CONVENTION

AUSTRALIA

Patents Act

APPLICATION FOR A STANDARD PATENT

632596

E.R. Squibb & Sons, Inc.
Lawrenceville-Princeton Road, Princeton, New Jersey, UNITED STATES OF AMERICA

hereby applies for the grant of a standard patent for an invention entitled:

PHOSPHONATE SUBSTITUTED AMINO OR IMINO ACIDS USEFUL AS ANTIHYPERTENSIVES

which is described in the accompanying complete specification.

Details of basic application(s):-
396,170 UNITED STATES OF AMERICA 21 August 1989

Address for Service:

PHILLIPS ORMONDE & FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne 3000 AUSTRALIA

DATED this EIGHTEENTH day of JULY 1990

PHILLIPS ORMONDE & FITZPATRICK
Attorneys for:
E.R. Squibb & Sons, Inc.

By: David B Fitzpatrick

Our Ref : 181632
POF Code: 8448/43804

6010

COMMONWEALTH OF AUSTRALIA

Patents Act

DECLARATION FOR A PATENT APPLICATION

▼ INSTRUCTIONS

(a) Insert "Convention" if applicable
(b) Insert FULL name(s) of applicant(s)
(c) Insert "of addition" if applicable
(d) Insert TITLE of invention

In support of the (a) convention application made by (b) E.R. SQUIBB & SONS, INC., a corporation duly organized and existing under the laws of the State of Delaware, United States of America, having its offices at Lawrenceville-Princeton Road, Princeton, New Jersey, United States of America, (hereinafter called "applicant") for a patent (c) for an invention entitled (d)

PHOSPHONATE SUBSTITUTED AMINO OR IMINO ACIDS USEFUL AS ANTIHYPERTENSIVES

(e) Insert FULL name(s) AND address(es) of declarant(s) (See headnote*)

I Nicholas P. Malatestinic of Princeton, New Jersey, United States of America,

do solemnly and sincerely declare as follows:

1. I am authorized to make this declaration on behalf of the applicant(~~s~~).

(f) Insert FULL name(s) AND address(es) of actual inventor(s)

2. (f) Donald S. Karanewsky
32 Ellsworth Drive
Robbinsville, NJ, USA

(g) Recite how applicant(s) derive(s) title from actual inventor(s) (See headnote**)

is/~~are~~ the actual inventor(~~s~~) of the invention and the facts upon which the applicant is entitled to make the application are as follows:

(g) The said E.R. SQUIBB & SONS, INC., is the assignee of the said

Donald S. Karanewsky

By virtue of an assignment dated August 16, 1989

(h) Insert country, filing date, and basic applicant(s) for the/or EACH basic application

3. The basic application(~~s~~) for patent or similar protection on which the application is based is/~~are~~ identified by ***country, filing date, and basic applicant(~~s~~)*** as follows:

(h)

In: United States of America on: August 21, 1989

By: Donald S. Karanewsky

4. The basic application(~~s~~) referred to in paragraph 3 hereof was ~~were~~ the first application(~~s~~) made in a Convention country in respect of the invention the subject of the application.

(k) Insert PLACE of signing
(l) Insert DATE of signing

Declared at (k) Princeton, New Jersey, U.S.A.,
Dated (l) July 9, , 1990

(m) Signature(s) of declarant(s)

(m) E.R. SQUIBB & SONS, INC.

Note: No legalization or other witness required

By [signature]
Nicholas P. Malatestinic
Assistant Secretary

To: The Commissioner of Patents

(SEAL)

PHILLIPS ORMONDE & FITZPATRICK
Patent and Trade Mark Attorneys

Patent Declaration
No legalization or other witness required

AU9059105

(12) PATENT ABRIDGMENT (11) Document No. AU-B-59105/90
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 632596

(54) Title
PHOSPHONATE SUBSTITUTED AMINO OR IMINO ACIDS USEFUL AS ANTIHYPERTENSIVES

International Patent Classification(s)
(51)[5] C07F 009/40 A61K 031/67 C07F 009/58 C07F 009/59
A61K 031/665 A61K 031/675 C07F 009/572 C07F 009/655

(21) Application No. : 59105/90 (22) Application Date : 18.07.90

(30) Priority Data

(31) Number (32) Date (33) Country
396170 21.08.89 US UNITED STATES OF AMERICA

(43) Publication Date : 21.02.91

(44) Publication Date of Accepted Application : 07.01.93

(71) Applicant(s)
E.R. SQUIBB & SONS, INC.

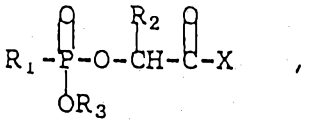
(72) Inventor(s)
DONALD S. KARANEWSKY

(74) Attorney or Agent
PHILLIPS ORMONDE & FITZPATRICK , 367 Collins Street, MELBOURNE VIC 3000

(56) Prior Art Documents
US 4616005

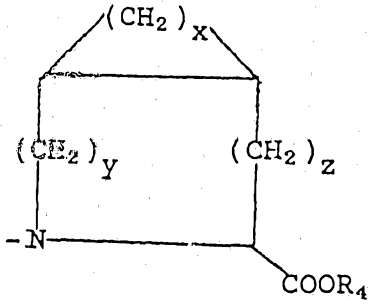
(57) Claim

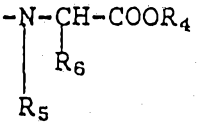
1. Substituted amino or imino acids of the formula

I 

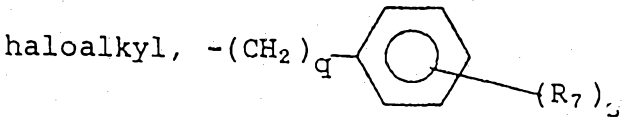
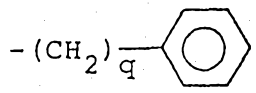
isomeric mixtures thereof and pharmaceutically acceptable salts thereof, wherein:

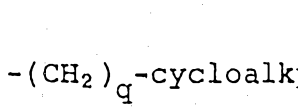
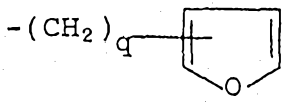
X is an imino or amino acid of the formula

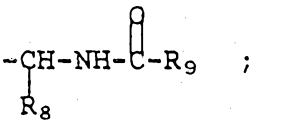


or  ;

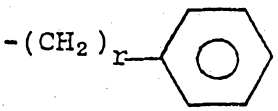
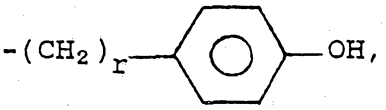
.../2

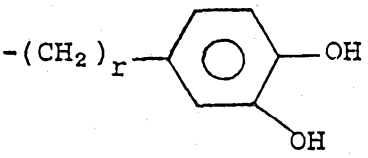
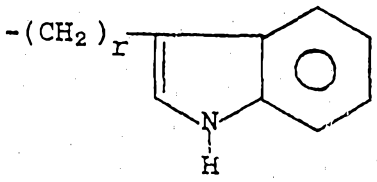
R_1 is alkyl of 1 to 10 carbons, aminoalkyl, haloalkyl,  ,  .

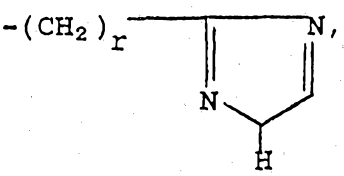
 ,  , or

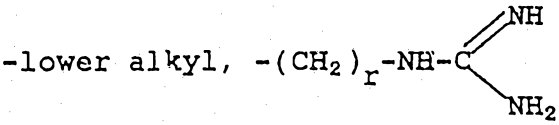
 ;

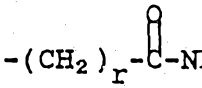
R_2 is hydrogen, lower alkyl, halo substituted lower alkyl,

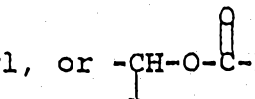
 ,  ,

 ,  ,

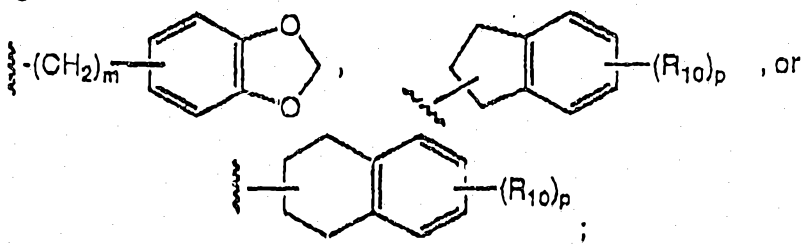
 , $-(CH_2)_r-NH_2$, $-(CH_2)_r-SH$,

$-(CH_2)_r$-S-lower alkyl,  or

 ;

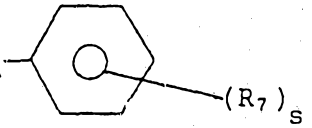
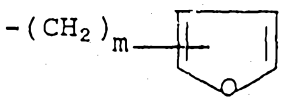
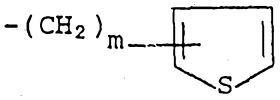
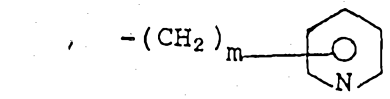
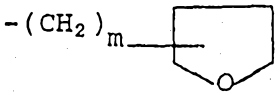
R_3 and R_4 are independently selected from hydrogen, lower alkyl, benzyl, alkali metal, benzhydryl, or  ;

R_5 is

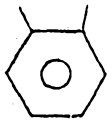


R_6 is hydrogen or lower alkyl;

R_7 is lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl, hydrogen, hydroxy, phenyl, phenoxy, phenylthio, or phenylmethyl;

R_8 and R_9 are independently selected from hydrogen, lower alkyl, halo-substituted lower alkyl, $-(CH_2)_m$-  , $-(CH_2)_q$-cycloalkyl,  ,  ,  , or  ;

R_{10} is hydrogen, lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl, or hydroxy;

R_{11} is hydrogen, lower alkyl, cycloalkyl, or phenyl, and R_{12} is hydrogen, lower alkyl, lower alkoxy, phenyl, or R_{11} and R_{12} taken together are $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH=CH-$, or  ;

a + b = two or three;

m is zero, one, two or three;

.../4

p is one, two or three, provided that p is more than one only if R_{10} is hydrogen, methyl, methoxy, chloro, or fluoro;

q is an integer from zero to seven;

r is an integer from one to four;

s is one, two, or three;

x is an integer from one to four;

y is zero, one, or two; and

z is zero, one, or two.

