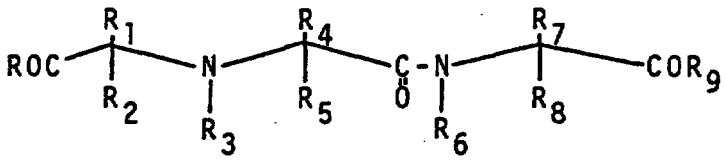
2095682

ACYL DIPEPTIDES HAVING HYPERTENSIVE AND ANGIOTENSIN CONVERTING ENZYME-INHIBITORY ACTIVITY

This invention relates to new chemical compounds having valuable pharmaceutical activity. It particularly relates to compounds possessing hypertensive and angiotensin converting enzyme inhibitory activity.

The present invention provides compounds of the formula



(I)

wherein,

R and R_9 are independently hydroxy, C_1-C_6 alkoxy, C_2-C_6 alkenoxy, di(C_1-C_6 alkyl)amino-C_1-C_6 alkoxy, hydroxy-C_1-C_6 alkoxy, acylamino-C_1-C_6 alkoxy, acyloxy-C_1-C_6 alkoxy, aryloxy, aryloxy-C_1-C_6 alkoxy, amino, C_1-C_6-alkylamino, di(C_1-C_6 alkyl)amino, hydroxy-amino, or aryl-C_1-C_6 alkylamino,

R_1, R_2, R_3, R_4, R_5, R_7 and R_8 are independently hydrogen, alkyl having from 1 to 20 carbon atoms, alkenyl having from 2 to 20 carbon atoms, alkynyl having from 2 to 20 carbon atoms, aryl-C_1-C_6 alkyl having 7 to 12 carbon atoms, heterocyclic-C_1-C_6 alkyl having from 7 to 12 carbon atoms, cycloalkyl or cycloalkylalkyl having 3 to 20 carbon atoms in the cycloalkyl group, or

R_2 and R_3 taken together with the carbon and nitrogen to which they are respectively attached, or R_3 and R_5 taken together with the nitrogen and carbon to which they are respectively attached, form an N-heterocycle containing from 3 to 5 carbon atoms or 2 to 4 carbon atoms and a sulfur atom;

R_6 is aryl having 6 to 10 carbon atoms, aryl-C_1-C_6 alkyl, aryl-C_2-C_6 alkenyl, or aryl-C_2-C_6 alkynyl; and

salts thereof with acids or bases, especially

pharmaceutically acceptable acid and base salts.

In a preferred embodiment, the invention provides compounds of formula I wherein

R and R_9 are independently hydroxy or C_1-C_6 alkoxy,

R_1 and R_2 are hydrogen or C_1-C_6 alkyl, aryl-C_1-C_6 alkyl having from 7 to 12 carbon atoms, or heterocyclic-C_1-C_6 alkyl having from 6 to 12 carbon atoms,

R_3, R_4, R_5, R_7 and R_8 are hydrogen or C_1-C_6 alkyl,

R_6 is aryl or aryl-C_1-C_6 alkyl, and the aryl group contains from 6 to 10 carbon atoms wherein the aryl groups can be substituted by C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, C_1-C_6 alkoxy, amino, C_1-C_6 alkylamino, di(C_1-C_6 alkyl)amino, thiol, C_1-C_6 alkylmercapto, hydroxy-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, thio-C_1-C_6 alkyl, nitro, halogen, trifluoromethyl, methylenedioxy, ureido and guanidino, and salts thereof especially pharmaceutically acceptable acid and base salts.

