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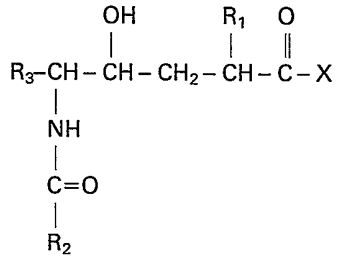
250 251 252 253 254 256 25Y 280 282 28X 30Y 311 313
31Y 320 321 323 32Y 337 342 34Y 351 355 360 361 362
364 365 366 367 368 36Y 373 37Y 57Y 603 604 613 614
628 62X 638 63X 652 658 65X 668 678 697 699 800 802
80Y AA KM KN KZ RE
U1S 2415 2417 C2C

(56) Documents cited
EP A1 0103496 EP A1 0045161

(58) Field of search
C2C

(54) **Acylamino hydroxyalkanoyl amino and imino acids and esters**

(57) New compounds of the formula



wherein R_1, R_2, R_3 and X are as defined herein, are useful as hypotensive agents due to their angiotensin converting enzyme inhibition activity and, depending upon the definition of X, may also be useful as analgesics due to their enkephalinase inhibition activity.

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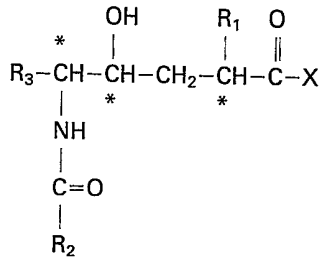
Formulae in the printed specification were reproduced from drawings submitted after the date of filing, in accordance with Rule 20(14) of the Patents Rules 1982.

SPECIFICATION

Acylamino hydroxyalkanoyl amino and imino acid and esters

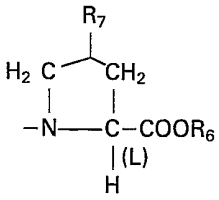
This invention is directed to the acylamino hydroxyalkanoyl amino and imino acids and esters of formula I and pharmaceutically acceptable salts thereof

(I)



wherein

X is an amino or imino acid or ester of the formula



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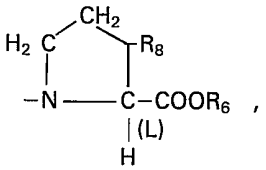

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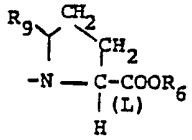

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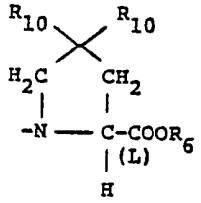

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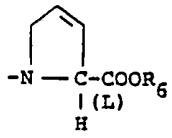

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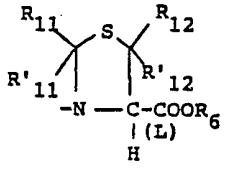

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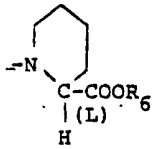

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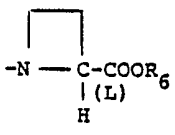

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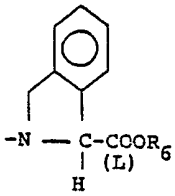

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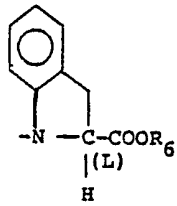

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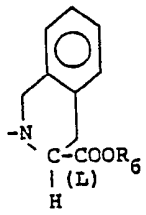
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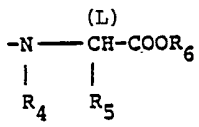
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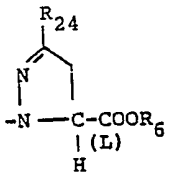
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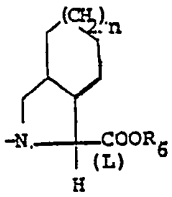
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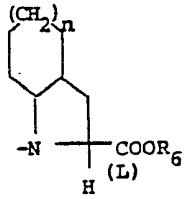
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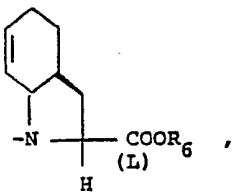
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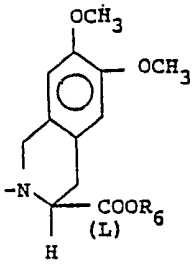
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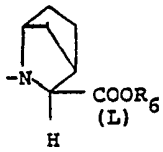
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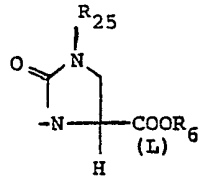
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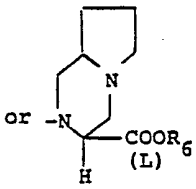
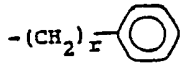

;

n is zero, one or two.

R_{25} is lower alkyl of 1 to 4 carbons or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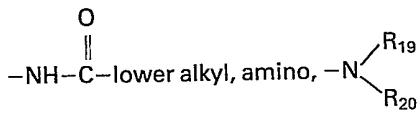
R_7 is hydrogen, lower alkyl, halogen, hydroxy,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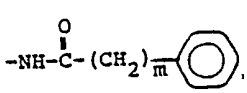
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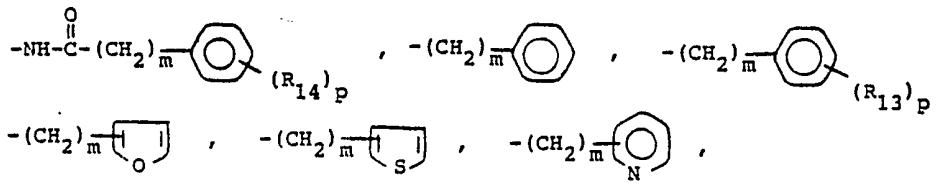
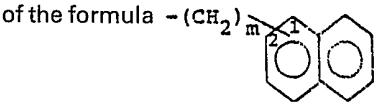
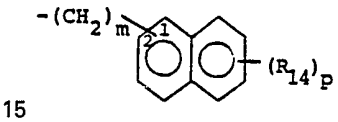
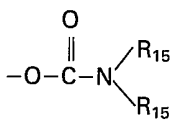
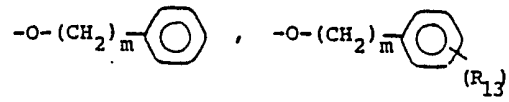
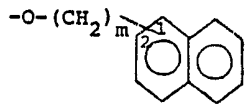
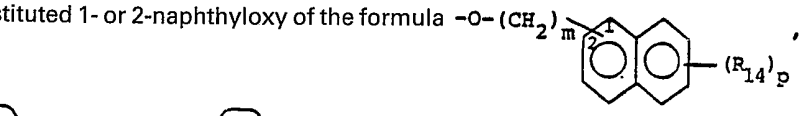
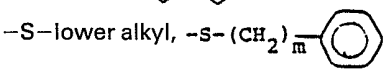


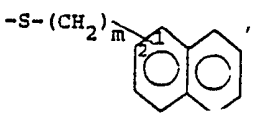
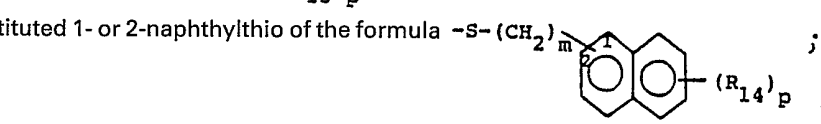
a 1- or 2-naphthyl of the formula  , a substituted 1- or 2-naphthyl of the formula

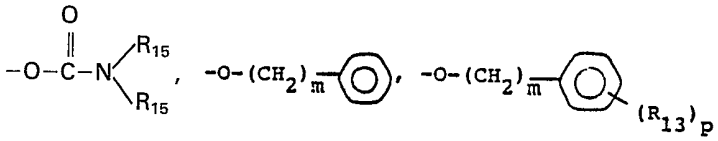
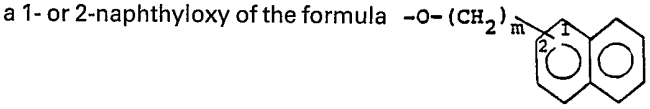
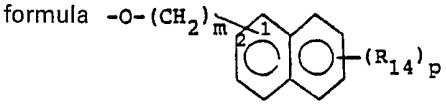
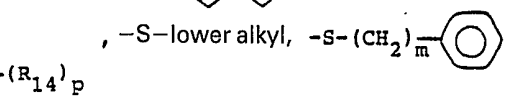
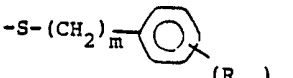
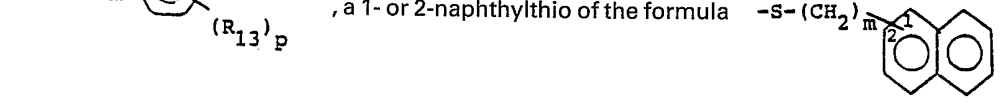
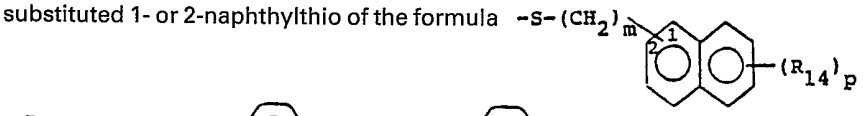
 , $-(CH_2)_m-$cycloalkyl,  , $-O-$lower alkyl,