AUSTRALIA

Patents Act

632596

COMPLETE SPECIFICATION
(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority

Related Art:

Applicant(s):

E.R. Squibb & Sons, Inc.
Lawrenceville-Princeton Road, Princeton, New Jersey, UNITED STATES OF AMERICA

Address for Service is:

PHILLIPS ORMONDE & FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne 3000 AUSTRALIA

Complete Specification for the invention entitled:

PHOSPHONATE SUBSTITUTED AMINO OR IMINO ACIDS USEFUL AS ANTIHYPERTENSIVES

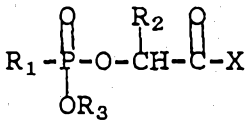
Our Ref : 181632
POF Code: 8448/43804

The following statement is a full description of this invention, including the best method of performing it known to applicant(s):

6006

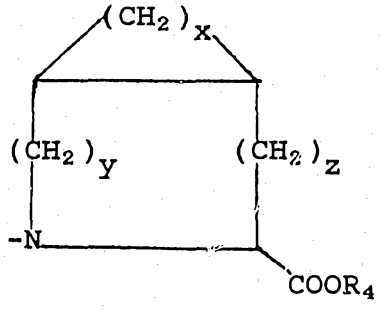
PHOSPHONATE SUBSTITUTED AMINO OR IMINO ACIDS USEFUL AS ANTIHYPERTENSIVES

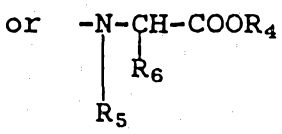
This invention is directed to new phosphonate substituted amino or imino acids of the formula

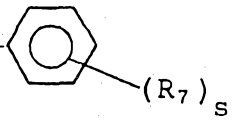
I 

isomeric mixtures thereof and pharmaceutically acceptable salts thereof, wherein in formula I and throughout this specification, the symbols are defined as follows:

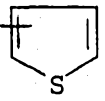
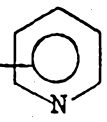
X is an imino or amino acid of the formula



or  ;

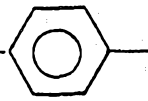
R_1 is alkyl of 1 to 10 carbons, aminoalkyl, haloalkyl, $-(CH_2)_q$-  , $-(CH_2)_q$-  ,

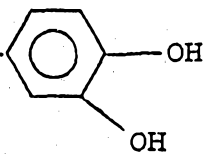
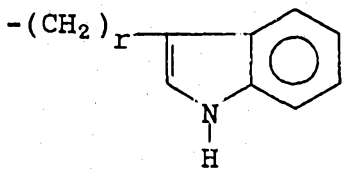
$-(CH_2)_q$-cycloalkyl, $-(CH_2)_q$-  ,

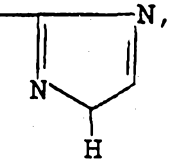
$-(CH_2)_q$-  , $-(CH_2)_q$-  , or

$-CH(R_8)-NH-C(=O)-R_9$;

R_2 is hydrogen, lower alkyl, halo substituted lower alkyl,

$-(CH_2)_r$-  , $-(CH_2)_r$-  ,

$-(CH_2)_r$-  , $-(CH_2)_r$-  .

$-(CH_2)_r$-  , $-(CH_2)_r-NH_2$, $-(CH_2)_r-SH$,

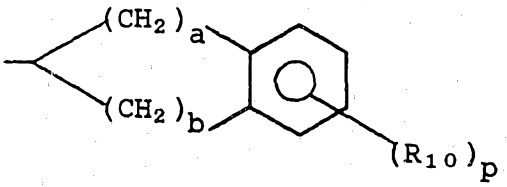
$-(CH_2)_r$-S-lower alkyl, $-(CH_2)_r$-NH-C(=NH)-NH_2 or

$-(CH_2)_r$-C(=O)-NH_2;

R_3 and R_4 are independently selected from hydrogen, lower alkyl, benzyl, alkali metal such as Li, Na or K, benzhydryl, or $-CH(R_{11})-O-C(=O)-R_{12}$;

R_5 is $-(CH_2)_m$-(phenyl)-$(R_7)_s$ or

$-(CH_2)_m$-(benzodioxole)-C(R_{13})(R_{13}), or

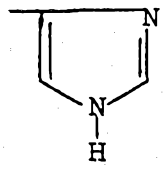


;

R_6 is hydrogen, lower alkyl,

$-(CH_2)_r$-(phenyl), $-(CH_2)_r$-(phenyl)-OH,

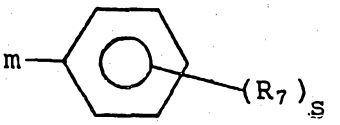
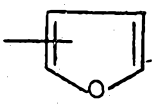
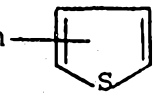
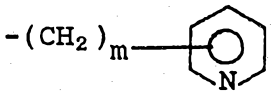
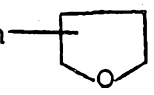
$-(CH_2)_r$-(dihydroxyphenyl), $-(CH_2)_r$-(indolyl),

$-(CH_2)_r$  , $-(CH_2)_r-NH_2$, $-(CH_2)_r-SH$,

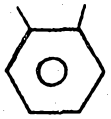
$-(CH_2)_r$-S-lower alkyl, $-(CH_2)_r-NH-C(=NH)-NH_2$, or

$-(CH_2)_r-C(=O)-NH_2$;

R_7 is lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl, hydroxy, phenyl, phenoxy, phenylthio, or phenylmethyl;

R_8 and R_9 are independently selected from hydrogen, lower alkyl, halo-substituted lower alkyl, $-(CH_2)_m$  , $-(CH_2)_q$-cycloalkyl, $-(CH_2)_m$  , $-(CH_2)_m$  , $-(CH_2)_m$  , or $-(CH_2)_m$  ;

R_{10} is hydrogen, lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl, or hydroxy;

R_{11} is hydrogen, lower alkyl, cycloalkyl, or phenyl, and R_{12} is hydrogen, lower alkyl, lower alkoxy, phenyl, or R_{11} and R_{12} taken together are $=(CH_2)_2-$, $-(CH_2)_3-$, $-CH=CH-$, or  ;

R_{13} is hydrogen or lower alkyl;

a + b = 2 or 3;

m is zero, one, two or three;

p is one, two or three, provided that p is more than one only if R_{10} is hydrogen, methyl, methoxy, chloro, or fluoro;

q is an integer from 0 to 7;

r is an integer from 1 to 4;

s is one, two or three;

x is an integer from 1 to 4;

y is zero, one, or two; and

z is zero, one, or two.

This invention in its broadest aspects relates to the phosphonate substituted imino or amino acid compounds of formula I above, to compositions containing such compounds and to the method of using such compounds as anti-hypertensive agents.

Definition of Terms

The following definitions apply to the terms as they are used throughout this specification, unless otherwise limited in specific instances.

The term "alkyl" refers to straight or branched chain hydrocarbon groups having up to ten

carbons, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, heptyl, octyl, decyl, etc. The term "lower alkyl" refers to straight or branched chain groups having up to seven carbons. The preferred lower alkyl groups have up to four carbons with methyl and ethyl most preferred. Similarly, the terms "lower alkoxy" and "lower alkylthio" refer to such lower alkyl groups attached to an oxygen or sulfur.

The term "cycloalkyl" refers to saturated rings of 3 to 7 carbon atoms, with cyclopentyl and cyclohexyl being most preferred.

The terms "halo" and "halogen" refer to fluorine, chlorine, and bromine.

The term "halo-substituted lower alkyl" refers to such lower alkyl groups described above in which one or more hydrogens have been replaced by chloro, bromo or fluoro groups, such as trifluoromethyl (which is preferred) pentafluoroethyl, 2,2,2-trichloroethyl, chloromethyl, bromomethyl, etc. Similarly, the term "amino-substituted lower alkyl" refers to lower alkyl groups in which one or more hydrogens have been replaced by $-NH_2$, i.e., aminomethyl, 2-aminoethyl, etc.

The compounds of this invention wherein at least one of R_3 or R_4 is hydrogen form basic salts with various inorganic and organic bases which are also within the scope of the invention. Such salts include ammonium salts, alkali metal salts such as lithium, sodium and potassium salts (which are preferred), alkaline earth metal salts

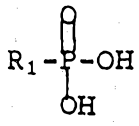
such as calcium and magnesium salts, salts with organic bases (e.g., dicyclohexylamine salts), benzathine, N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as arginine, lysine and the like. The nontoxic, physiologically acceptable salts are preferred, although other salts are also useful, for example, in isolating or purifying the products. The salts are formed using conventional techniques. All of the foregoing are within the meaning of the term "pharmaceutically acceptable salts."

The amino or imino acid or ester portion of the molecule of the products of formula I represented by X is in the L-configuration. Depending upon the definitions of R_2 and R_8, other asymmetric centers may be present in the phosphonyl sidechain. Thus, some of the compounds can exist in diastereoisomeric forms or in mixtures thereof. The above-described processes can utilize racemates, enantiomers or diastereomers as starting materials. When products containing only a single diastereomer are preferred, they can be separated by conventional chromatographic or fractional crystallization methods. The products of formula I wherein the imino acid ring is monosubstituted give rise to cis-trans isomerism. All of the foregoing are within the meaning of the term "isomeric mixtures."

