is acyl, R^2 is hydrogen, and A is lower alkylene, lower alkenylene or hydroxy(lower) alkylene, or the pharmaceutical acceptable salts thereof for the treatment of an infectious disease in non-human animals caused by a pathogenic microorganism.

66. A use of the compound according to claim 65 wherein R^1 is lower alkanoyl, and A is lower alkylene, lower alkenylene or hydroxy(lower) alkylene for the treatment of an infectious disease in non-human animals caused by a pathogenic microorganism.

67. A use of the compound according to claim 66, wherein R^1 is formyl or acetyl, and A is trimethylene, propenylene or hydroxytrimethylene for the treatment of an infectious disease in non-human animals caused by a pathogenic microorganism.

68. A method of producing a medicament having an antimicrobial activity, characterized in that a compound of the formula:



wherein R^1 is hydrogen or acyl, R^2 is hydrogen, lower alkyl, ar(lower)alkyl or acyl, and A is lower alkylene, lower alkenylene or hydroxy(lower) alkylene, or the esters at the phosphono group thereof or the pharmaceutical acceptable salts thereof is brought into a form suitable for the purpose of medical administration.

69. A medicament having an antimicrobial activity produced by the method according to claim 68.

70. A tablet, pellet, capsule, suppository, solution, emulsion, aqueous suspension for parenteral administration containing a compound according to claim 1.

Agents for the Applicants

STEVENS, HEWLETT & PERKINS,
Chartered Patent Agents,
5, Quality Court,
Chancery Lane,
London W.C.2.
Tel. 01-405 8393

Printed for Her Majesty's Stationery Office, by Croydon Printing Company Limited, Croydon, Surrey, 1980.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY,from which copies may be obtained.