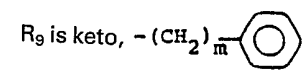
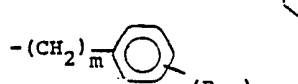
 , a 1- or 2-naphthyloxy of the formula

 , a substituted 1- or 2-naphthyloxy of the formula  ,

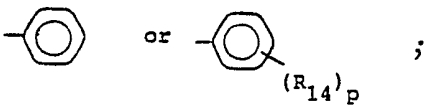
$-S-$lower alkyl,  , a 1- or 2-naphthylthio of the formula

 , or a substituted 1- or 2-naphthylthio of the formula  ;

R_8 is halogen,  , a 1- or 2-naphthyloxy of the formula  , a substituted 1- or 2-napthyloxy of the formula  , $-S-$lower alkyl,  ,  , a 1- or 2-naphthylthio of the formula  , or a substituted 1- or 2-naphthylthio of the formula  ;

R_9 is keto,  , or  ;

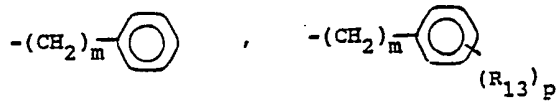
R_{10} is halogen or $-Y-R_{16}$;

R_{11}, R'_{11}, R_{12} and R'_{12} are independently selected from hydrogen and lower alkyl or R'_{11}, R_{12} and R'_{12} are hydrogen and R_{11} is  ;

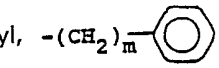
R_{13} is lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl, hydroxy, phenyl, phenoxy, phenylthio, or phenylmethyl;

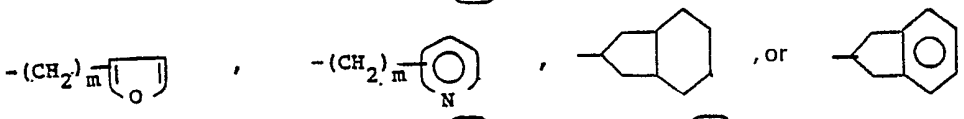
R_{14} is lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl or hydroxy;

m is zero, one two, three, or four;
p is one, two or three provided that p is more than one only if R_{13} or R_{14} is methyl, methoxy, chloro, or fluoro;
R_{15} is hydrogen or lower alkyl of 1 to 4 carbons;
Y is oxygen or sulfur;
R_{16} is lower alkyl of 1 to 4 carbons,



or the R_{16} groups join to complete an unsubstituted 5- or 6-membered ring or said ring in which one or more of the carbons has a lower alkyl of 1 to 4 carbons or a di(lower alkyl of 1 to 4 carbons) substituent;

R_4 is hydrogen, lower alkyl,  , $-(CH_2)_m$-cycloalkyl, ,



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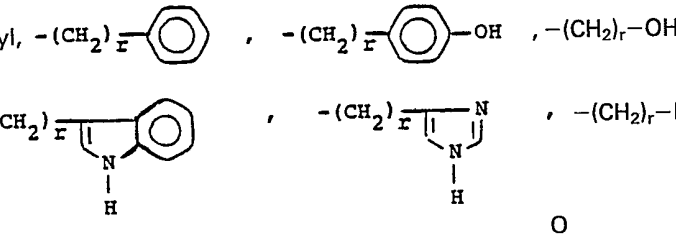
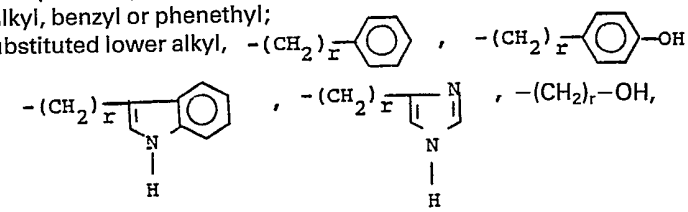
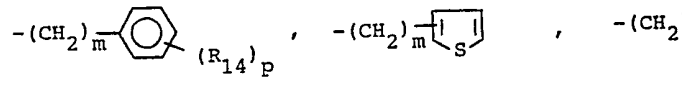
R_5 is hydrogen, lower alkyl, 

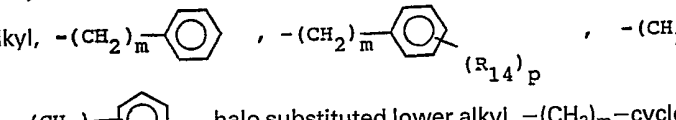
$-(CH_2)_r-SH$, $-(CH_2)_r-S-$lower alkyl, $-(CH_2)_r-NH-C(=NH)-NH_2$, or $-(CH_2)_r-C(=O)-NH_2$;

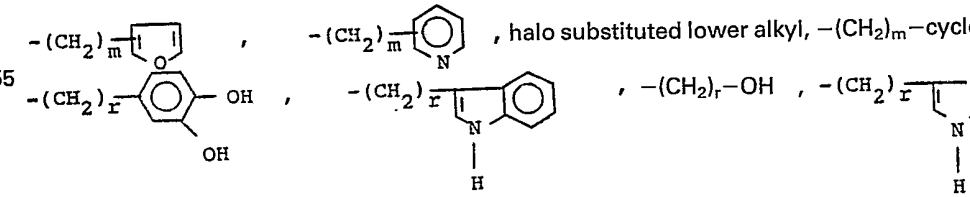
r is an integer from 1 to 4;
R_{19} is lower alkyl, benzyl or phenethyl;
R_{20} is hydrogen, lower alkyl, benzyl or phenethyl;
R_1 is lower alkyl, halo substituted lower alkyl, 

$-(CH_2)_r-S-$lower alkyl, $-(CH_2)_2-S-(CH_2)_2-NH_2$, $-(CH_2)_r-NH-C(=NH)-NH_2$, or $-(CH_2)_r-C(=O)-NH_2$;

R_2 is 

;

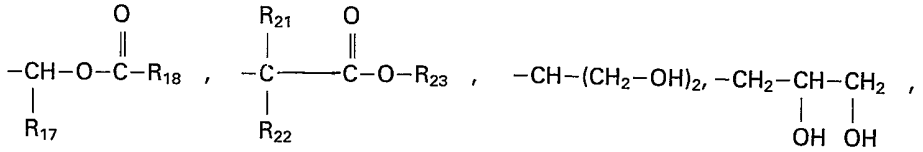
R_3 is hydrogen, lower alkyl,  , halo substituted lower alkyl, $-(CH_2)_m-$cycloalkyl,



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

wherein m, R_{14}, p and r are as defined above;

R_6 is hydrogen, lower alkyl, benzyl, benzhydryl, a pharmaceutically acceptable salt forming ion,

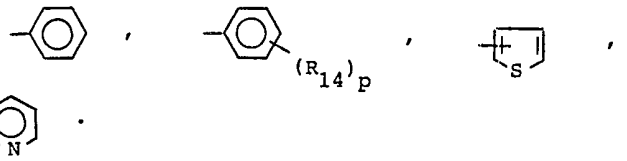


R_{17} is hydrogen, lower alkyl, cycloalkyl, or phenyl;

R_{18} is hydrogen, lower alkyl, lower alkoxy or phenyl;

R_{21} and R_{22} are independently selected from hydrogen and lower alkyl;

R_{23} is lower alkyl; and

R_{24} is hydrogen, lower alkyl, 

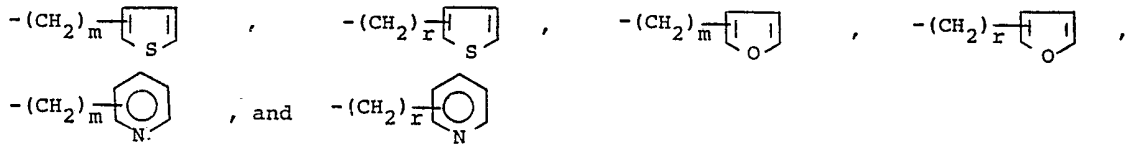
The term lower alkyl used in defining various symbols refers to straight or branched chain radicals having up to seven carbons. The preferred lower alkyl groups are up to four carbons with methyl and ethyl most preferred. Similarly the terms lower alkoxy and lower alkylthio refer to such lower alkyl groups attached to an oxygen or sulfur.

The term cycloalkyl refers to saturated rings of 4 to 7 carbon atoms with cyclopentyl and cyclohexyl being most preferred.

The term halogen refers to chloro, bromo and fluoro.

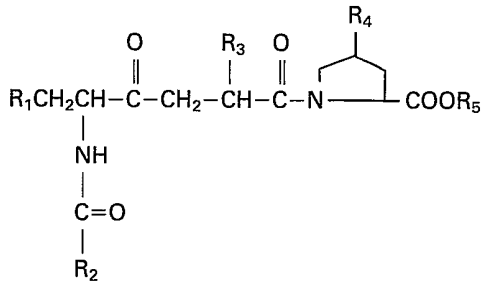
The term halo substituted lower alkyl refers to such lower alkyl groups described above in which one or more hydrogens have been replaced by chloro, bromo or fluoro groups such as trifluoromethyl, which is preferred, pentafluoro, 2,2,2-trichloroethyl, chloromethyl, bromomethyl, etc.

The symbols



represent that the alkylene bridge is attached to an available carbon atom.

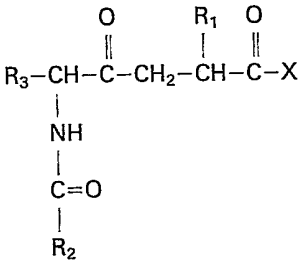
Almquist et al. in United States Patent 4,329,473 disclose angiotensin converting enzyme inhibitors of the formula



wherein R_1 is aryl; R_2 is aryl, alkyl, or alkoxy; R_3 is hydrogen or lower alkyl; R_4 is hydrogen or hydroxy, and R_5 is hydrogen or lower alkyl.