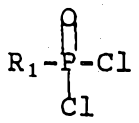
Process of Preparation

The compounds of formula I wherein R_1 is other than $-\underset{R_8}{\overset{|}{C}}H-NH-\overset{\overset{||}{O}}{\overset{|}{C}}-R_9$ are prepared according to

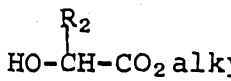
the following procedures. A phosphonic acid of formula

II 

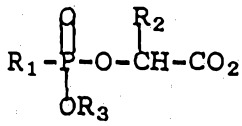
is treated with a chlorinating agent (e.g., phosphorus pentachloride) in the presence of an inert organic solvent (e.g., benzene) to form a compound of the formula

III  .

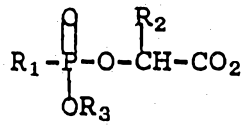
Compound III is reacted with a lactate of the formula

IV 

in the presence of an organic base (e.g., triethylamine) followed by an alcohol ROH (where R_3 is lower alkyl, benzyl, or benzhydryl) to form a compound of the formula

V 

The formula V compound is then treated with strong base (e.g., sodium hydroxide or lithium hydroxide) in a mixture of water and an organic solvent (e.g., dioxane) to form the corresponding acid

VI 

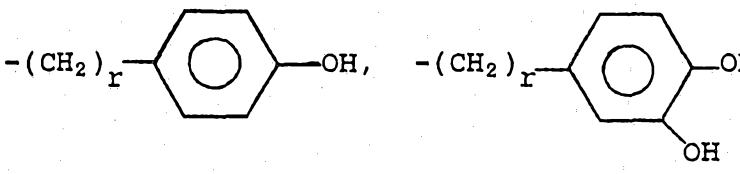
The acid VI or its activated form is then coupled with an imino or amino acid or ester of the formula

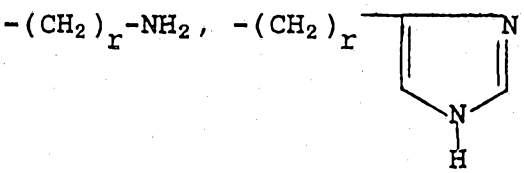
VII

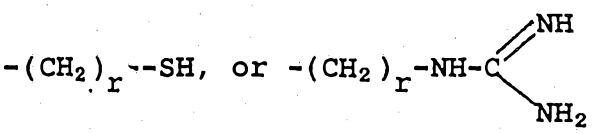
H-X.

The term "activated form" refers to the conversion of the acid to a mixed anhydride, symmetrical anhydride, acid chloride, or activated ester; see Methoden der Organischen Chemie (Houben-Weyl), Vol. XV, part II, page 1 et seq. (1974) for a review of the methods of acylation. Preferably, the reaction is performed in the presence of a coupling agent such as 1,1-carbonyldiimidazole, thionyl chloride, or dicyclohexylcarbodiimide.

In the above reaction, if R_2 is



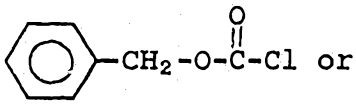


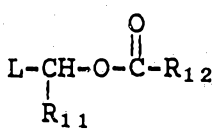


then the hydroxyl, amino, imidazolyl, mercaptan, or guanidinyl function should be protected during the coupling reaction. Suitable protecting groups include benzyloxycarbonyl, t-butoxycarbonyl, benzyl, benzhydryl, trityl, etc., and nitro in the case of guanidinyl. The protecting group is removed by hydrogenation, treatment with acid, or other known methods following completion of the reaction.

Similarly, if in the above reaction R_1 is aminoalkyl, then the amino group should be similarly protected, preferably by phthalidyl. The protecting group is removed by treatment with hydrazine following completion of the reaction.

The products of formula I wherein R_3 or R_4 is hydrogen can be derived by hydrogenating those products wherein either or both of R_3 and R_4 are benzyl, or benzhydryl. Such hydrogenation can be effected, for example, by treatment with hydrogen in the presence of a palladium on carbon catalyst. Products in which R_3 and/or R_4 are alkyl can be converted to products in which R_3 and R_4 are hydrogen by chemical treatment, such as with sodium hydroxide in aqueous dioxane or trimethylsilylbromide in dichloromethane.

The ester products of formula I wherein R_4 is $-\underset{\displaystyle R_{11}}{\overset{\displaystyle |}{CH}}-O-\overset{\displaystyle O}{\overset{\displaystyle ||}{C}}-R_{12}$ may be obtained by employing the imino or amino acid of formula V in the above reactions with the ester group already in place. Such ester reactants can be prepared by treating peptide, imino, or amino acids with an acid chloride such as  or $(CH_3)_3COCCl$ so as to protect the N-atom. The protected acid compound is then reacted in the presence of base with a compound of the formula VIII



wherein L is a leaving group such as chlorine, bromine, tolysulfonyloxy, etc., followed by removal of N-protecting group (e.g., by treatment with acid or hydrogenation).

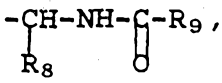
The ester products of formula I wherein R_4 is $-\underset{R_{11}}{\underset{|}{CH}}-O-\overset{O}{\overset{\|}{C}}-R_{12}$ can also be obtained by treating the product of formula I wherein R_4 is hydrogen with a molar equivalent of the compound of formula VIII. The diester products wherein R_3 and R_4 are the same and are $-\underset{R_{11}}{\underset{|}{CH}}-O-\overset{O}{\overset{\|}{C}}-R_{12}$ can be obtained by treating the product of formula I wherein R_3 and R_4 are both hydrogen or an alkali metal salt with two or more equivalents of the compound of formula VIII.

The ester products of formula I wherein R_3 is $-\underset{R_{11}}{\underset{|}{CH}}-O-\overset{O}{\overset{\|}{C}}-R_{12}$ can be obtained by treating the product of formula I wherein R_3 is hydrogen or an alkali metal salt and R_4 is benzyl or benzhydryl with the compound of formula VIII in the presence of base. Removal of the R_4 ester group (e.g., by hydrogenation) yields the products of formula I wherein R_3 is $-\underset{R_{11}}{\underset{|}{CH}}-O-\overset{O}{\overset{\|}{C}}-R_{12}$ and R_4 is hydrogen.

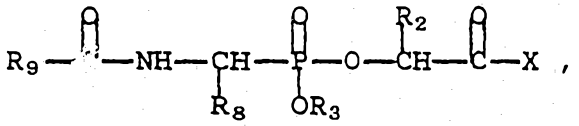
The various imino and amino acids and esters of formula V are described in the literature and in the various patents referred to above. Various

substituted prolines are also disclosed by Mauger et al., Chem. Review, Vol. 66, p. 46-86 (1966). When the amino or imino acid is known, it can be readily converted to the ester by conventional means. For example, the esters wherein R_4 is t-butyl can be obtained by treating the corresponding N-carbobenzyloxyimino acid with isobutylene under acidic conditions and then removing the N-carbobenzyloxy protecting group by catalytic hydrogenation. The esters wherein R_4 is benzyl can be obtained by treating the imino acid with benzyl alcohol and thionyl chloride.

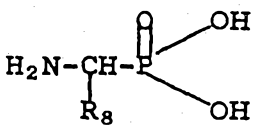
The compounds of formula I wherein R_1 is



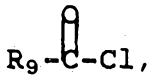
that is

XIII 

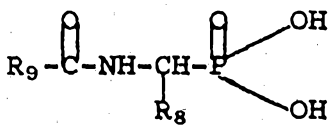
may be prepared by reacting an aminophosphonic acid of the formula

XIV 

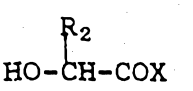
with an acid chloride having the formula

XV 

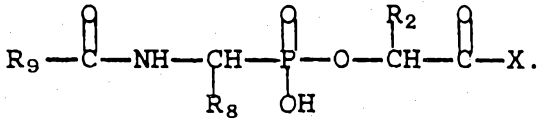
such as benzoyl chloride, in the presence of an inert organic solvent (e.g., dioxane) and a weak organic base (e.g., triethylamine) to yield

XVI 

The formula XVI compound is then coupled with an imino or amino acid or ester of formula XVII

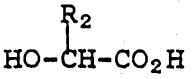
XVII 

in the presence of a coupling agent (e.g., dicyclohexylcarbodiimide) as described above to form

XVIII 

Where X includes a protecting group, it may be removed by (1) hydrogenation where the protecting group is phenylmethoxycarbonyl or by (2) treatment with hydrazine where the protecting group is phthalidyl, to yield the compounds of formula XIII.

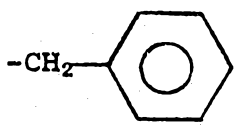
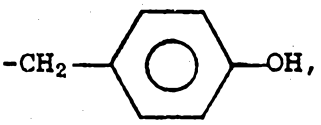
The compounds of formula XVII may be prepared by coupling a hydroxy acid of formula

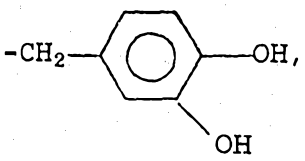
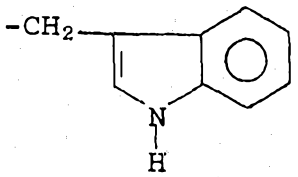
XIX 

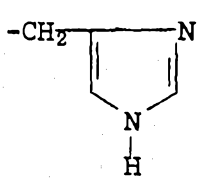
as the free acid or corresponding sodium salt with an imino or amino ester of formula VII, preferably in the presence of a coupling agent such as diphenyl phosphorylazide.

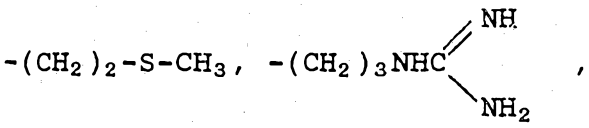
Preferred Moieties

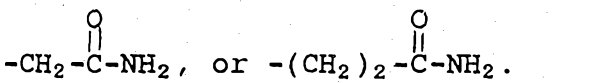
Preferred compounds of this invention with respect to the amino or imino acid or ester part of the structure of formula I are those wherein the symbols are defined as follows.