According to certain preferred embodiments of the invention:-

a) compounds wherein R_1 is C_1-C_6 alkyl or aryl-C_1-C_6 alkyl, R_4 is C_1-C_6 alkyl and R_2, R_3, R_4, R_5, R_7 and R_8 are hydrogen, and wherein preferably R and R_9 are hydroxy or R is ethoxy and R_9 is hydroxy;

b) compounds wherein R_1 and R_4 are methyl or wherein R_1 is phenethyl and R_4 is methyl, R is ethoxy, R_9 is hydroxy, and R_2, R_3, and R_5 to R_8 have the meanings given in (a) above, and

c) compounds wherein R_6 is p-tolyl,

The alkyl groups per se or when present as substituents have from 1 to 6 carbon atoms and may be straight chain or branched. These groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl, n-amyl and n-hexyl.

The alkenyl and alkynyl groups per se or when

present as substituents have from 2 to 6 carbon atoms and may be straight chain or branched. These groups include vinyl, propenyl, allyl, isopropenyl, and ethynyl.

The alkyl, alkenyl and alkynyl groups may carry substituents such as hydroxy, C_1 -C_6 alkoxy, thio, C_1 -C_6 alkylmercapto, amino, C_1 -C_6 alkylamino, di(C_1-C_6 alkyl)amino, halogen and nitro.

The aryl-C_1-C_6 alkyl and heterocyclic-C_1-C_6 alkyl groups include benzyl, phenethyl, naphthylmethyl, indolylethyl, indanylmethyl, and indanylethyl.

The cycloalkyl groups contain from 3 to 20 carbons and may be mono or polycyclic. These groups include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, bornyl, and nor-bonyl. These groups may be partially unsaturated and carry substituents such as halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino C_1 -C_6 alkylamino, di(C_1 -C_6 alkyl)amino, thiol, C_1 -C_6 alkylmercapto, nitro, and trifluoromethyl.

The aryl groups preferably contain from 6 to 10 carbon atoms and include such groups as phenyl and α- or β-naphthyl and fused phenyl-cycloalkyl.

The aryl and aralkyl groups may carry one or more substituents such as C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, C_1-C_6 alkoxy, amino, C_1-C_6 alkylamino, di(C_1-C_6 alkyl)amino, thiol, C_1-C_6 alkylmercapto, hydroxy-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, thio-C_1-C_6 alkyl, nitro, halogen, trifluoromethyl, methylene-dioxy, ureido, or guanidino.

The acyl groups are preferably alkanoyl containing from 1 to 6 carbon atoms and benzoyl.

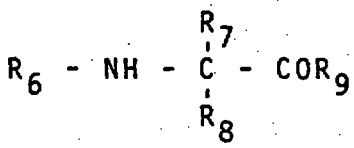
The halogen group may be fluorine, chlorine, bromine and iodine.

Suitable acid addition salts may be formed from inorganic acids such as hydrochloric, sulfuric and phosphoric, and organic acids such as acetic, lactic, citric, malic, maleic, fumaric, succinic, benzoic, hydroxybenzoic, aminobenzoic, nicotinic, and toluene sulfonic.

Suitable basic salts may include the salts of alkali and alkali earth metals such as sodium, lithium, potassium, magnesium and calcium, as well as iron and salts of ammonia and amines, and quaternary ammonium salts.

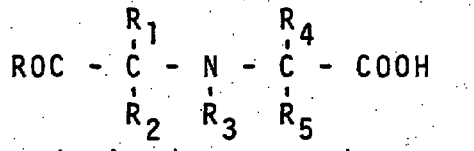
The compounds of the present invention may contain one (1) or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these forms are contemplated to be within the scope of the present invention.

The compounds of the present invention are prepared by amide-forming reaction of a compound of the formula:



(II)

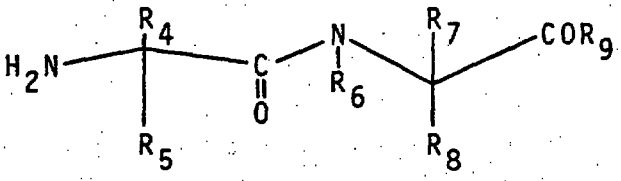
with an acylating derivative of an acid of the formula



(III)

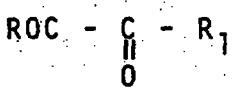
to give the desired compound.