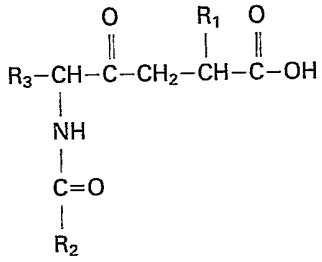
This invention in its broadest aspects relates to the substituted amino and imino acids and esters of formula I above, to compositions and the method of using such compounds as pharmaceutical agents.

The compounds of formula I are obtained by treating a compound of the formula (II)



with a conventional reducing agent such as sodium borohydride, sodium cyanoborohydride, diisobutyl aluminum hydride, lithium tri t-butoxy aluminum hydride, etc.

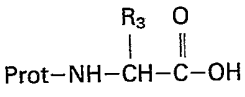
The compounds of formula II can be prepared by various methods. For example, a keto carboxylic acid of the formula (III)



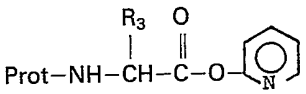
can be coupled with the amino or imino acid ester of the formula (IV)

wherein R_6 in the definition of X is an easily removable protecting group such as benzyl, benzhydryl, t-butyl, etc. This coupling reaction is preferably performed in the presence of a catalyst such as dicyclohexylcarbodiimide. Alternatively, the acid of formula III can be converted to an activated form such as the acid chloride, mixed anhydride, symmetrical anhydride, etc.

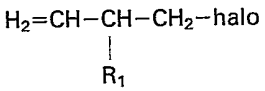
The acid of formula III can be prepared as follows. An amino acid of the formula (V)



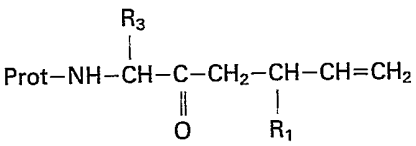
wherein Prot is a protecting group such as t-butoxycarbonyl is converted to the ester of the formula (VI)



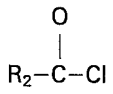
by treating with 2-hydroxypyridine in dry pyridine in the presence of dicyclohexycarbodiimide. The halide of the formula (VII)



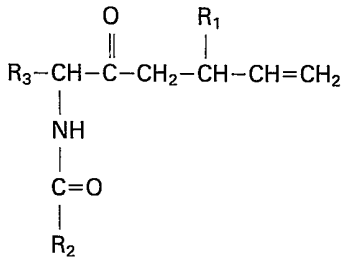
wherein halo is Cl or Br is treated with magnesium and the resulting Grignard reagent is reacted with the ester of formula VI to give (VIII)



Removal of the protecting group followed by reaction with the acid chloride of the formula (IX)

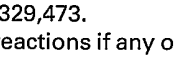
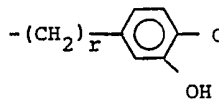
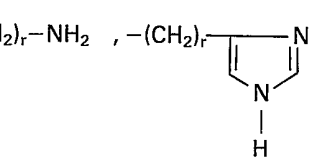
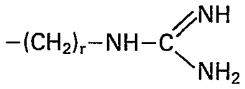


gives the intermediate (X)



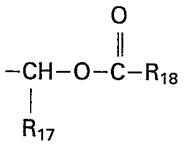
The intermediate of formula X is oxidized and treated with Jones reagent (chromic anhydride in dilute sulfuric acid) to give the carboxylic acid of formula III.

Other procedures for preparing the keto compounds of formula II are disclosed by Almquist et al. in United States Patent 4,329,473.

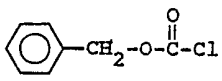
In the above reactions if any or all of R_1, R_3 and R_5 are  ,  , $-(CH_2)_r-NH_2$,  , $-(CH_2)_r-SH$, $-(CH_2)_r-OH$, or 

then the hydroxyl, amino, imidazolyl, mercaptan or guanidinyl function should be protected during the 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.

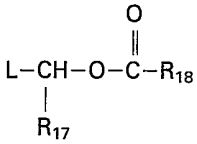
The ester products of formula I wherein R_6 is



may be obtained by employing the amino or imino acid of formula IV in the above reactions with such ester group already in place. Such ester reactants can be prepared by treating the amino or imino acid of formula IV wherein R_6 is hydrogen with an acid chloride such as

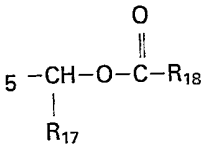


or with di-t-butyl carbonate so as to protect the N-atom. The protected compound is then reacted in the presence of a base with a compound of formula (XI)



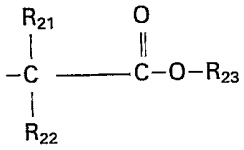
wherein L is a leaving group such as chlorine, bromine, tolylsulfonyl, etc., followed by removal of the N-protecting group such as by treatment with acid or hydrogenation.

The ester products of formula I wherein R_6 is

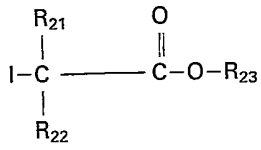


can also be obtaind by treating the product of formula I wherein R_6 is hydrogen with a molar excess of the compound of formula XI.

The ester products of formula I wherein R_6 is



can be prepared by treating the product of formula I wherein R_6 is hydrogen with a molar excess of the compound of the formula (XII)

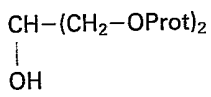


.

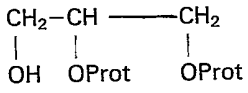
The ester products of formula I wherein R_6 is

$-CH-(CH_2-OH)_2$ or $-CH_2-\underset{\underset{OH}{|}}{CH}-\underset{\underset{OH}{|}}{CH_2}$ can be

prepared by coupling the product of formula I wherein R_6 is hydrogen with a molar excess of the compound of the formula (XIII)

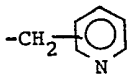


or the formula (XIV)



in the presence of a coupling agent such as dicyclohexylcarbodiimide followed by removal of the hydroxyl protecting groups.

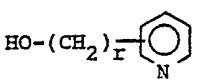
Similarly, the ester products of formula I wherein R_6 is $-(CH_2)_2-N(CH_3)_2$ or



can be prepared by coupling the product of formula I wherein R_6 is hydrogen with a molar excess of the compound of formula (XV)

$HO-CH_2-CH_2-N-(CH_3)_2$

or the formula (XVI)

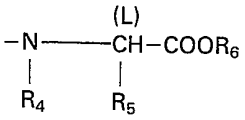
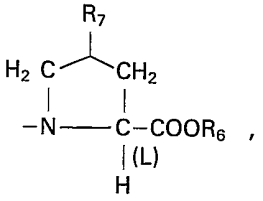


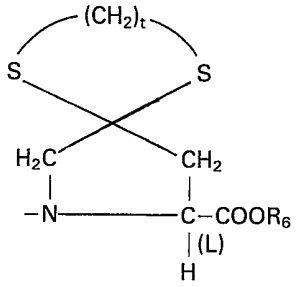
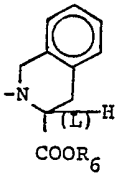
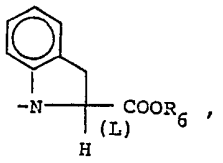
in the presence of a coupling agent such as dicyclohexylcarbodiimide.

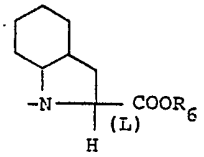
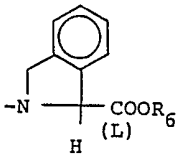
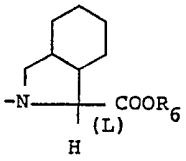
The products of formula I wherein R_7 is amino may be obtained by reducing the corresponding products of

formula I wherein R_7 is azido.

Preferred compounds of this invention are those of formula I wherein:

X is  ,  ,

 ,  ,  ,

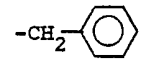
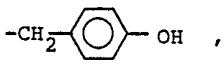
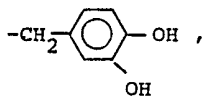
 ,  or  .

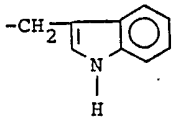
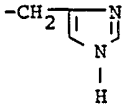
R_1 is straight or branched chain lower alkyl of 1 to 4 carbons or $-(CH_2)_r-NH_2$ wherein r is an integer from 1 to 4.

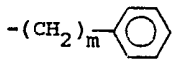
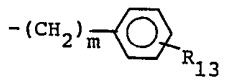
R_6 is hydrogen, straight or branched chain lower alkyl of 1 to 4 carbons, or an alkali metal ion.

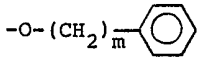
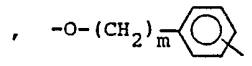
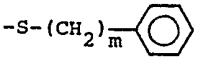
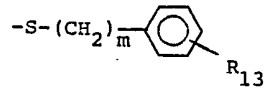
R_4 is cyclohexyl or phenyl and R_5 is hydrogen.

R_4 is hydrogen and R_5 is methyl,

$-CH_2-CH(CH_3)_2$,  ,  ,  ,

 , or  .