R_6 is hydrogen, lower alkyl of 1 to 4 carbons,  ,  ,

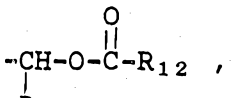






$-CH_2-\overset{O}{\overset{\|}{C}}-NH_2$, or $-(CH_2)_2-\overset{O}{\overset{\|}{C}}-NH_2$.

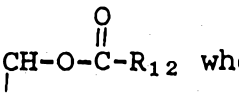
R_4 is hydrogen, an alkali metal salt, or



, wherein R_{11} is hydrogen, methyl or isopropyl and R_{12} is straight or branched chain lower alkyl of 1 to 4 carbons or phenyl.

Preferred compounds of this invention with respect to the phosphonyl sidechain of the structure of formula I are those wherein:

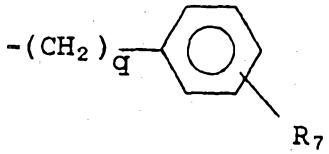
R_2 is hydrogen, lower alkyl of 1 to 4 carbons, amino-substituted lower alkyl, guanidino-substituted lower alkyl or CF_3;

R_3 is hydrogen, an alkali metal salt, lower alkyl of 1 to 4 carbons, or  wherein R_{11} is hydrogen, methyl or isopropyl and R_{12} is hydrogen or straight or branched chain lower alkyl of 1 to 4 carbons or phenyl, especially hydrogen,

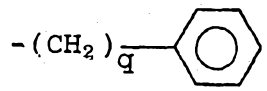
alkali metal salt, ethyl, $-CH(CH_3)-O-C(=O)-CH_3$,

$-CH_2-O-C(=O)-C(CH_3)_3$ or $-CH(CH(CH_3)_2)-O-C(=O)-C_2H_5$.

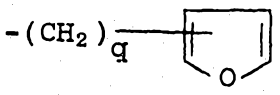
R_1 is alkyl of 1 to 10 carbons;



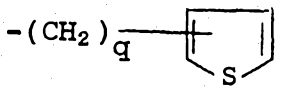
wherein q is an integer from 0 to 5 and R_7 is methyl, methoxy, methylthio, chloro, bromo, fluoro, or hydroxy; $-(CH_2)_q-$ cycloalkyl wherein cycloalkyl is of 5 or 6 carbons and q is zero, one or two;



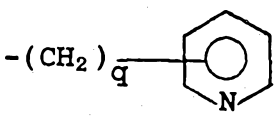
wherein q is an integer from 0 to 5;



wherein q is an integer from 0 to 5;



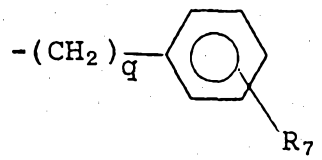
wherein q is an integer from 0 to 5;



wherein q is an integer from 0 to 5; or

$-CH(R_8)-NH-C(=O)-R_9$.

R_8 and R_9 are independently selected from lower alkyl of 1 to 4 carbons or



wherein q is an integer from 0 to 5 and R_7 is hydrogen, methyl, methoxy, methylthio, chloro, bromo, fluoro, or hydroxy, especially wherein R_8 is phenylethyl and R_9 is phenyl.

Use and Utility

The compounds of formula I, and the pharmaceutically acceptable salts thereof, are hypotensive agents. They inhibit the conversion of the decapeptide angiotensin I to angiotensin II and, therefore, are useful in reducing or relieving angiotensin-related hypertension. The action of the enzyme renin on angiotensinogen, a psuedo-globulin in blood pressure, produces angiotensin I. Angiotensin I is converted by angiotensin converting enzyme (ACE) to angiotensin II. The latter is an active pressor substance which has been implicated as the causative agent in several forms of hypertension in various mammalian species, e.g., humans. The compounds of this invention intervene in the angiotensiongen→(renin)→angiotensin I→angiotensin II sequence by inhibiting angiotensin converting enzyme and reducing or eliminating the formation of the pressor substance angiotensin II. Thus, by the administration of a composition containing one (or a combination) of the compounds of this invention, angiotensin-dependent hypertension in a species of mammal

(e.g., humans) suffering therefrom is alleviated. A single dose, or preferably two to four divided daily doses, provided on a basis of about 0.1 to 100 mg per kilogram of body weight per day is appropriate to reduce blood pressure. The substance is preferably administered orally, but parenteral routes such as the subcutaneous, intramuscular, intravenous or intraperitoneal routes can also be employed.

The compounds of this invention can also be formulated in combination with a diuretic for the treatment of hypertension. A combination product comprising a compound of this invention and a diuretic can be administered in an effective amount which comprises a total daily dose of about 30 to 600 mg (preferably about 30 to 330 mg) of a compound of this invention, and about 15 to 300 mg (preferably about 15 to 200 mg) of the diuretic, to a mammalian species in need thereof. Exemplary of the diuretics contemplated for use in combination with a compound of this invention are the thiazide diuretics, e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methyclothiazide, trichloromethiazide, polythiazide or benzthiazide as well as ethacrynic acid, tricynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamterene, amiloride and spironolactone and salts of such compounds.

The compounds of formula I can be formulated for use in the reduction of blood pressure in compositions such as tablets, capsules or elixirs for oral administration, or in sterile solutions or

suspensions for parenteral administration. About 10 to 500 mg of a compound of formula I is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservatives, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the range indicated is obtained.

Specific Embodiments

The following working examples are illustrative and present preferred embodiments of the invention. Preparation of intermediate compounds appears just below the names of intermediate compounds. The intermediate prepared in part A of a working example will be referred to as "compound A" or "intermediate A" as a shorthand reference, and likewise for compounds prepared in parts B, C, D, etc. Except where otherwise indicated, all temperatures are in degrees Celsius.

Example 1

N-[(S)-6-Amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-N-(2,3-dihydro-1H-inden-2-yl)glycine, dilithium salt

A. N-(2,3-Dihydro-1H-inden-2-yl)glycine, phenylmethyl ester

A stirred, cooled (to 0°C in an ice bath) mixture of 2-aminoindan · hydrochloride (3.0 g, 0.018 mol) and triethylamine (4.9 ml, 0.035 mol) in dry ethyl ether (20 ml) was treated dropwise with an ethereal solution of benzylbromoacetate (2.55 ml, 0.016.1 mol in 10 ml ethyl ether). After completed bromide addition, the suspension was stirred overnight under argon at room temperature. After the suspension was filtered, the filtrate was evaporated, taken up in the ethyl acetate, washed with saturated sodium bicarbonate and water and brine, dried over anhydrous sodium sulfate, and evaporated to a brown oil. The crude oil was purified by flash chromatography on LPS-1 silica gel, eluting with 1:1 ethyl ether:hexanes. Product fractions were evaporated to a clear oil which was dissolved in ethyl ether (15 ml) and added by pipette portions to a hydrochloric acid saturated ethyl ether solution (75 ml) maintained at 0°C. The precipitated salt was collected by filtration, rinsed with ethyl ether and dried in vacuo to give 2.272 g (45%) of a benzyl ester (intermediate A) as a granular, white, hydrochloride salt with consistent C^{13} NMR (CD_3OD, 15 MHz) spectral data.

R_f = 0.17, UV + PMA.

B. (S)-2-[[Hydroxy(4-phenylbutyl)phosphinyl]oxy]-6-[[(phenylmethoxy)carbonyl]amino]hexanoic acid

This compound was prepared as described in United States Patent No. 4,616,005, Example 137, parts A through G.

C. N-(2,3-Dihydro-1H-inden-2-yl)-N-[(S)-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-6-[[(phenylmethoxy)carbonyl]amino]-1-oxohexyl]-glycine, phenylmethyl ester

A mixture of intermediate A (474 mg, 0.0015 mol) and phosphonic acid B (549 mg, 0.0012 mol) in dry tetrahydrofuran (8 ml) and triethylamine (230 µl, 0.0015 mol) was treated with dicyclohexylcarbodiimide (833 mg, 0.004 mol) and the white suspension was stirred overnight under argon. The mixture was diluted with ethyl acetate and water, filtered, the organic phase washed with 5% potassium bisulfate, saturated sodium bicarbonate, filtered, washed with brine, dried over anhydrous sodium sulfate and evaporated to an oil plus residual dicyclohexylurea. The crude oil was purified by chromatography on a 2 cm pad of LPS-1 silica gel eluting with neat methylene chloride, 95:5 methylene chloride:Acetone, and 95:1:1 methylene chloride:methanol:acetic acid. Product fractions were evaporated, taken up in ethyl acetate, washed with 1.0 N hydrochloric acid and brine, dried over anhydrous sodium sulfate and evaporated to a yellow oil. The oil was dissolved

in ethyl acetate, treated with a small amount of activated charcoal, filtered and evaporated to give 583 mg (69%) of a phosphonic di-ester (intermediate C) as a pale yellow oil with consistent C^{13} NMR spectral data ($CDCl_3$, 15 MHz).
Thin layer chromatography: (7:2:1) iPrOH-ammonium hydroxide-water.
R_f = 0.76, UV + PMA.

D. N-[(S)-6-Amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-N-(2,3-dihydro-1H-inden-2-yl)glycine, dilithium salt

20% palladium on charcoal (87 mg, 15% by weight) was added to an argon-purged solution of the di-ester intermediate C (583 mg) in methanol (10 ml) and the black suspension was stirred under H_2 for 45 minutes. The catalyst was removed by filtration through dry, packed "Celite" and the filtrate evaporated. The residue was taken up in 1.0 N lithium hydroxide (4 ml), diluted with water, filtered through a polycarbonate membrane and evaporated. The residue was dissolved in water and chromatographed on HP-20 resin, eluting with a neat water, neat acetonitrile linear gradient. Product fractions were evaporated, taken up in water (50 ml), filtered through a polycarbonate membrane, frozen, and lyophilized to give 341 mg (77% based on a hydrate of 2.4 moles water, molecular weight = 571.68) of Example 1 as a fluffy white di-lithium salt.