As an alternative approach, a dipeptide of the structure



(IV)

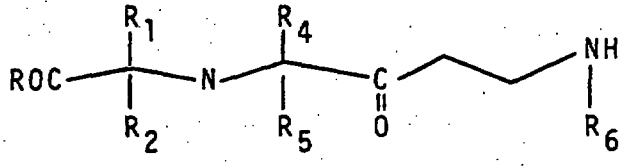
is reacted with an ∝-keto-acid or ester of the structure



(V)

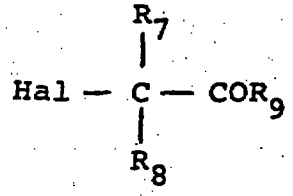
to form the corresponding imine and the imine is reduced to give a compound of formula I in which R_2 and R_3 are each H.

As a further variation, the present new compounds can be prepared by reaction of a compound of the formula:



(VI)

with an α-halo compound of the formula



VII

by cleavage of hydrogen halide.

The aforementioned condensation reaction to form imines with subsequent hydrogenation can be conveniently carried out in a single reaction zone by the expediency of mixing the α-keto acid or derivative with the reactive compound of formula IV under hydrogenation conditions. For practical purposes, the aforesaid reactants can be hydrogenated over noble metal catalyst such as palladium, platinum, rhodium, and ruthenium, and the two stage occurs under such conditions to produce the desired end-product.

As in any organic reaction, solvents can be employed such as methanol, ethanol, n-propanol, acetone, tetrahydrofuran, dioxane, dimethylformamide, and diethyl acetamide. The reaction is normally effected at or near room temperature, although temperatures from 0°C up to the reflux temperature of the reaction mixture can be employed.

In the above sequence of reactions, R - R_9 are the same as described above and Hal is halogen.

Preferably, R and R_9 are hydrogen or C_1-C_6 alkyl, R_2, R_5, R_7 and R_8 are hydrogen, R_1 and R_4 are C_1-C_6 alkyl, R_3 is hydrogen, and R_6 is aryl, and aralkyl.

The amide forming conditions referred to herein involve the use of known derivatives of the described acids, such as the acyl halides, anhydrides, mixed anhydrides, lower alkyl esters, carbodiimides, and carbonyl diimidazoles. The reactions are carried out in organic solvents such as acetonitrile, tetrahydrofuran, dioxane, acetic acid, methylene chloride and ethylene chloride.

The amide forming reaction will occur at room temperature or at elevated temperature. The use of elevated temperature is for convenience in that it permits somewhat shortened reaction periods. Temperatures ranging from 0°C. up to the reflux temperature of the reaction system can be used. As a further convenience the amide forming reaction can be effected in the presence of a base such as tertiary organic amines, e.g., trimethylamine, pyridine, and picolines particularly where hydrogen halide is formed by the amide-forming reaction, e.g., acyl halide and amino compound. Of course, in those reactions where hydrogen halide is produced, any of the commonly used hydrogen halide acceptors can also be used.

In the condensation of an alpha haloacid derivative of formula VIII herein, similar reaction conditions, solvents and hydrogen halide acceptors can be used as for amide formation.

Various substituents on the present new compounds, e.g., as defined for R_8, can be present in the starting compounds or added after formation of the amide products by the known methods of substitution or conversion reactions. Thus, the nitro group can be added to the final product by nitration of the aromatic ring and the nitro group converted to other groups, such as amino by reduction, and halo by

diazotization of the amino group and replacement of the diazo group. Other reactions can be effected on the formed amide product. Amino groups can be alkylated to form mono and dialkylamino groups, mercapto and hydroxy groups can be alkylated to form corresponding ethers. Thus, substitution or alteration reactions can be employed to provide a variety of substituents throughout the molecule of the final products. Of course, reactive groups where present should be protected by suitable blocking groups during any of the aforesaid reactions particularly the condensation reactions to form the amide linkages.