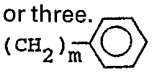
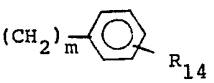
R_7 is hydrogen, cyclohexyl, lower alkoxy of 1 to 4 carbons,  ,  ,

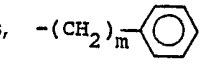
 ,  ,  , or  .

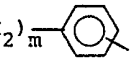
R_{13} is methyl, methoxy, methylthio, Cl, Br, F, or hydroxy.

m is zero, one or two.

t is two or three.

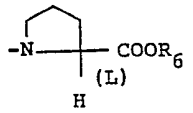
R_2 is  or  .

R_3 is straight or branched chain lower alkyl of 1 to 4 carbons,  , or

 .

R_{14} is methyl, methoxy, methylthio, Cl, Br, F, or hydroxy.

Most preferred compounds of this invention are those of formula I wherein:

X is  .

R_1 is methyl.
R_6 is hydrogen or an alkali metal ion.
R_2 is benzyl.
R_3 is phenyl.

The compounds of formula I wherein R_6 is hydrogen form salts with a variety of inorganic or organic bases. The nontoxic, pharmaceutically acceptable salts are preferred, although other salts are also useful in isolating or purifying the product. Such pharmaceutically acceptable salts include alkali metal salts such as sodium, potassium or lithium, alkaline earth metal salts such as calcium or magnesium, and salts derived from amino acids such as arginine, lysine, etc. The salts are obtained by reacting the acid form of the compound with an equivalent of the base supplying the desired ion in a medium in which the salt precipitates or in aqueous medium and then lyophilizing.

Several asymmetric centers are present as represented by the * in formula I. Of course, if R_3 is hydrogen, then one less center is present. Thus, the compounds of formula I can exist in diastereometric forms or in mixtures thereof. The above described processes can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric products are prepared, 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. The configuration of the final product will depend upon the configuration of the R_7, R_8 and R_9 substituent in the starting material of formula IV.

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 pseudoglobulin in blood plasma, 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 angiotensinogen → (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., preferably about 1 to 50 mg., per kg. 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 dosage 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 of this invention are the thiazide diuretics, e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methyclothiazide, trichloromethiazide, polythiazide or benzthiazide as well as ethacrynic acid, ticrynafen, 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 physiologically acceptable vehicle, carrier, excipient, binder, preservative, 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.

The compounds of formula I wherein X is $-NH-\underset{\displaystyle R_5}{\underset{|}{CH}}-COOR_6$ also possess enkephalinase inhibition activity and are useful as analgesic agents. Thus, by the administration of a composition containing one or a combination of such compounds of formula I or a pharmaceutically acceptable salt thereof, pain is alleviated in the mammalian host. A single dose, or preferably two to four divided daily doses, provided on a basis of about 0.1 to about 100 mg. per kilogram of body weight per day, preferably about 1 to about 50 mg. per kilogram per day, produces the desired analgesic activity. The composition is

preferably administered orally but parenteral routes such as subcutaneous can also be employed.

The following examples are illustrative of the invention. Temperatures are given in degrees centigrade.

Example 1

(2R,5S)-1-[5-(Benzoylamino)-4-hydroxy-2-methyl-1-oxo 6-phenylhexyl]-L-proline

a) *1-Bromo-2-methyl-3-butene*

Methanesulfonyl chloride (15 ml., 1.1 eq.) is added dropwise over 15 minutes to a solution of 2-methyl-3-buten-1-ol (15.0 g., 0.174 mole) and diisopropylethylamine (45.5 ml., 1.5 eq.) in dry dichloromethane at −10° under argon. After stirring for one hour at −10° to 0°, the resulting mixture is washed with water, 1N hydrochloric acid (twice), 1N sodium bicarbonate, and brine. After drying over $MgSO_4$, the solvent is removed at reduced pressure to give the mesylate as a yellow oil. TLC (silica gel, ether) $R_f = 0.54$.

A mixture of this crude mesylate (approximately 0.174 mole) and lithium bromide (30.22 g., 2 eq.) in dry dimethylformamide (80 ml.) under argon is heated at 100° for 1.5 hours. After cooling, the mixture is diluted with water (100 ml.) and extracted with pentane (2 × 150 ml.). The pentane extracts are combined and washed with water, 1N sodium bicarbonate, and brine. After drying over anhydrous $MgSO_4$, the solvent is removed by distillation at atmospheric pressure. Distillation of the residue gives 16.49 g. of 1-bromo-2-methyl-3-butene as a colorless liquid; b.p. 111° – 115°.

b) *N-[(1,1-Dimethylethoxy)carbonyl]-L-phenylalanine, 2-pyridyl ester*

Dicyclohexylcarbodiimide (15.5 g., 1.1 eq.) is added to a 0° solution of N-[(1,1-dimethylethoxy)-carbonyl]-L-phenylalanine (18.1 g., 68.2 mmole) and freshly sublimed 2-hydroxypyridine (7.13 g., 1.1 eq.) in dry pyridine (130 ml.) under argon. After stirring at 0° for two hours, the reaction mixture is kept at 5° for two days. It is then filtered to remove dicyclohexylurea and the pyridine is removed at reduced pressure (about 0.1 mm. of Hg) at room temperature. The residue is dissolved in ethyl acetate and refiltered to remove additional dicyclohexylurea. The filtrate is washed with ice cold water (twice), ice cold 1N sodium bicarbonate, and brine. After drying over anhydrous $MgSO_4$, the solvent is removed at reduced pressure. The residue is chased twice with cyclohexane to remove any remaining pyridine. After filtration and washing with cyclohexane, 18.95 of N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanine, 2-pyridyl ester is obtained as a colorless solid.

c) *(6S)-6-[[(1,1-Dimethylethoxy)carbonyl]amino]-3-methyl-5-oxo-7-phenyl-1-heptene*

A mixture of 1-bromo-2-methyl-3-butene (3.8 g., 25.7 mmole) and magnesium turnings (0.94 g., 38.6 mmole) in anhydrous tetrahydrofuran (30 ml.) under argon is irradiated at room temperature with an ultrasonic cleaner for two hours to give the corresponding Grignard reagent.

This Grignard reagent is added dropwise over 15 minutes to a −5° solution of N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanine, 2-pyridyl ester (4.0 g., 11.7 mmole) in anhydrous tetrahydrofuran (25 ml.) under argon. The resulting mixture is stirred at −5° to 0° for 2.5 hours and then quenched with 10% ammonium chloride. The mixture is extracted with ether and the ether extract is washed successively with water, 1N hydrochloric acid (twice), 1N sodium bicarbonate, and brine. After drying over anhydrous $MgSO_4$, the solvent is removed at reduced pressure to give a pale yellow oil. This material is combined with that obtained from an identical experiment and flash chromatographed on silica gel LPS-1 eluting with hexane:acetone (96:4) to give 3.13 g. (42%) of (6S)-6-[[(1,1-dimethylethoxy)carbonyl]amino]-3-methyl-5-oxo-7-phenyl-1-heptene as a colorless solid. TLC (silica gel; hexane:acetone 4:1) $R_f = 0.36$.

d) *(6S)-6-Benzoylamino-3-methyl-5-oxo-7-phenyl-1-heptene*

A solution of (6S)-6-[[(1,1-dimethylethoxy)-carbonyl]amino]-3-methyl-5-oxo-7-phenyl-1-heptene (3.13 g., 9.86 mmole) in trifluoroacetic acid (50 ml.) is stirred for 30 minutes at 0° and then at room temperature for two hours. The trifluoroacetic acid is removed at reduced pressure and chased twice with toluene to give an amber oil. This material is then dissloved in anhydrous tetrahydrofuran (60 ml.) and the resulting solution is treated with sodium bicarbonate (6.0 g., 7.14 mmole) and benzoyl chloride (4.0 ml., 34.5 mmole). After stirring for 24 hours, the mixture is diluted with ethyl acetate and the resulting solution is washed with water, 1N hydrochloric acid (twice), 1N sodium bicarbonate, and brine. After drying over anhydrous $MgSO_4$, the solvent is removed at reduced pressure to give a pale yellow solid. Recrystallization from hexane/ethyl acetate gives 1.56 g. of (6S)-6-benzoylamino-3-methyl-5-oxo-7-phenyl-1-heptene as a colorless solid. TLC (silica gel; hexane:ethyl acetate) $R_f = 0.39$.

e) *(5S)-Benzoylamino-2-methyl-4-oxo-6-phenylhexanoic acid*

A solution of (6S)-6-benzoylamino-3-methyl-5-oxo-7-phenyl-1-heptene (970 mg., 3.02 mmole) in methanol:dichloromethane (50 ml., 1:1) at −78° is treated with an ozone/oxygen stream until a blue color persists. The mixture is stirred for an additional 30 minutes and then the excess ozone is removed with a nitrogen stream. Dimethyl sulfide (4 ml.) is added and the mixture is warmed to room temperature. After 5 hours, the solvent is removed at reduced pressure and chased three times with acetone and the residue is then dissolved in acetone (35 ml.). After cooling to 0°, the solution is treated dropwise with 10 ml. of Jones reagent (chromic anhydride in dilute sulfuric acid). After stirring for 15 minutes, the mixture is warmed to room temperature. After stirring for 30 minutes, the mixture is recooled to 0° and quenched with excess

isopropyl alcohol. After dilution with ethyl acetate, the resulting solution is washed with water (three times) and brine. After drying over anhydrous $MgSO_4$, the solvent is removed at reduced pressure to give crude product as a nearly colorless solid. This material is partitioned between ether and 1N sodium bicarbonate. The aqueous fraction is washed with ether and the ether fractions are discarded. The aqueous fraction is acidified with 10% hydrochloric acid and extracted with ethyl acetate (2 × 200 ml.). The extracts are combined and washed with water and brine. After drying over anhydrous $MgSO_4$, the solvent is removed at reduced pressure to give 0.9 g. of (5S)-benzoylamino-2-methyl-4-oxo-6-phenylhexanoic acid as a colorless solid. TLC (silica gel; ethyl acetate: pyridine:acetic acid:water, 350:20:6:11) $R_f = 0.51$.