Thin layer chromatography: (7:2:1) iPrOH-ammonium hydroxide-water, R_f = 0.33, UV + PMA.

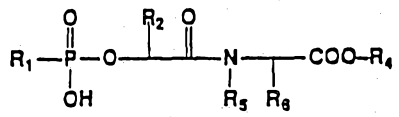
Microanalysis for $C_{27}H_{35}N_2O_6P \cdot Li_2$ + 2.4 moles H_2O:

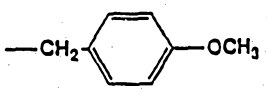
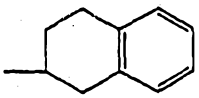
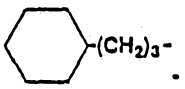
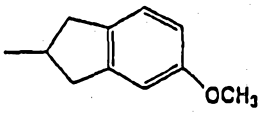
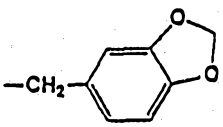
Calculated: C, 56.70; H, 7.02; N, 4.90; P, 5.41

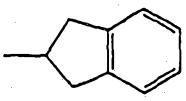
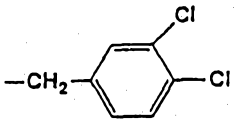
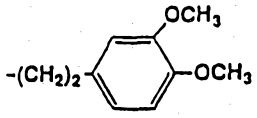
Found: C, 56.70; H, 6.69; N, 4.82; P, 5.40

Examples 2 to 8

The following compounds were prepared by the methods used in Example 1.



No.	R_1	R_2	R_4	R_5	R_6
2	Ph-$(CH_2)_4$-	-$(CH_2)_4$-NH_2	H		H
3	Ph-$(CH_2)_4$-	-$(CH_2)_4$-NH_2	CH_2CH_3		CH_3
4		-$(CH_2)_4$-CH_3	H		$CH(CH_3)_2$
5	CH_3-$(CH_2)_5$-	-$(CH_2)_3$-Ph	H		H

6	$Ph-(CH_2)_2-$	$-(CH_2)_4-NH_2$	CH_3		H
7	$CH_3-(CH_2)_7-$	$-(CH_2)_4-NH_2$	H		CH_3
8	$Ph-(CH_2)_5-$	CH_3	H		H

Example 9

(S)-[[6-Amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl](3,4-dimethoxyphenyl)amino]acetic acid, dilithium salt

A. (3,4-Dimethoxyphenylamino)acetic acid, methyl ester

4-Aminoveratrole (5.6 g, 0.37 mole), methylbromoacetate (4.6 g, 0.03 mole) and triethylamine (3.0 g, .03 mole) were dissolved in 40 ml of dry tetrahydrofuran and stirred under argon overnight. The black reaction mixture was concentrated in vacuo, dissolved in ethylacetate and stirred with 4 g of activated charcoal for 1 hour. This solution was filtered through a pad of silica (LPS-1) and the filtrate was evaporated to yield product as a tan solid with consistent ^{13}C spectral data (CD_3CN, 15 MHz).

Melting point 61-64°C

R_f 0.4 (1:1 Acetone-Hexane).

B. (S)-2-(Acetyloxy)-6-[[(phenylmethoxy) carbonyl]amino]hexanoic acid

To a solution of (S)-6-[[(phenylmethoxy)-carbonyl]amino]-2-hydroxyhexanoic acid (prepared as described in United States Patent No. 4,616,005, Example 137, part B) (5.62 g, 20.0 mmol) in dry tetrahydrofuran (40 ml) at 0°C (ice bath) under argon was added triethylamine (5.6 ml, 40.0 mmol) and acetyl chloride (2.84 ml, 40.0 mmole) and the resulting mixture stirred at 0°C for 2 hours. The suspension was filtered, cooled to 0°C, treated with half saturated $NaHCO_3$ (40 ml) and stirred at 0°C for 1 hour. The mixture was partitioned between ethyl acetate and 5% $KHSO_4$, the organic phase washed with saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuo to give 8.20 g of crude acid as a yellow oil.

The crude acid was purified by conversion to its 1-adamantanamine salt. Thus, the crude acid was taken up in ethyl ether (25 ml) and treated with a solution of 1-adamantanamine (3.00 g, 19.8 mmol) in ethyl ether (20 ml). The resulting white precipitate was collected, washed with ethyl ether, and dried in vacuo to give adamantanamine salt (8.53 g, 90% overall) as a white solid.

To regenerate the free acid, the salt (8.53 g) was partitioned between ethyl acetate and 1 N HCl, the organic phase washed with 1 N HCl (2 x 30 ml) and saturated NaCl, dried over Na_2SO_4 and evaporated to give pure intermediate B (5.80 g, 91%) as a colorless, viscous oil:

Thin layer chromatography (CH_2Cl_2/MeOH/AcOH, 20:1:1) R_f 0.82; ^{13}C NMR (CD_3OD) δ 22.6, 24.3, 27.9, 33.5, 36.6, 40.2, 56.0 (CH_3), 71.2 (CH), 115.8 (C), 126.6 (CH), 129.3 (CH), 130.5 (CH), 136.4 (CH), 143.6 (C), 160.8 (C), 174.5 (C).

C. (S)-[[2-(Acetyloxy)-1-oxo-6-[[phenylmethoxy)-carbonyl]amino]hexyl](3,4-dimethoxyphenyl)-amino]acetic acid, methyl ester

To a solution of acetate ester, intermediate B (1.29 g, 4 mmole) in 10 ml of tetrahydrofuran at 0°C was added triethylamine (0.61 ml, 4.4 mmole), pivaloylchloride (0.54 ml, 4.4 mmole) and dimethylaminopyridine (0.2 g) and stirred at 0°C for 2 hours. Intermediate A (0.98 g, 4.4 mmole) was added and the reaction mixture was stirred at room temperature under argon overnight. To drive the reaction to completion, 4 ml of pyridine was added. The resulting solution was stirred an additional 24 hours, evaporated, and the resulting residue was partitioned between ethyl acetate and 1 N hydrochloric acid. The organic phase was washed with brine, dried (magnesium sulfate), and concentrated in vacuo. The residue was chromatographed on silica LPS-1 (150 g) using a 3:7 Acetone:Hexane solvent system. The appropriate fractions were evaporated to yield 0.67 g (32.5%) of intermediate C with consistent ^{13}C spectral data (CD_3CN, 15 MHz).

D. (S)-[[2-Hydroxy-1-oxo-6-[[(phenylmethoxy)-carbonyl]amino]hexy](3,4-dimethoxyphenyl)-amino]acetic acid, diphenylmethyl ester

The N-phenylglycine derivative intermediate C (0.67 g, 1.3 mmole) was stirred with 7 ml 1 N lithium hydroxide and 7 ml of dioxane for 1 hour. The reaction mixture was diluted with 200 ml ethyl acetate and washed with 10% potassium bisulfate, water, brine, dried (magnesium sulfate) and concentrated to 40 ml. Diphenyldiazomethane (0.5 g, 2.6 mmole) was added and the reaction mixture was stirred for 48 hours under argon, concentrated to 10 ml and chromatographed on 600 ml LPS-1 silica using a 7:3 ethyl acetate:Hexane solvent system. The appropriate fractions were combined and concentrated in vacuo to yield 0.61 g (73.5%) of intermediate D with consistent ^{13}C spectral data (CD_3CN, 15 MHz).

E. (S)-[[(2-Hydroxy-4-phenylbutylphosphinyl)oxy]-1-oxo-6-[[(phenylmethoxy)carbonyl]amino]-hexyl](3,4-dimethoxyphenyl)amino]acetic acid, diphenylmethyl ester

Phenylbutyl phosphonous acid (0.2 g, 1 mmole), and intermediate D (0.61 g, 0.96 mmole) were dissolved in 4 ml of tetrahydrofuran at 0°C under argon. Dicyclohexylcarbodiimide (0.21 g, 1 mmole) and dimethylaminopyridine (0.1 g) were added and the reaction was stirred at room temperature for 4 hours. Because no reaction was indicated by thin layer chromatography, 4 ml of pyridine was added and the reaction mixture was stirred at 40°C for 3 hours and at room temperature

overnight. After addition of 250 ml of ethyl acetate, the solution was filtered, washed with 5% potassium bisulfate, saturated sodium bicarbonate, water, and brine. It was concentrated in vacuo and theoretical yield of product was assumed.

The resulting phenylbutyl phosphonous acid ester was dissolved in 5 ml of dioxane and added to a 5 ml water solution of sodium metaperiodate (0.22 g). This was stirred under argon overnight, diluted with ethyl acetate and washed with 1% sodium bisulfite, water, 5% potassium bisulfate, water, and brine. The organic phase was dried and concentrated in vacuo to yield crude intermediate E. This compound was partially purified by preparation of its adamantamamine salt in ether-hexane. The semisolid adamantamamine salt of intermediate E was partitioned between ethyl acetate and 1 N hydrochloric acid. The ethyl acetate solution was washed with water and brine, dried (magnesium sulfate) and concentrated in vacuo to yield 0.61 g of intermediate E with consistent ^{13}C spectral data (CD_3CN, 15 MHz).

F. (S)-[[6-Amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl](3,4-dimethoxyphenyl)amino]acetic acid, dilithium salt

Intermediate E (0.61 g) was hydrogenated in 10 ml of methanol using 20% palladium on charcoal as catalyst at 1 atmosphere of hydrogen gas pressure. After 45 minutes, the solution was filtered through "Celite" and concentrated in vacuo. The residue was dissolved in acetone:1 N lithium hydroxide (PH 11.2) and chromatographed

on 60 ml of HP-20 using 200 ml each of water, 5% acetone-water, and 10% acetone-water. The appropriate fractions were combined, concentrated in vacuo to 5 ml and filtered through millipore. The filtrate was lyophilized to yield 0.29 g of Example 4 as a white solid.