The acid and base salts of the present new compounds can be formed using standard procedures. Often, they are formed in situ during the preparation of the present new amido amino acids.

The present compounds obviously exist in stereoisomeric forms and the products obtained thus can be mixtures of the isomers, which can be resolved. Alternatively, by selection of specific isomers as starting compounds, the preferred stereoisomer can be produced. Therefore, the preferred forms, where each asymmetric center (chairal center) is S-configuration, are preferably prepared by the stereospecific route rather than attempting resolution of mixtures of isomers. The compounds in which the S-configuration exists at all asymmetric centers are the most active; those in which the R-configuration exists are of less activity; and those where both R- and S-configurations exist are of intermediate activity.

The invention is further illustrated by the following examples, in which all temperatures are expressed in degrees Centigrade, "ether" is diethyl ether, percentages are by weight (unless otherwise indicated), and "hexane" is n-hexane, CELITE and DOWEX are Registered Trade Marks,

EXAMPLE 1

A. N'-(Carbobenzyloxy)-L-Alanyl-N-(p-Tolyl)-Glycine t-Butyl Ester

p-Tolyl-glycine t-butyl ester (20 g, 0.0954 mol) was taken up in a 3-necked round bottom flask (IL) equipped with a dropping funnel, condenser (drying tube), thermometer and a stirring bar. The ester was dissolved in 250 ml methylene chloride, and to this was added a solution of N, N-dicyclohexylcarbodiimide (27 g, 0.1311 mol) in methylene chloride (100 ml). The temperature of the reaction mixture was brought to 0°C (ice bath). Carbobenzyloxy-L-alanine (33.5 g, 0.15 mol) in methylene chloride was added dropwise (1.5 h). On completion of the addition the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was again cooled down to 0°C to completely precipitate the DCC urea, filtered and the filtrate was concentratred on rotary evaporator to give a crude yellow thick liquid. The crude product was dissolved in diethyl ether (anhydrous, 400 ml) and extracted 3x with IN HCl and 3x with sodium bicarbonate (saturated). The ether solution was dried on magnesium sulfate (anhydrous) and the ether was evaporated to give a very thick yellow liquid.

B. N'-(Carbobenzyloxy)-L-Alanyl-N-(p-Tolyl)-Glycine

To a solution of 9.5 g N'-(carbobenzyloxy)-L-alanyl-N-(p-tolyl)-glycine t-butyl ester in methylene chloride (16 ml) was added dropwise 10 ml of TFA at 0°C. On completion of TFA addition the temperature of the reaction mixture was allowed to come up to room temperature and the mixture was stirred for 54h. At the end of the reaction methylene chloride was evaporated in vacuo and the residue was dissolved in carbon tetrachloride (100 ml). This solution

was washed 3x with distilled water (50 ml portions) and carbon tetrachloride was evaporated. The resulting residue was dissolved in diethyl ether (150 ml) and extracted 3x with sodium bicarbonate (saturated). The combined sodium bicarbonate layers were acidified with 10% hydrochloric acid to pH 4-5 and extracted with diethyl ether. Ether was evaporated in vacuo to give the pure acid. TLC (methanol-ethyl acetate, 2:3) gave one spot. NMR spectrum was consistent with the assigned structure.

C. L-Alanyl-N-(p-Tolyl)-Glycine Hydrobromide

N'-(Carbobenzyloxy)-alanyl-N-(p-tolyl)-glycine (1.7 g, 0.0046 mol) was dissolved in acetic acid (glacial, 5 ml) and the solution was cooled to 0°C (ice bath). To this solution was added a saturated solution of hydrogen bromide in acetic acid (glacial, 4.6 ml). The reaction mixture was allowed to warm to room temperature and stirred for an additional half hour. The reaction mixture was diluted with 150 ml of ether to give a semi-solid hydromide salt. The salt was dissolved in distilled water (100 ml) and was washed 3x with 50 ml portions of ether. The water soluble salt gave a single spot on TLC (methanol) and also n-butanol-acetic acid-water. The solid salt was obtained after evaporating the water on a freeze drier. The hydrobromide was hygroscopic, mp 83-87°C.