f) *(2R,5S)-1-[5-(Benzoylamino)-2-methyl-1,4-dioxo-6-phenylhexyl]-L-proline, phenylmethyl ester*

Disisopropylethylamine (0.53 ml., 1.05 eq.) is added to a 0° solution of (5S)-benzoylamino-2-methyl-4-oxo-6-phenylhexanoic acid (0.98 g., 2.88 mmole), L-proline, phenylmethyl ester, hydrochloride salt (0.767 g., 1.1 eq.), 1-hydroxybenzotriazole hydrate (398 mg., 1.02 eq.) in anhydrous tetrahydrofuran under argon. To the resulting mixture is added a solution of dicyclohexylcarbodiimide (0.60 g., 1.0 eq.) in tetrahydrofuran (3 ml.). After stirring at 0° for one hour, the mixture is warmed to room temperature and stirred for 22 hours. The resulting mixture is filtered to remove dicyclohexylurea and the filtrate is diluted with ethyl acetate and washed with water, 1N hydrochloric acid (twice), 1N sodium bicarbonate, and brine. After drying over anhydrous $MgSO_4$, the solvent is removed at reduced pressure to give a yellow oil. This material is combined with some crude material from a smaller run and flash chromatographed on silica gel LPS-1 eluting with cyclohexane:acetone (3:1) to give 1.62 g. of (2R,2S), (5S)-1-[5-(benzoylamino)-2-methyl-1,4-dioxo-6-phenylhexyl]-L-proline, phenylmethyl ester, a mixture of diastereomers, as a pale yellow oil. TLC (silica gel; cyclohexane:acetone 3:1) $R_f = 0.18$.

This diastereomeric mixture of esters is divided into equal portions and each portion is flash chromatographed (silica gel LPS-1; eluting with benzene:acetone 4:1) on the same column. The fractions containing the desired diastereomer are combined and the mixed fractions are rechromatographed on the same column used for the above separations. Combination of the fractions containing the desired diastereomer and removal of the solvent at reduced pressure gives 0.60 g. of (2R,5S)-1-[5-(benzoylamino)-2-methyl-1,4-dioxo-6-phenylhexyl]-L-proline, phenylmethyl ester as a colorless oil. TLC (silica gel; benzene:acetone 4:1) $R_f = 0.33$.

g) *(2R,5S)-1-[5-(Benzoylamino)-2-methyl-1,4-dioxo-6-phenylhexyl]-L-proline*

A mixture of the ester product from part (f) (0.57 g., 1.08 mmole) and 10% palladium on carbon catalyst (106 mg.) in ethyl acetate (35 ml.) is stirred under hydrogen (balloon) for 6 hours. The resulting mixture is millipore filtered and the filtrate is concentrated at reduced pressure. After drying *in vacuo*, 430 mg. of (2R,5S)-1-[5-(benzoylamino)-2-methyl-1,4-dioxo-6-phenylhexyl]-L-proline is obtained as a glassy solid; $[\alpha]_D^{20} = -95.7°$ (c = 1.14, 95% ethanol). TLC (silica gel; ethyl acetate:pyridine:acetic acid:water, 180:20:6:11) $R_f = 0.27$.

Anal. calc'd. for $C_{25}H_{28}N_2O_5$ 0.25 $CH_3COOC_2H_5$:

C, 68.10; H, 6.64; N, 6.11

Found: C, 68.08; H, 6.62; N, 5.95.

h) *(2R,5S)-1-[5-(Benzoylamino)-4-hydroxy-2-methyl-1-oxo-6-phenylhexyl]-L-proline*

Sodium borohydride (50 mg., 5.2 eq.) is added to a solution of (2R,5S)-1-[5-(benzoylamino)-2-methyl-1,4-dioxo-6-phenylhexyl]-L-proline (110 mg., 0.252 mmole) in tetrahydrofuran (4 ml.) and water (1 ml.) at 0°. After stirring at 0° for 15 minutes, the mixture is warmed to room temperature. After 2.5 hours, the mixture is quenched with 1N hydrochloric acid and extracted with ethyl acetate. The ethyl acetate fraction is washed with water, 1N hydrochloric acid (twice), water, and brine. After drying over anhydrous $MgSO_4$, the solvent is moved at reduced pressure to give 94 mg. of (2R,5S)-1-[5-(benzoylamino)-4-hydroxy-2-methyl-1-oxo-6-phenylhexyl]-L-proline as a colorless solid; m.p. 146-152°; $[\alpha]_D^{20} = -89.5°$. TLC (silica gel; ethyl acetate;pyridine:acetic acid:water, 100:20:6:11) $R_f = 0.27$.

Anal. calc'd. for $C_{25}H_{30}N_2O_5$:

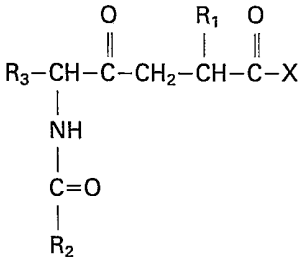
C, 68.47; H, 6.89; N, 6.39

Found: C, 68.15; H, 6.99; N, 6.14.

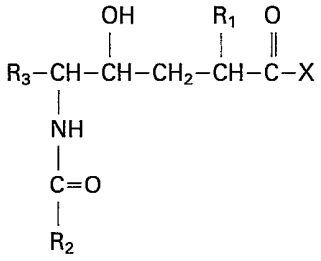
Examples 2 – 27

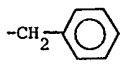
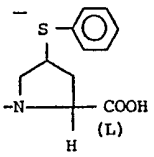
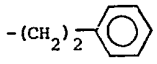
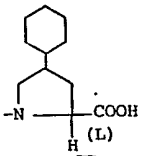
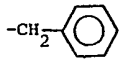
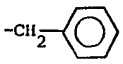
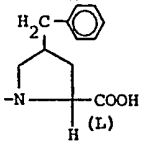
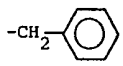
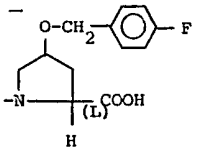
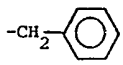
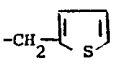
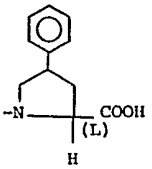
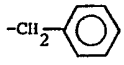
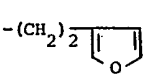
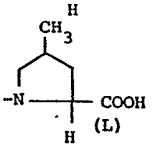
Following the procedure of Example 1 the diketo compound shown in Col. I is treated with a reducing agent, preferably sodium borohydride, to give the hydroxy product shown in Col.II.

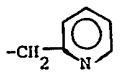
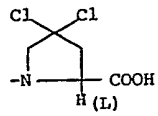
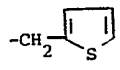
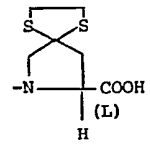
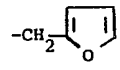
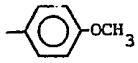
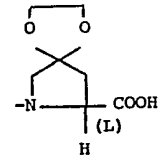
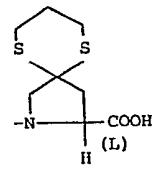
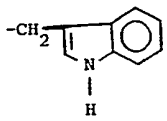
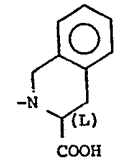
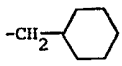
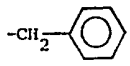
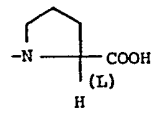
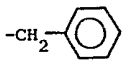
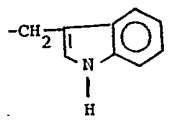
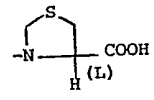
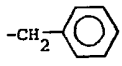
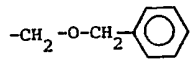
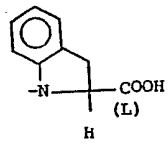
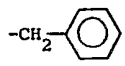
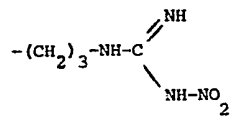
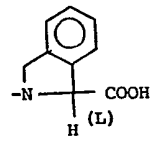
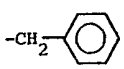
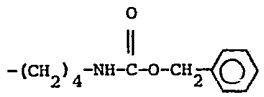
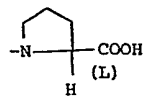
Col. I