Melting point 185-195°C.

Analysis Calculated for $C_{26}H_{35}N_2PO_8Li_2$ L·1.35 water: C, 54.52; H,6.64; N,4.89; P,5.41.

Found: C, 54.52; H,6.51; N,4.88; P,5.3.

Example 10

[[(S)-6-Amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl](4-methoxyphenyl)amino]-acetic acid, lithium salt

A. (4-Methoxyphenyl)aminoacetic acid, ethyl ester

p-Anisidine and ethyl bromoacetate were reacted according to the procedure given in Example 9, part A to give intermediate A as a light yellow solid in 68% yield.

Thin layer chromatography: R_f = 0.5 7:3 hexane/acetone.

B. (S)-[[2-(Acetyloxy)-1-oxo-6-[[phenylmethoxy)-carbonyl]amino]hexyl](4-methoxyphenyl)amino]-acetic acid, ethyl ester

Intermediate A and Intermediate B from Example 9 were reacted according to the procedure given in Example 9, part C to give intermediate B in 43% yield.

Thin layer chromatography: R_f = 0.9 7:3 hexane/actone.

C. (S)-[[2-Hydroxy-1-oxo-6-[[(phenylmethoxy)-carbonyl]amino]hexyl](4-methoxyphenyl)amino] acetic acid, diphenylmethyl ester

Intermediate B was reacted according to the procedure given in Example 9, part D to give intermediate C in 74% yield.
Thin layer chromatography: R_f = 0.15 2:5 hexane/ethyl acetate.

D. (S)-[[(2-Hydroxy-4-phenylbutylphosphinyl)oxy]-1-oxo-6-[[(phenylmethoxy)carbonyl]amino]hexyl](4-methoxyphenyl)amino]acetic acid diphenylmethyl ester

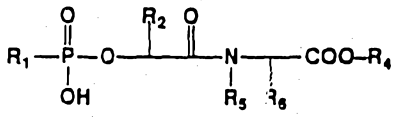
Intermediate C was reacted according to the procedure given in Example 9, part E to give intermediate D in 74% yield.
Thin layer chromatography: (CH_2Cl_2/MeOH/AcOH, 20:1:1) R_f = 0.92.

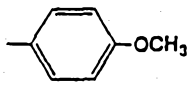
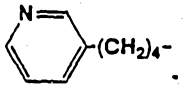
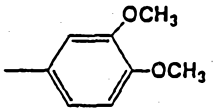
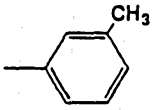
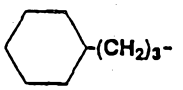
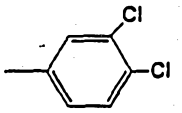
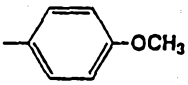
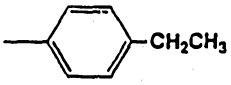
E. [[(S)-6-Amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl](4-methoxyphenyl)amino]-acetic acid, lithium salt

Intermediate D was reacted according to the procedure given in Example 9, part F to give Example 10 as a white solid dilithium salt.
Analysis $C_{25}H_{33}N_2O_7PLi_2 \cdot 1.2H_2O$: C,55.60; H,6.60; N,5.19; p,5.73.
Found: C,55.59; H,6.58; N,5.14; P,5.50.
$[\alpha]_D$ + 63.6° (c = 0.5, methanol).

Examples 11 to 16

The following compounds were prepared by the methods used in Example 9.



No.	R_1	R_2	R_4	R_5	R_6
11	Ph-$(CH_2)_2$-	-$(CH_2)_5$-NH_2	H		H
12		-$(CH_2)_4$-CH_3	H		$CH(CH_3)_2$
13	CH_3-$(CH_2)_5$-	-$(CH_2)_3$-Ph	H		H
14		-$(CH_2)_4$-NH_2	H		H
15	CH_3-$(CH_2)_7$-	-$(CH_2)_4$-NH_2	H		CH_3
16	Ph-$(CH_2)_5$-	CH_3	H		H

Example 17

[2S-[2α,3aβ,7aβ]]-1-[(S)-6-Amino-2-[[hydroxy-(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-octahydro-1H-indole-2-carboxylic acid, dilithium salt

A. [2α,3aβ,7aβ]Octahydro-1H-indole-2-carboxylic acid, ethyl ester hydrochloride

A mixture of ethyl(S)indoline-2-carboxylate hydrochloride (2.0 g, 8.8 mmole) and 10% palladium on charcoal (0.6 g) in 60 ml of absolute ethanol was hydrogenated overnight. The reaction was filtered through "Celite", rinsing with ethanol. The filtrate was concentrated in vacuo to a yellowish oil. The product was crystallized from ethyl acetate (60 ml). The product was collected and dried in vacuo to yield 1.3 g (63.5%) of intermediate A.

Melting point 138-140°C Lit. (139-140°C).

$[\alpha]_D$ = -27.2° (c = 1.0, water) [Lit.$[\alpha]_D$ = -27.8° (c = 1, water)].

Thin layer chromatography: [7:2:1 Isopropanol, ammonium hydroxide, water] Rf = 0.55 PMA visualized.

B. (S)-2-Hydroxy-6-[(phenylmethoxy)carbonyl]-amino]hexanoic acid

This compound was prepared as described in United States Patent No. 4,616,005, Example 137, part B.

C. [2S-[2α,3aβ,7aβ]]-1-[[(S)-2-Hydroxy-1-oxo-6-[(phenylmethoxy)carbonyl]amino]hexyl]-octahydro-1H-indole-2-carboxylic acid, ethyl ester

A solution of intermediate B (1.20 g, 4.49 mmole), intermediate A (1.30 g, 5.56 mmole), and triethylamine (.072 ml, 5.17 mmole) in dry tetrahydrofuran (15 ml) was cooled to 0°C under argon. 1,3 Dicyclohexylcarbodiimide (1.01 g, 4.90 mmole) and 1-hydroxybenzotriazole hydrate

(0.66 g, 4.90 mmole) were added. The reaction was stirred at 0°C for 3 hours and at room temperature for one hour. The reaction was diluted with ethyl acetate and filtered to remove dicyclohexylurea. The filtrate was washed with 5% potassium bisulfate (twice), saturated sodium bicarbonate, and brine, and dried over sodium sulfate. The solvent was removed in vacuo to yield 2.1 grams of oil, which was chromatographed on silica gel and eluted with hexanes:ethyl acetate (2:1) to yield 1.6 g (77.5%) of intermediate C.

$[\alpha]_D$ = -34.22°C (c = 1.73, ethanol).

Thin layer chromatography: (20:1:1) CH_2Cl_2: methanol:acetic acid

R_f = 0.6 PMA visualized.

D. [2S-[2α,3aβ,7aβ]]-1-[(S)-2-[[hydroxy-(4-phenylbutyl)phosphinyl]]oxy]-1-oxo-6-[(phenylmethoxy)carbonyl]aminohexyl]-octahydro-1H-indole-2-carboxylic acid, ethyl ester

To a solution of intermediate C (1.6 g, 3.48 mmole) and phenylbutylphosphonous acid (1.03 g, 5.2 mmoles) in dry tetrahydrofuran (20 ml) was added dicyclohexylcarbodiimide (1.07 g. 5.2 mmol) and dimethylaminopyridine (0.2 g). The reaction was stirred at room temperature for 2 hours. Additional phosphonous acid (0.5 g, 2.6 mmole) and dicyclohexylcarbodiimide (0.53 g, 2.6 mmole) were added. The reaction was stirred for 48 hours. The mixture was diluted with ethyl acetate and filtered. The filtrate was washed with 5% potassium bisulfate (twice), saturated sodium bicarbonate, brine, and dried over sodium sulfate.

The solvent was removed in vacuo and the residue was dissolved in ethyl acetate:hexanes (1:1, filtered, and concentrated to yield 1.9 g of the coupled product.

Thin layer chromatography: (7:3) ethyl acetate: hexanes

R_f = 0.2 (7:3) ethyl ether:acetone R_f = 0.5

The residue was dissolved in 25 ml dioxane and treated with a solution of sodium metaperiodate (0.96 g, 4.5 mmole) in 5 ml of water. The reaction was stirred overnight at room temperature then diluted with ethyl acetate. The organic phase was washed with 1% potassium bisulfate (twice), diluted with sodium bisulfate (twice), brine, and dried over sodium sulfate. The solvent was removed in vacuo and the residue was dissolved in diethyl ether (9 ml). A solution of 1-adamantanamine (0.55 g) in 2 ml of ether was then added. After stirring 15 minutes, hexanes were added to precipitate the adamantanamine salt. The mother liquor was decanted. The salt was triturated repeatedly with hexane, then partitioned between ethyl acetate and 1 N hydrochloric acid. The organic phase was washed with brine and dried over sodium sulfate. The solvent was removed to yield 1.35 g of intermediate D.

The crude acid intermediate D was dissolved in sodium bicarbonate (250 ml). The aqueous phase was extracted with ethyl ether (five times) then acidified to pH 2 and extracted with ethyl acetate (four times). The combined extracts were washed with brine and dried over sodium sulfate. The

solvent was removed in vacuo to yield 1.25 g (55%) of a yellow oil (intermediate B).
Thin layer chromatography: [(20:1:1) methylene chloride:methanol:acetic acid.
R_f = 0.2.

E. [2S-[2α,3aβ,7aβ]]-1-[(S)-6-Amino-2-[[hydroxy-(4-phenylbutyl)phosphinyl]]oxy]-1-oxohexyl]-octahydro-1H-indole-2-carboxylic acid, ethyl ester

A mixture of intermediate D (1.25 g, 1.90 mmole) and 10% palladium on charcoal (0.3 g) in absolute ethanol was hydrogenated at atmospheric pressure overnight. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to yield 0.75 g [H908-008-1] of an oil. Thin layer chromatography [(7:2:1) isopropanol:ammonium hydroxide:water, R_f = 0.7] indicated two spots. Chromatography on HP-20, using a gradient system of acetonitrile: water gave purer product.