D. N'-(1-Carboethoxyethyl)-L-Alanyl-N-(p-Tolyl)-Glycine T-Butyl Ester

In a dry hydrogenation bottle N'-(carbobenzyloxy)-L-alanyl-N-(p-tolyl)glycine t-butyl ester (25 g, 0.0590 mol) was dissolved in ethanol (absolute, 60 ml). To this were added acetic acid (glacial, 30 ml), ethyl pyruvate (13 g, 0.1126 mol) and 10% palladium/charcoal (4.5 g). An overnight

hydrogenation of this mixture used 12 psi (0.183 MPa). The reaction mixture was worked up by adding 5 g of Celite and filtering the palladium/charcoal. Ethanol and acetic acid were removed in vacuo. The crude product examined on TLC (ethyl acetate) was found to contain two diastereomers of the required product. The diastereomers can be separated by HPLC (hexane-ethyl acetate). A mixture of diastereomers of the separated isomers were characterized by NMR and mass spectroscopy.

E. N'-(1-Carboethoxyethyl)-L-Alanyl-N-(p-Tolyl)-Glycine and Its Calcium Salt

To a solution of N'-(1-carboethoxyethyl)-L-alanyl-N-(p-tolyl)-glycine t-butyl ester (2.6 g, 0.0066 mol) in methylene chloride (26 ml) was added dropwise trifluoroacetic acid (14.4 ml, 0.19 mol) at 0°C (ice bath). The temperature was allowed to go to room temperature and the reaction mixture was stirred for 72 h. At the end of the reaction methylene chloride and trifluoroacetic acid were evaporated in vacuo. The crude product thus obtained was purified by chromatography on IR-120 resin. The resin was washed with water and acidified with 6NCl. The compound was dissolved in 2 ml of distilled water and loaded onto the column. The column was washed with water and eluted with 5% ammonia to give 0.65 g of the desired compound. 0.57 g of the free acid was dissolved in water (25 ml) and reacted with calcium oxide (47.6 mg. 0.0009 mol). Any unreacted calcium oxide was removed by filtration and the resulting solution was freeze dried to give 0.61 g of the calcium salt, mp 165-170°C.

EXAMPLE 2

A. Ethyl N-Carbobenzyloxy-L-Alanyl-N-Benzyl-Glycinate

To a solution of ethyl N-benzyl-glycinate (47.5 g, 0.268 mol) and N-carbobenzyloxy-L-alanine (60.0 g, 0.268 mol) in 600 ml of methylene chloride at 0°C was added dropwise a solution of N, N'-dicyclohexylcarbodiimide (55.2 g, 0.268 mol) in 600 ml methylene chloride over a 1 hour period. After the addition was complete the solution was stirred for 10 min., warmed to room temperature and continued stirring overnight. The solution was filtered, washed with dilute aqueous HCl, H_2O, saturated $NaHCO_3$, brine, dried ($MgSO_4$). Concentration of the solution in vacuo yielded the oily product.

B. N-Carbobenzyloxy-L-Alanyl-N-Benzyl-Glycine

To ethyl N-carbobenzyloxy-L-alanyl-N-benzyl glycinate (11.2 g, 28.1 mmol) in 60 ml ethanol was added sodium hydroxide (2.2 g, 55.0 mmol). The mixture was stirred at room temperature for 18 hours. The solution was concentrated in vacuo and the remaining residue dissolved in water. The aqueous solution was washed with ether twice, cooled in an ice bath and acidified with concentrated HCl. The acidic solution was extracted thoroughly with ether. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to provide the carboxylic acid.