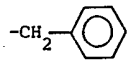
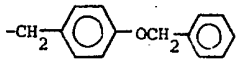
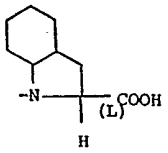
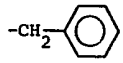
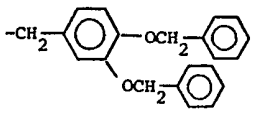
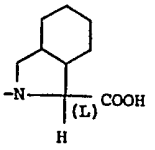
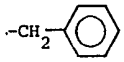
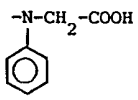
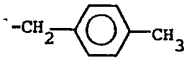
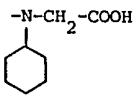
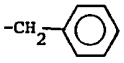
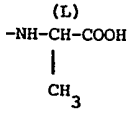
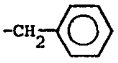
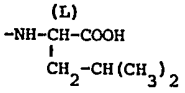
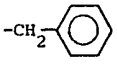
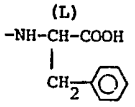
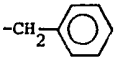
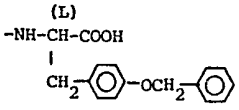
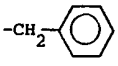
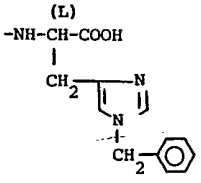
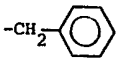
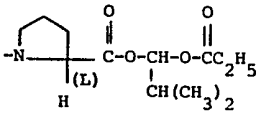


Col. II



Example	R_3	R_2	R_1	X
2			$-CH_3$	
3			$-CH_3$	
4			$-CH_3$	
5			$-CH_3$	
6			$-CH_3$	
7			$-C_2H_5$	

Example	R_3	R_2	R_1	X
8			$-CH_3$	
9			$-CH_3$	
10			$-C_3H_7$	
11	$-C_2H_5$		$-CF_3$	
12			$-CH_3$	
13				
14				
15				
16				
17				

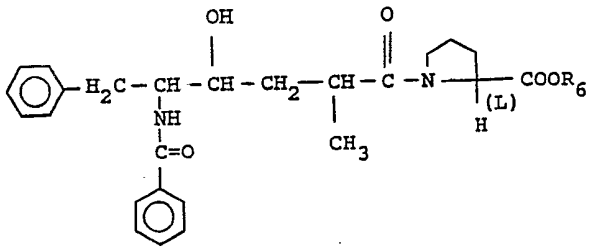
Example	R_3	R_2	R_1	X
18				
19				
20			$-CH_3$	
21			$-CH_3$	
22			$-CH_3$	
23			$-CH_3$	
24			$-CH_3$	
25			$-CH_3$	
26			$-CH_3$	
27			$-CH_3$	

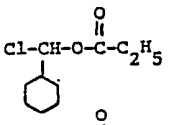
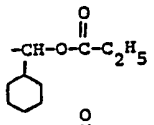
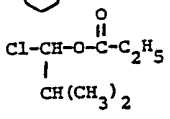
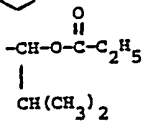
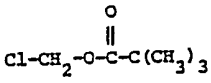
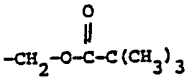
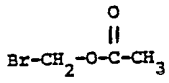
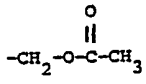
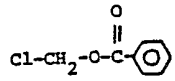
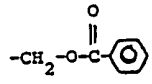
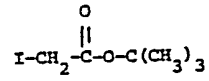
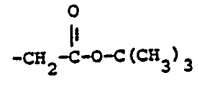
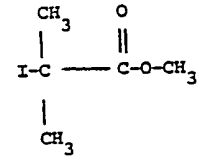
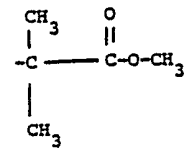
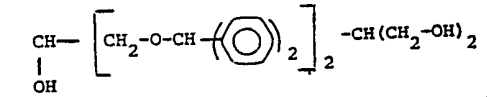
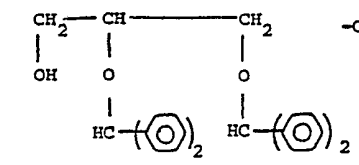
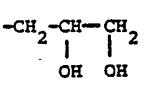
The R_1 protecting groups in Examples 16 to 19 and the R_5 protecting groups in Examples 25 and 26 are removed as the last step in the synthesis.

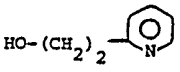
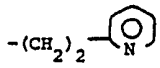
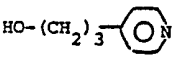
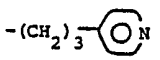
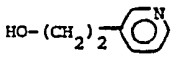
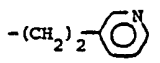
Examples 28 – 40

(2R,5S)-1-[5-(Benzoylamino)-4-hydroxy-2-methyl-1-oxo-6-phenylhexyl]-L-proline is treated with the reagent listed below in Col. I to give the product shown in Col. II

Col. II



Example	Col. I	R_6
28		
29		
30		
31		
32		
33		
34		
35		
36		

Example	Col. I	R_6
37	$HO-CH_2-CH_2-N(CH_3)_2$	$-CH_2-CH_2-N(CH_3)_2$
38		
39		
40		

In the case of Examples 35 to 40, the reaction with the reagent listed in Col. I is performed in the presence of a coupling agent such as dicyclohexylcarbodiimide.

Example 41

1000 tablets each containing the following ingredients

(2R,5S)-1-[5-(Benzoylamino)-4-hydroxy-2-methyl-1-oxo-6-phenylhexyl]-L-proline	100 mg.
Cornstarch	50 mg.
Gelatin	7.5 mg.
Avicel (microcrystalline cellulose)	25 mg.
Magnesium stearate	2.5 mg.
	185 mg.

are prepared from sufficient bulk quantities by mixing the (2R,5S)-1-[5-(benzoylamino)-4-hydroxy-2-methyl-1-oxo-6-phenylhexyl]-L-proline, and cornstarch with an aqueous solution of the gelatin. The mixture is dried and ground to a fine powder. The Avicel and then the magnesium stearate are admixed with granulation. This mixture is then compressed in a tablet press to form 1000 tablets each containing 100 mg. of active ingredient.

In a similar manner, tablets containing 100 mg. of the product of any of Examples 2 to 40 can be prepared. A similar procedure can be employed to form tablets containing 50 mg. of active ingredient.

Example 42

Two piece #1 gelatin capsules each containing 50 mg. of (2R,5S)-1-[5-(benzoylamino)-4-hydroxy-2-methyl-1-oxo-6-phenylhexyl]-L-proline are filled with a mixture of the following ingredients:

(2R,5S)-1-[5-(benzoylamino)-4-hydroxy-2-methyl-1-oxo-6-phenylhexyl]-L-proline	50 mg.
Magnesium stearate	7 mg.
Lactose	193 mg.
	250 mg.

In a similar manner capsules containing 50 mg. of the product of any of Examples 2 to 40 can be prepared.

Example 43

An injectable solution is prepared as follows:

(2R,5S)-1-[5-(Benzoylamino)-4-hydroxy-2-methyl-1-oxo-6-phenylhexyl]-L-proline	500 g.
Methyl paraben	5 g.
Propyl paraben	1 g.
Sodium chloride	25 g.
Water for injection	5 l

The active substance, preservatives, and sodium chloride are dissolved in 3 liters of water for injection and then the volume is brought up to 5 liters. The solution is filtered through a sterile filter and aseptically filled into presterilized vials which are closed with presterilized rubber closures. Each vial contains 5 ml. of solution in a concentration of 100 mg. of active ingredient per ml. of solution for injection.

In a similar manner, an injectable solution containing 100 mg. of active ingredient per ml. of solution can be prepared for the product of any of Examples 2 to 40.

Example 44

1000 tablets each containing the following ingredients

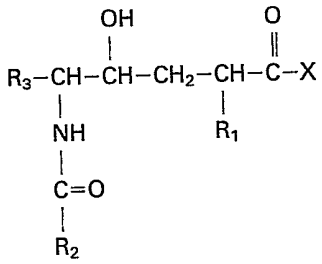
(2R, 5S)-1-[5-(Benzoylamino)-4-hydroxy-2-methyl-1-oxo-6-phenylhexyl]-L-proline	100 mg.
Avicel	100 mg.
Hydrochlorothiazide	12.5 mg.
Lactose	113 mg.
Cornstarch	17.5 mg.
Stearic Acid	7 mg.
	350 mg.

are prepared from sufficient bulk quantities by slugging the (2R,5S)-1-[5-(benzoylamino)-4-hydroxy-2-methyl-1-oxo-6-phenylhexyl]-L-proline, Avicel, and a portion of the stearic acid. The slugs are ground and passed through a #2 screen, then mixed with the hydrochlorothiazide, lactose, cornstarch, and remainder of the stearic acid. The mixture is compressed into 350 mg. capsule shaped tablets in a tablet press. The tablets are scored for dividing in half.

In a similar manner, tablets can be prepared containing 100 mg. of the product of any of Examples 2 to 40.