This product (0.30 g) was rechromatographed on HP-20 to yield 280 mg (28.2%) pure intermediate E.

F. [2S-[2α,3aβ,7aβ]]-1-[(S)-6-Amino-2-[[hydroxy-(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-octahydro-1H-indole-2-carboxylic acid, dilithium salt

A solution of intermediate E (280 mg, 0.536 mmole) in 5 ml of 1 N lithium hydroxide and 4 ml of methanol was stirred at room temperature overnight. Saponification was judged completed by

thin layer chromatography (7:2:1 isopropanol: ammonium hydroxide:water, R_f = 0.35). The reaction was concentrated in vacuo to remove methanol, and the aqueous solution was chromatographed on HP-20. The column was eluted with a gradient from 100% water to 50% water:acetonitrile. Fractions containing intermediate F were concentrated in vacuo. The resulting oil was dissolved in distilled water and filtered, then lyophilized to yield 0.21 g (81%) of Example 17.

Example 18

[2S-[1(R*),2α,3αβ,3αβ,6αβ]]-1-[6-Amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-octahydrocyclopenta[β]pyrrole-2-carboxylic acid, dilithium salt

A. [2α,3αβ,3αβ,6αβ]-Octahydrocyclopenta[β]-pyrrole-2-carboxylic acid, phenylmethyl ester

The preparation of this compound is described in Tetrahedron Letters, Vol. 26, No. 15, pp. 1839-1842, by H. Urbach and R. Henning. A second equivalent of N-benzylglycine ethyl ester was used as base in the pyrrole synthesis rather than triethylamine. The compound was resolved as described in Tetrahedron Letters, Vol. 25, No. 40, pp. 4479-4482, by V. Teetz, R. Geiger and H. Gaul. $[\alpha]_D$ = -34.7 (c = 1.00, water) Lit. $[\alpha]_D$ = -38.4.

B. (S)-6-[[(Phenylmethoxy)carbonyl)amino]-2-hydroxy heranoic acid

This compound was prepared as described in United States Patent No. 4,616,005, Example 137, part B.

C. [2S[1(R*),2α,3αβ,3αβ,6aβ]]-1-[[(S)-2-Hydroxy-1-oxo-6-[(phenylmethoxy)carbonyl]amino]hexyl]-octahydrocyclopenta[β]pyrrole-2-carboxylic acid, phenylmethyl ester

Intermediate compound A (434 mg, 1.54 mmol) and Intermediate compound B (434 mg, 1.54 mmol) were dissolved in 10 ml tetrahydrofuran and cooled to 0°. Triethylamine (0.31 ml, 0.22 g, 2.22 mmol), dicyclohexylcarbodiimide (340 mg, 1.65 mmol), and hydroxybenzotriazole (222 mg, 1.64 mmol) were added. The reaction mixture was stirred for two hours at 0°, warned to room temperature and stirred an additional two hours. The [see 29,644] product was chromatographed on LPS-1 using 4:1 hexane:acetone.
Product-containing fractions were combined to give 550 mg (1.15 mmol, 75%) of compound C.
^{13}C NMR showed that this was contaminated with a small amount of the corresponding lactone.
Thin layer chromatography: (1:1 hexane:acetone) R_f = 0.52, with no sign of the less polar epimer.

D. [2S-[1(R*),2α,3αβ,3αβ,6aβ]]-1-[(S)-2-[[hydroxy-(4-phenylbutyl)phosphinyl]]oxy]-1-oxo-6-[(phenylmethoxy)carbonyl]aminohexyl]-octahydrocyclopenta[β]pyrrole-2-carboxylic acid, phenylmethyl ester

Intermediate compound C (550 mg, 1.15 mmol) and phenylbutylphosphonous acid (1.5 mmol, 296 mg) were dissolved in 10 ml tetrahydrofuran.

Dicyclohexylcarbodiimide (309 mg, 1. mmol) and dimethylaminopyridine (50 mg) were added and the reaction stirred for four hours at room temperature. The intermediate phosphonous ester was oxidized to the phosphonic monoester with 340 mg sodium metaperiodate, [using reaction and workup conditions described in Example 9, part E] giving 730 mg (1.04 mmol, 90%) Intermediate D. Thin layer chromatography: R_f = 0.23 (20:1:1 methylene chloride:methanol:acetic acid).

E. [2S-[1(R*),2α,3αβ,3αβ,6αβ]]-1-[6-Amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]octahydrocyclopenta[β]pyrrole-2-carboxylic acid, dilithium salt

Intermediate compound D (730 mg, 1.04 mmol) was dissolved in 50 ml methanol and stirred under atmospheric pressure hydrogen with 70 mg of Adams catalyst until uptake of hydrogen ceased. The solution was filtered through "Celite" and concentrated in vacuo. The product was not very water-soluble, so 1 N lithium hydroxide was added to the compound in 20 ml water until the solution was basic. This solution was then loaded onto an HP-20 column, which was eluted with 1:1 water:acetonitrile gradient. Product-containing fractions were combined and concentrated, then dissolved in 25 ml water, filtered through a polycarbonate membrane, frozen and lyophilized. This gave 170 mg (0.33 mmol, 32%) of Example 18. $[\alpha]_D$ = -1.4 (c = 0.5, methanol).
Melting point 195-200°C.

Electrophoresis (pH 9.2, 300V, 90 minutes) B12 0.0 cm, Compound +2.4, NANOS + 6.0, DPP - 5.7.

C,H,N,P Analysis: calculated for $C_{24}H_{35}N_2O_6PLi_2 \cdot$water:

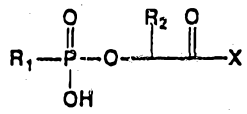
Calculated: C,56.45; H,7.30; N,5.49; P,6.07.

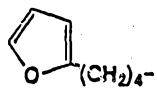
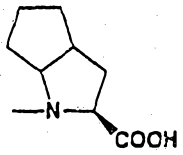
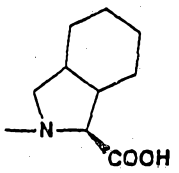
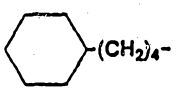
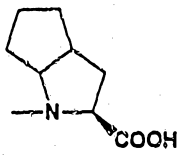
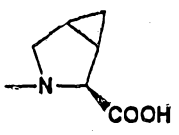
Found: C,56.45; H,7.49; N,5.62; P,5.8.

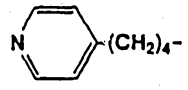
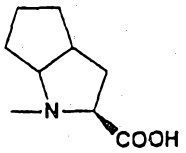
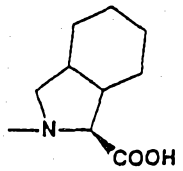
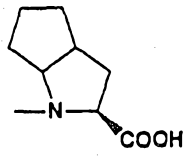
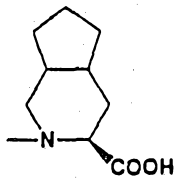
Thin layer chromatography (7:2:1 isopropanol:ammonium hydroxide:water) $R_f \approx 0.25$.

Examples 19 to 27

The following compounds were prepared by the methods used in Example 18.



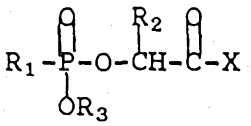
No.	R_1	R_2	X
19	Ph-$(CH_2)_2$-	-$(CH_2)_5$-NH_2	H
20		-CH_3	
21	Ph-$(CH_2)_5$-	-$(CH_2)_4$-NH_2	
22		-$(CH_2)_3$-NH_2	
23	Ph-$(CH_2)_4$-	-$(CH_2)_2$-Ph	

24		$-(CH_2)_2-OH$	
25	$CH_3-(CH_2)_5-$	$-(CH_2)_3-CH_3$	
26	$CH_3-(CH_2)_5-$	$-(CH_2)_3-NH_2$	
27	$CH_3-(CH_2)_5-$	$-(CH_2)_4-NH_2$	

The foregoing examples represent specific embodiments of the invention. These examples are illustrative rather than limiting; the scope of the invention is limited only by the claims appended hereto.

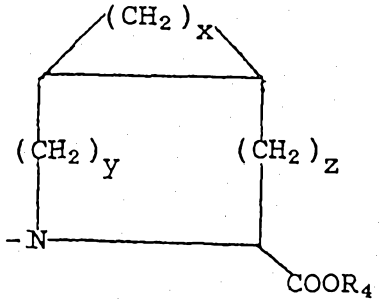
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

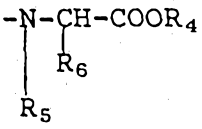
1. Substituted amino or imino acids of the formula

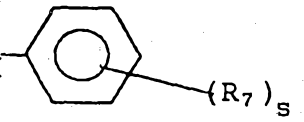
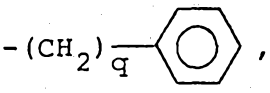
I 

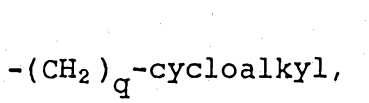
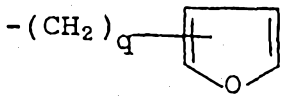
isomeric mixtures thereof and pharmaceutically acceptable salts thereof, wherein:

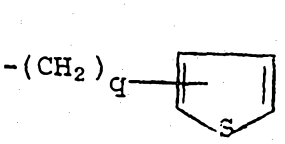
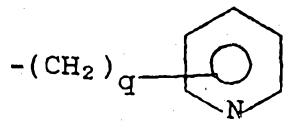
X is an imino or amino acid of the formula

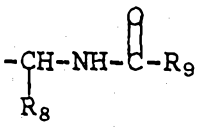


or  ;