C. L-Alanyl-N-Benzyl-Glycine

A solution of N-carbobenzyloxy-L-alanyl-N-benzyl glycine (6.0 g) and 10% palladium on carbon (2.0 g) in 200 ml ethanol was hydrogenated at 50 psi (0.445 MPa) for 4 hours and filtered. Concentration of the volatiles in vacuo provided a residue which was dissolved in H_2O and filtered. The aqueous solution was acidified with 25% aqueous HBr until pH 1 was

obtained. The solution was lyophilized. The crystalline product was recrystallized from ether-acetonitrile (m.p. 84-85°C).

D. N-(1-Carboxyethyl)-L-Alanyl-N-Benzyl-Glycine Pyruvate

To a solution of N-carbobenzyloxy-L-alanyl-N-benzyl glycine (5.8 g, 15.6 mmol) and pyruvic acid (3.5 g, 39.1 mmol) in 200 ml absolute ethanol was added 10% palladium on carbon (0.5 g). The mixture was hydrogenated at 50 psi (0.445 MPa) for 4 hours. The solution was filtered and concentrated in vacuo at room temperature. The residue was dissolved in H_2O and ethyl acetate. The aqueous layer was washed twice with ethyl acetate and once with ether and lyophilized to provide the crystalline product, m.p. 105-108°C.

EXAMPLE 3

A. N'-(Carbobenzyloxy)-L-isoleucyl-N-(p-Tolyl)-Glycine t-Butyl-Ester

The reaction was carried out in a similar manner as described in example 1A. p-Tolyl-glycine t-butyl ester (8.67 g, 0.0396 mol) was dissolved in methylene chloride (45 ml), mixed with a solution of N, N-dicyclohexylcarbodiimide (9.15 g, 0.0396 mol) in methylene chloride (30 ml) and reacted with a solution of carbobenzyloxy-L-isoleucine (10 g, 0.0377 mol) in methylene chloride (60 ml).

B. N'-(Carbobenzyloxy)-L-Isoleucyl-N-(p-Tolyl) Glycine

N'-CBZ-L-isoleucyl-N-(p-tolyl)-glycine t-butyl ester (8 g) was dissolved in methylene chloride (13.5 ml) and reacted with TFA (8 ml) at 0°C. The reaction mixture was stirred at room temperature for 72 hours and worked up similarly as in example 3B. The pure acid isolated was a single spot on TLC (methanol-ethyl acetate, 2:3) and had the expected NMR spectrum.

C. L-Isoleucyl-N-(p-Tolyl) Glycine

N'-CBZ-L-isoleucyl-N-(p-tolyl)-glycine (1 g, 0.00024 mol) was dissolved in acetic acid (glacial, 3.5 ml) and reacted with hydrogen bromide/acetic acid (2.5 ml). The reaction procedure is as described in example 2C. The product obtained after freeze drying was characterized by TLC (methanol), NMR and mass spectroscopy.

EXAMPLE 4

N-(1-Carboxyethyl)-L-valyl-N-benzyl-glycine pyruvate

To a solution of N-carbobenzoxy-L-valyl-N-benzyl glycine (17.2g, 44.6 mmol) and pyruvic acid (19.6g, 0.223 mol) in 400 ml absolute ethanol was added 10% palladium on carbon (1.5g). The mixture was hydrogenated at 50 psi (0.445 MPa) for 4 hours. Filtration and concentration *in vacuo* provided an oily product which was purified as in Example 2D.

EXAMPLE 5

N-(1-Carboxyethyl)-L-alanyl-N-(4-methylbenzyl)-glycine pyruvate

To a solution of N-carbobenzoxy-L-alanyl-N-(4-methylbenzyl)-glycine (5.8g, 15.1 mmol) and pyruvic acid (3.3g, 37.8 mmol) in 200 ml absolute ethanol was added 10% palladium on carbon (0.5g). The mixture was hydrogenated at 30 psi (0.307 MPa) for 4 hours and filtered. Concentration of the volatiles *in vacuo* provided an oil product which was purified as in Example 2D.