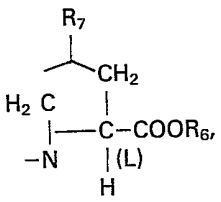
CLAIMS

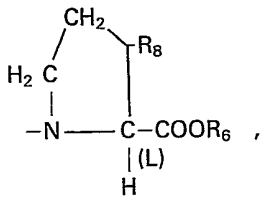
1. A compound of the formula

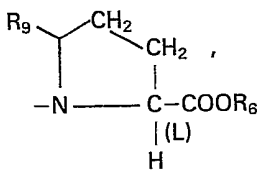


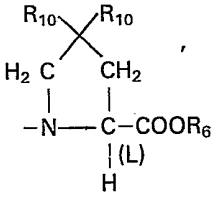
or such a compound in pharmaceutically acceptable salt form wherein:

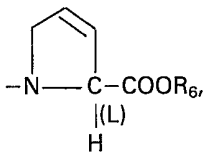
X is

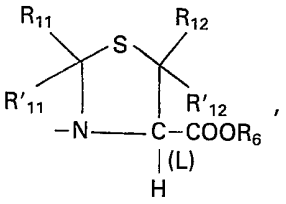


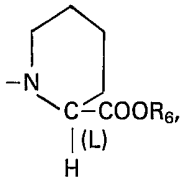


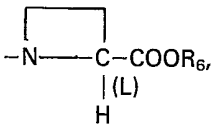


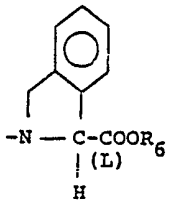


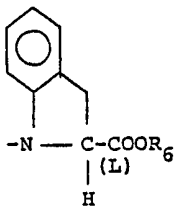


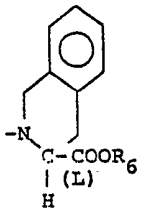


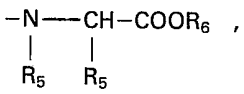


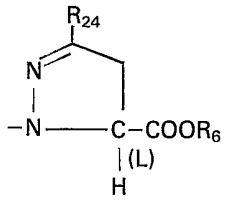


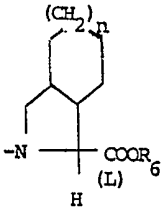


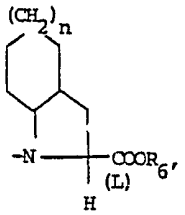


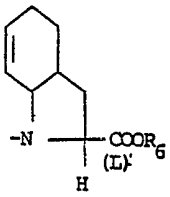


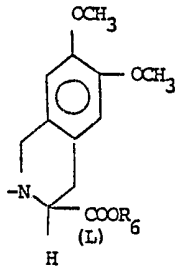


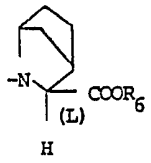


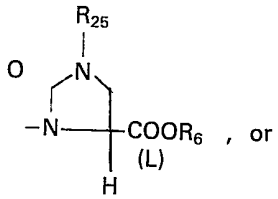


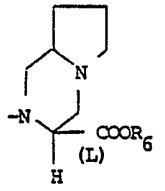








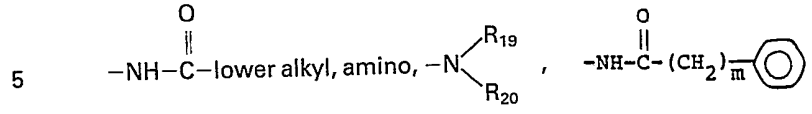


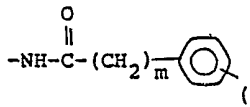


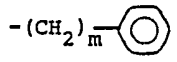
n is zero, one, or two:
R_{25} is lower alkyl of 1 to 4 carbons

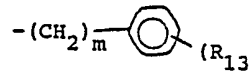
or  ;

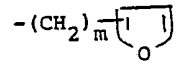
R_7 is hydrogen, lower alkyl, halogen, hydroxy,





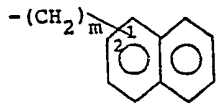
, a 1- or 2-naphthyl of the formula 

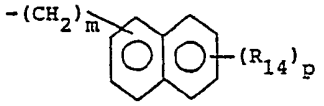


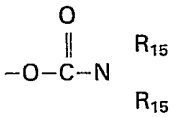
, 

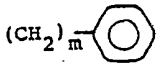
,

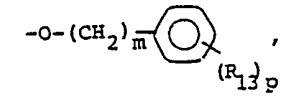
,

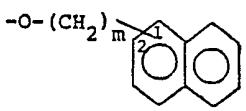
, a substituted 1- or 2-naphthyl of the formula 

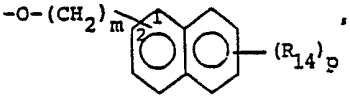
, a substituted 1- or 2-naphthyloxy of the formula 

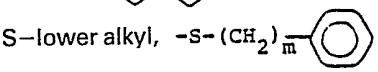
, –$(CH_2)_m$–cycloalkyl, 

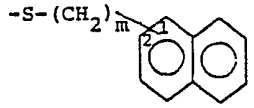
, –O–lower alkyl, 

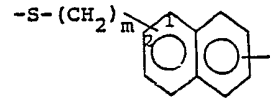
, 

, a 1- or 2-naphthyloxy of the formula 

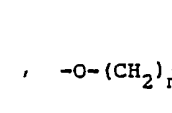
, a substituted 1- or 2-naphthyloxy of the formula 

, –S–lower alkyl, 

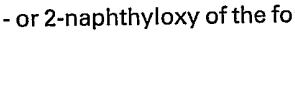
, a 1- or 2-naphthylthio of the formula 

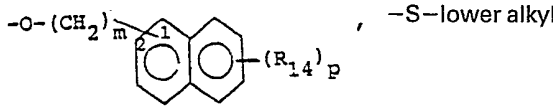
, or a substituted 1- or 2-naphthylthio of the formula 

;

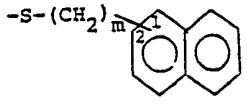
R_8 is halogen, 

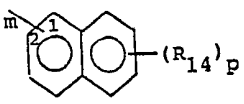
,

, –O–lower alkyl, a 1- or 2-naphthyloxy of the formula 

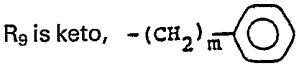
, a substituted 1- or 2-napthyloxy of the formula 

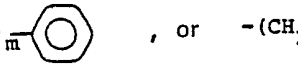
, –S–lower alkyl,

, a 1- or 2-naphthylthio of the formula 

, or a substituted 1- or 2-naphthylthio of the formula 

;

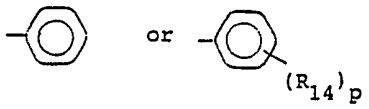
R_9 is keto, 

, or 

;

R_{10} is halogen or $-Y-R_{16}$;

R_{11}, R'_{11}, R_{12} and R'_{12} are independently selected from hydrogen and lower alkyl or R'_{11}, R_{12} and R'_{12} are hydrogen and R_{11} is



;

R_{13} 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_{14} 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 or hydroxy;

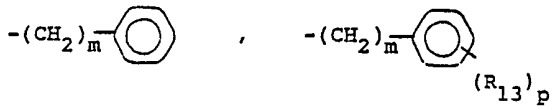
m is zero, one two, three, or four;

p is one, two or three provided that p is more than one only if R_{13} or R_{14} is methyl, methoxy, chloro, or fluoro;

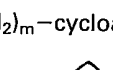
R_{15} is hydrogen or lower alkyl of 1 to 4 carbons;

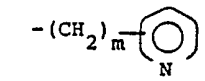
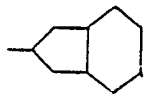
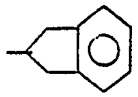
Y is oxygen or sulfur;

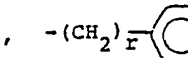
R_{16} is lower alkyl of 1 to 4 carbons,

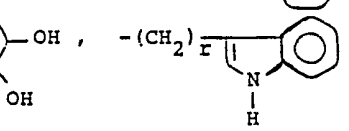
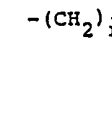


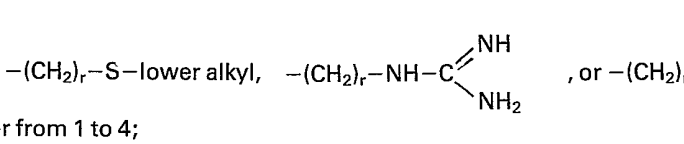
or the R_{16} groups join to complete an unsubstituted 5– or 6-membered ring or said ring in which one or more of the carbons has a lower alkyl of 1 to 4 carbons or a di(lower alkyl of 1 to 4 carbons) substituent;

R_4 is hydrogen, lower alkyl,  , $-(CH_2)_m-$cycloalkyl,  ,

,  ,  , or  ;

R_5 is hydrogen, lower alkyl,  ,  , $-(CH_2)_r-OH$,

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

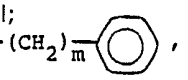


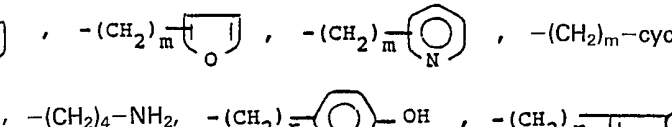
$-(CH_2)_r-SH$, $-(CH_2)_r-S-$lower alkyl, $-(CH_2)_r-NH-C(=NH)-NH_2$, or $-(CH_2)_r-C(=O)-NH_2$;

r is an integer from 1 to 4;

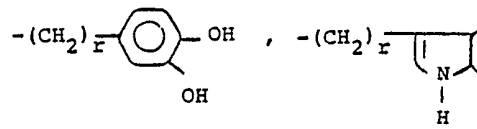
R_{19} is lower alkyl, benzyl, or phenethyl;

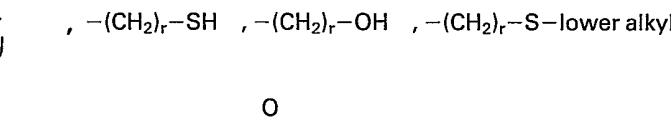
R_{20} is hydrogen, lower alkyl, benzyl or phenethyl;

R_1 is lower alkyl, halo substituted lower alkyl  ,  ,

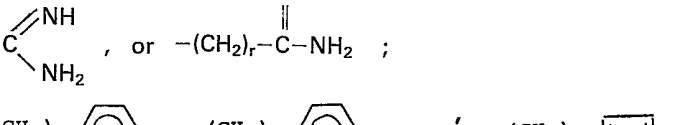


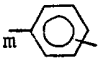
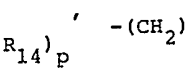
$-(CH_2)_m-$cycloalkyl, $-(CH_2)_2-NH_2$,