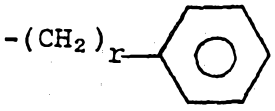
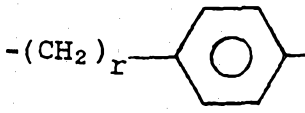
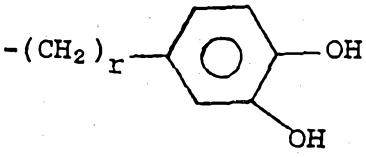
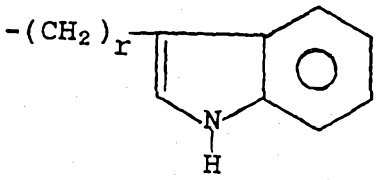
R_1 is alkyl of 1 to 10 carbons, aminoalkyl, haloalkyl,  ,  ,

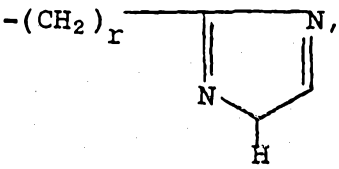
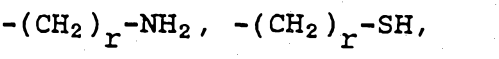
 , 

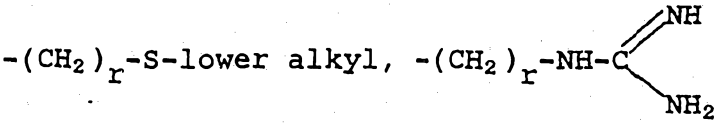


, or

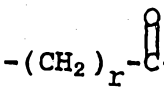

;

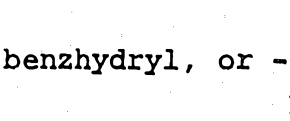
R_2 is hydrogen, lower alkyl, halo substituted lower alkyl,





.

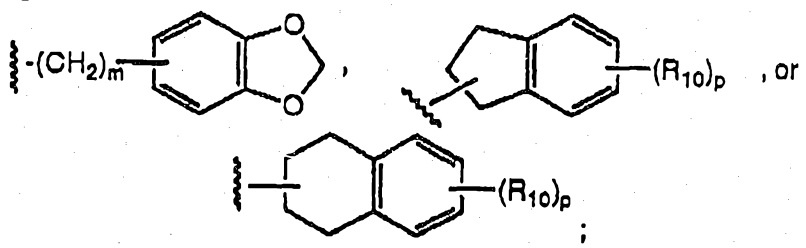




or


;

R_3 and R_4 are independently selected from hydrogen, lower alkyl, benzyl, alkali metal, benzhydryl, or 
;

R_5 is

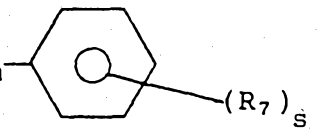
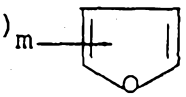
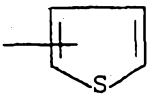
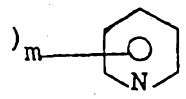
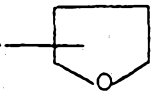


, or

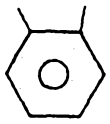
;

R_6 is hydrogen or lower alkyl;

R_7 is lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl, hydrogen, hydroxy, phenyl, phenoxy, phenylthio, or phenylmethyl;

R_8 and R_9 are independently selected from hydrogen, lower alkyl, halo-substituted lower alkyl, $-(CH_2)_m$  , $-(CH_2)_q$-cycloalkyl, $-(CH_2)_m$  , $-(CH_2)_m$  , $-(CH_2)_m$  , or $-(CH_2)_m$  ;

R_{10} is hydrogen, lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl, or hydroxy;

R_{11} is hydrogen, lower alkyl, cycloalkyl, or phenyl, and R_{12} is hydrogen, lower alkyl, lower alkoxy, phenyl, or R_{11} and R_{12} taken together are $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH=CH-$, or  ;

a + b = two or three;

m is zero, one, two or three;

p is one, two or three, provided that p is more than one only if R_{10} is hydrogen, methyl, methoxy, chloro, or fluoro;

q is an integer from zero to seven;

r is an integer from one to four;

s is one, two, or three;

x is an integer from one to four;

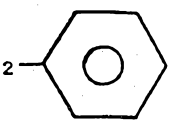
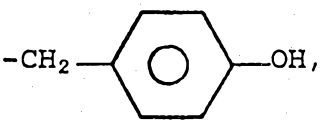
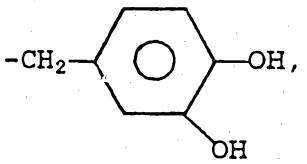
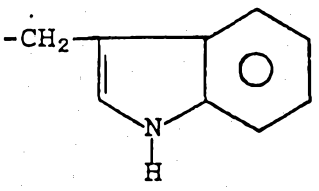
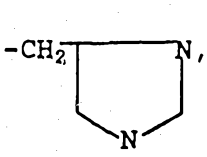
y is zero, one, or two; and

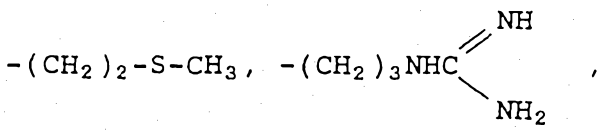
z is zero, one, or two.

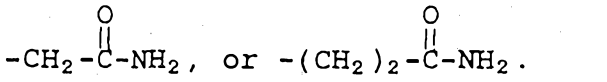
2. A compound of Claim 1, wherein:

R_4 is hydrogen, an alkali metal salt, or $-CH(R_{11})-O-\overset{O}{\overset{\|}{C}}-R_{12}$, wherein R_{11} is hydrogen, methyl or isopropyl and R_{12} is straight or branched chain lower alkyl of 1 to 4 carbons or phenyl.

3. A compound of Claim 1, wherein:

R_6 is hydogen, lower alkyl of 1 to 4 carbons,  ,  ,  ,  ,  , $-(CH_2)_4-NH_2$, $-CH_2SH$,

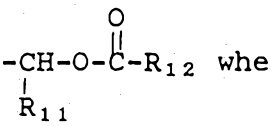




4. A compound of Claim 1, wherein:

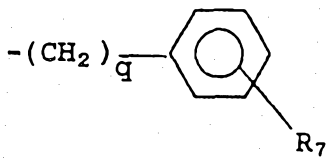
R_2 is hydrogen, lower alkyl of 1 to 4 carbons, amino-substituted lower alkyl, guanidino-substituted lower alkyl or CF_3.

5. A compound of Claim 1, wherein:

R_3 is hydrogen, an alkali metal salt, lower alkyl of 1 to 4 carbons, or  wherein R_{11} is hydrogen, methyl or isopropyl and R_{12} is straight or branched chain lower alkyl of 1 to 4 carbons or phenyl.

6. A compound of Claim 1, wherein:

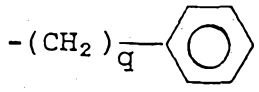
R_1 is alkyl of 1 to 10 carbons;



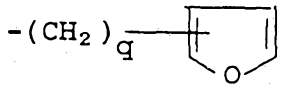
wherein q is an integer from 0 to 5 and

R_7 is hydrogen, methyl, methoxy, methylthio,

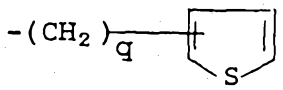
chloro, bromo, fluoro, or hydroxy; $-(CH_2)_q-$ cycloalkyl wherein cycloalkyl is of 5 or 6 carbons and q is zero, one or two;



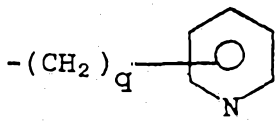
wherein q is an integer from 0 to 5;



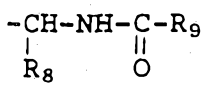
wherein q is an integer from 0 to 5;



wherein q is an integer from 0 to 5;

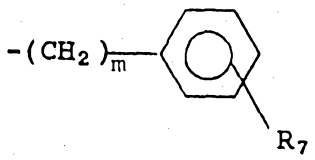


wherein q is an integer from 0 to 5; or



7. A compound of Claim 1, wherein:

R_8 and R_9 are independently selected from lower alkyl of 1 to 4 carbons or



wherein R_7 is hydrogen, methyl, methoxy, methylthio, chloro, bromo, fluoro, or hydroxy.

8. The compound of Claim 1, N-[(S)-6-Amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-N-(2,3-dihydro-1H-inden-2-yl)glycine, dilithium salt.

9. The compound of Claim 1, [[(S)-6-Amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl](4-methoxyphenyl)amino]-acetic acid, dilithium salt.

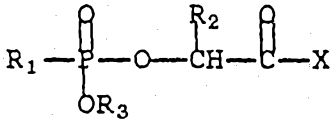
10. The compound of Claim 1, (S)-[[6-Amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]phenylamino]acetic acid, dilithium salt.

11. The compound of Claim 1, (S)-[[6-Amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl](3,4-dimethoxyphenyl)-amino]acetic acid, dilithium salt.

12. The compound of Claim 1, [2S-[2α,3aβ,7aβ]]-1-[(S)-6-Amino-2-[[hydroxy-(4-phenylbutyl)-phosphinyl]oxy]-1-oxohexyl]-octahydro-1H-indole-2-carboxylic acid, dilithium salt.

13. The compound of Claim 1, [2S-[1(R*),2α,3αβ,3αβ,6αβ]]-1-[6-Amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-octahydrocyclopenta[β]pyrrole-2-carboxylic acid, dilithium salt.

14. A composition useful for treating hypertension comprising a pharmaceutically acceptable carrier and an effective amount of a hypotensive agent or pharmaceutically acceptable salt thereof of the formula



wherein X, R_1, R_2 and R_3 are as defined in Claim 1.

15. The composition of Claim 14 also including a diuretic.

16. A method of alleviating hypertension in a mammalian species, which comprises administering an effective amount of the compound of Claim 1.

Dated: 17 July 1990

PHILLIPS ORMONDE & FITZPATRICK
Attorneys for:
E.R. SQUIBB & SONS, INC.

David B Fitzpatrick