EXAMPLE 6

A. tert-Butyl N-(β-phenylethyl)glycinate hydrochloride

Acetonitrile (800 ml) was added to β-phenethyl amine (50 g, 0.413 mole) followed by the addition of water (100 ml) and concentrated ammonium hydroxide (75 ml). To the resulting stirring solution tert-butyl bromoacetate (82 g, 0.421 (mole) in acetonitrile (150 ml) was added dropwise at room temperature. The resulting mixture was stirred overnight at room temperature. The acetonitrile was evaporated on a rotary evaporator and then water was added to the residue and the product was extracted several times into methylene chloride. The combined methylene chloride extract was washed twice with water, dried over magnesium sulfate, filtered and evaporated to afford the crude product as a tan oil. The crude product was purified further by silica-gel chromatography (chloroform). The desired fractions were concentrated and the hydrochloride was prepared with anhydrous hydrogen chloride in ether to give tert-butyl N-(β-phenylethyl) glycinate hydrochloride as a colorless solid (62 g, 55%); m.p. 143°; mass spectra (CI): 143.8 (30.84%); 133.8 (40.93%); 104.8 (38.33%; 87.8 (100%).

B. tert-Butyl N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-(S)-alanyl-N-(β-phenylethyl) glycinate

To crude N-[1-(S)-ethoxycarbonyl-3-phenylpropyl -(S)-alanyl-N-carboxyanhydride which had been prepared from 5 grams of the corresponding (SS)-acid in methylene chloride was added tert-butyl N-(β-phenylethyl) glycinate (5g, 21.3 mmole). The resulting solution was stirred overnight at room temperature. The solvent was evaporated and the residue was chromatographed over silica-gel using chloroform as eluent. The desired fractions were combined and concentrated to give

pure tert butyl N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-(S)-alanyl-N-(β-phenylethyl) glycinate (6.2 g, 69.7%) as a pale yellow oil; mass spectra (CI): 497 (m+1, 52%); 350 (100%).

C. N-[1-(S)-Ethoxycarbonyl-3-phenylpropyl]-(S)-alanyl-N-(β-phenethyl)glycine hydrochloride

To tert-butyl N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-(S)-alanyl-N-(β-phenethyl) glycinate (2g, 4.03 mmoles) was added p-dioxane which had been saturated with anhydrous hydrogen chloride (75 ml). The resulting solution was stirred for three hours at 45° and then the solvent was evaporated to afford N-[1-(S)-ethoxycarbonyl-3-phenylproply]-(S)-alanyl-N-(β-phenethyl)glycine hydrochloride as a colorless powder (1.62 g, 84.2%): m.p. 72°; $[\alpha]_D^{CHCL_3}$ = + 10.95°; mass spectra (CI): 423 (m + 1 - H_2O, 100%).

Analysis calculated for $C_{25}H_{32}N_2O_5 \cdot HCl \cdot \frac{1}{2}H_2O$: C, 61.78; H, 7.05; N, 5.77

Found: C, 61.37; H, 6.71; N, 5.15

By following the procedures in the above examples, the following additional compounds were prepared:

N-[1-(S)-Ethoxycarbonyl-3-methylbutyl]valyl-N-(p-bromophenyl)-glycine

N-[1-(S)-Ethoxycarbonyl-3-phenylpropyl]isoleucyl-N-[(2-chloro-5-methoxy)phenyl]-glycine

N-[1-(S)-Ethoxycarbonyl-3-methylthiopropyl]alanyl-N-(3-cyanophenyl)-glycine

N-[1-Ethoxycarbonyl-4-methylpentyl]alanyl-N-(3,4-dimethoxybenzyl)-alanine

N-[1-(S)-Ethoxycarbonyl-3-phenylpropyl]alanyl-N-(3,5-dimethylphenyl)glycine

N-[1-(S)-Ethoxycarbonyl-2-(3-indolyl)ethyl]valyl-N-(m-tolyl)glycine

N-[1-(S)-Ethoxycarbonylethyl](p-chlorophenylalanyl)-N-(m-trifluoromethylphenyl)glycine