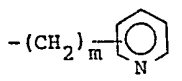
$-(CH_2)_3-NH_2$, $-(CH_2)_4-NH_2$,  ,



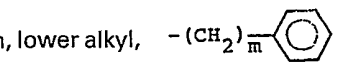
$-(CH_2)_r-SH$, $-(CH_2)_r-OH$, $-(CH_2)_r-S-$lower alkyl,

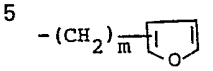


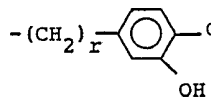
R_2 is  ,  , , , or

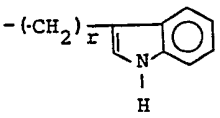


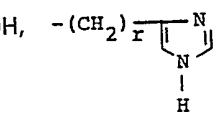
;

R_3 is hydrogen, lower alkyl, 

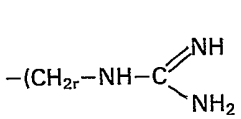


halo substituted lower alkyl, $-(CH_2)_m-$cycloalkyl, 

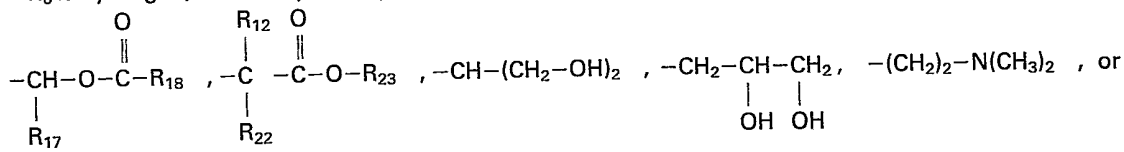


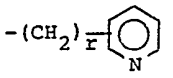
$-(CH_2)_r-OH$, 

$-(CH_2)_r-NH_2$, $-(CH_2)_r-SH$, $-(CH_{2r}-S-$lower alkyl,



R_6 is hydrogen, lower alkyl, benzyl, benzhydryl, a pharmaceutically acceptable salt forming ion,

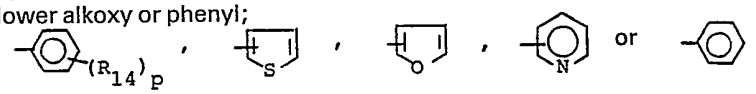




;

R_{17} is hydrogen, lower alkyl, cycloalkyl or phenyl;

R_{18} is hydrogen, lower alkyl, lower alkoxy or phenyl;

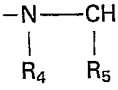
R_{24} is hydrogen, lower alkyl, 

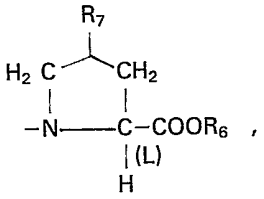
R_{21} and R_{22} are independently selected from hydrogen and lower alkyl;

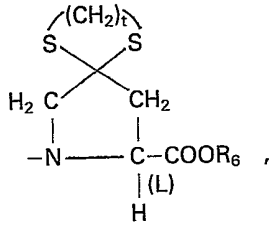
and;

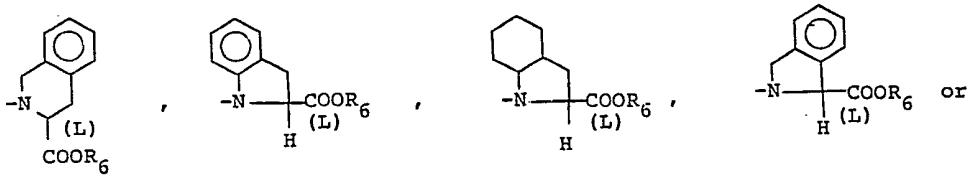
R_{23} is lower alkyl.

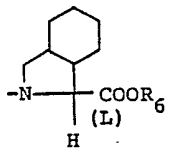
2. A compound of Claim 1 wherein:

X is 





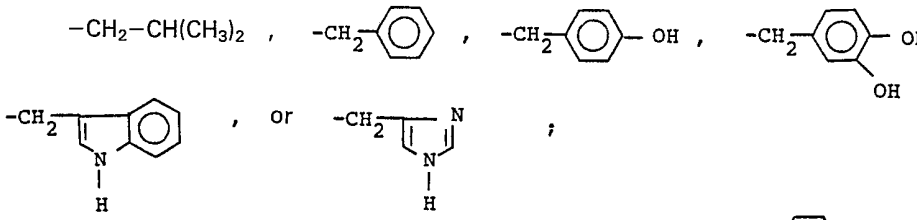




;

R_6 is hydrogen or an alkali metal ion;

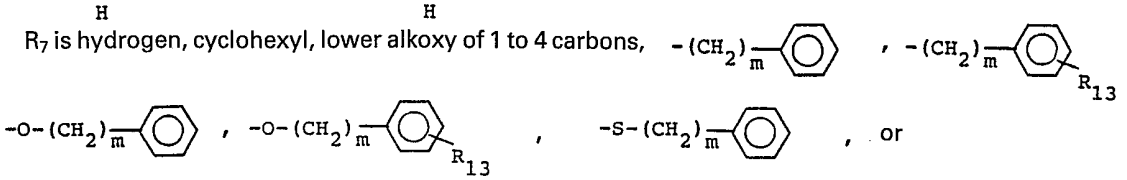
R_4 is cyclohexyl or phenyl and R_5 is hydrogen or R_4 is hydrogen and R_5 is methyl,



; or

;

R_7 is hydrogen, cyclohexyl, lower alkoxy of 1 to 4 carbons,



;

m is zero, one or two;

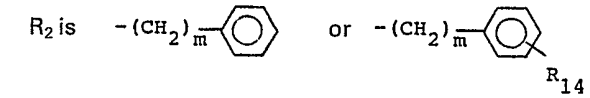
R_{13} is methyl, methoxy, methylthio, chloro, bromo, fluoro, or hydroxy; and

t is 2 or 3.

3. A compound of Claim 1 or 2 wherein

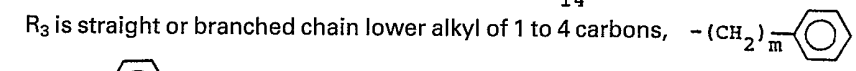
R_1 is straight or branched chain lower alkyl of 1 to 4 carbons or $-(CH_2)_r-NH_2$;

R_2 is

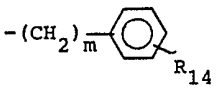


;

R_3 is straight or branched chain lower alkyl of 1 to 4 carbons,



, or



;

r is an integer from 1 to 4;

m is zero, one, or two; and

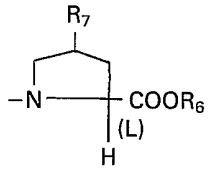
R_{14} is methyl, methoxy, methylthio, Cl, Br, F, or hydroxy.

4. A compound of Claim 1, 2 or 3 wherein:

R_1 is methyl.

5. A compound of Claim 1, 2, 3 or 4 wherein

X is



.

6. A compound of Claim 1, 2, 3, 4 or 5 wherein

R_3 is benzyl;

R_2 is phenyl; and

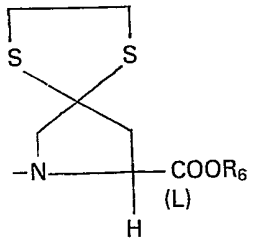
R_7 is hydrogen.

7. The compound of Claim 1, (2R,5S)-1-[5-(benzoylamino)-4-hydroxy-2-methyl-1-oxo-6-phenylhexyl]-L-proline.

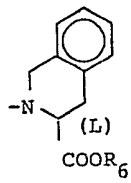
8. A compound of Claim 1, 2, 3 or 4 wherein

X is $-NH-\underset{\displaystyle R_5}{\underset{|}{CH}}-COOR_6$.

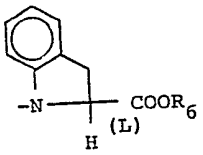
9. A compound of Claim 1, 2, 3 or 4 wherein
X is



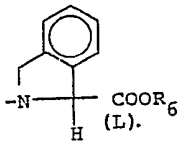
10. A compound of Claim 1, 2, 3 or 4 wherein:

X is 

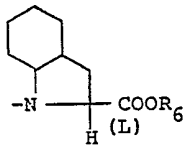
11. A compound of Claim 1, 2, 3 or 4 wherein:

X is 

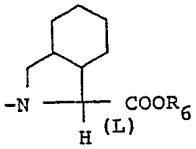
12. A compound of Claim 1, 2, 3 or 4 wherein:

X is 

13. A compound of Claim 1, 2, 3 or 4 wherein:

X is 

14. A compound of Claim 1, 2, 3 or 4 wherein

X is 

15. A pharmaceutical composition useful for treating hypertension comprising a pharmaceutically acceptable carrier and a hypotensive compound of any one of claims 1 to 14.

16. The method of treating hypertension in a mammalian host which comprises administering an effective amount of the composition of Claim 15.

17. A pharmaceutical composition useful as an analgesic comprising a pharmaceutically acceptable carrier and an enkephalinase inhibiting compound of claim 8.

18. The method of relieving pain in a mammalian host which comprises administering an effective amount of the composition of Claim 17.

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