N-[1-Ethoxycarbonyl-3-methylbutyl]alanyl-N-(m-methoxyphenyl)glycine

N-[1-Ethoxycarbonylhexyl]phenylalanyl-N-(p-isopropylphenyl)glycine

N-(1,3-Dicarboxypropyl)isoleucyl-N-[(3,4-dimethoxyphenethyl)]glycine

N-[1-(S)-Ethoxycarbonyl-3-phenylpropyl]isoleucyl-N-[p-(n-butyl-phenyl)]-glycine

N-[1-(S)-Ethoxycarbonylethyl]methionyl-N-(4-t-butylphenyl)alanine

N-[1-(S)-carboxyethyl]valyl-N-(3-methylthiophenyl)alanine

N-[1-(S)-Carboxy-3-phenylpropyl]alanyl-N-(α-napthyl)glycine

N-[1-(S)-Ethoxycarbonyl-2-phenylethyl]phenylalanyl-N-

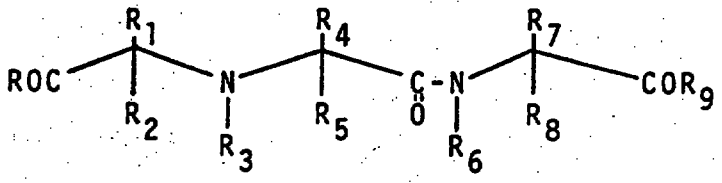
(2-chlorobenzyl)glycine
N-[1,3-Diethoxycarbonylpropyl]alanyl-N-(p-nitrophenyl) glycine
N-[1-(S)-Carboxy-3-methylbutyl]alanyl-N-(3,4-dihydroxy-phenethyl)glycine
N-[1-(S)-Ethoxycarbonyl-3-phenylpropyl]alanyl-N-(o-carboxy phenyl)glycine
N-[1-(S)-Carboxy-2-phenylethyl]valyl-N-(m-biphenyl)glycine

The compounds of the present invention have demonstrated potent activity (of the order of I_{50} of 0.1 to 10.0 micromols) in inhibiting the angiotensin converting enzyme (ACEI activity) when tested by the method described in Science 196, 441-4 (1977). The compounds of the present invention have also demonstrated an I_{50} of 1 to 10 mg/kg P.O. in inhibiting infused angiotensin I in rats. As such, these would be very useful in the treatment of hypertension.

The compounds may be administered orally or parenterally in the treatment of hypertension, and it will be within the professional judgment and skill of the practioner to determine the amount to be administered. Suitable dosage forms include tablets, capsules, elixirs and injectables.

CLAIMS:

1. Compounds of the formula



(I)

wherein

R and R_9 are independently hydroxy, C_1-C_6 alkoxy, C_2-C_6 alkenoxy, di(C_1-C_6 alkyl)amino-C_1-C_6 alkoxy, hydroxy-C_1-C_6 alkoxy, acylamino-C_1-C_6 alkoxy, acyloxy-C_1-C_6 alkoxy, aryloxy, aryloxy-C_1-C_6 alkoxy, amino, C_1-C_6-alkylamino, di(C_1-C_6 alkyl) amino, hydroxyamino, or aryl-C_1-C_6 alkylamino,

R_1, R_2, R_3, R_4, R_5, R_7 and R_8 are independently hydrogen, alkyl having from 1 to 20 carbon atoms, alkenyl having from 2 to 20 carbon atoms, alkynyl having from 2 to 20 carbon atoms, aryl-C_1-C_6 alkyl having 7 to 12 carbon atoms, heterocyclic-C_1-C_6 alkyl having from 7 to 12 carbon atoms, cycloalkyl or cycloalkylalkyl having 3 to 20 carbon atoms in the cycloalkyl group, or

R_2 and R_3 taken together with the carbon and nitrogen to which they are respectively attached, or R_3 and R_5 taken together with the nitrogen and carbon to which they are respectively attached, form an N-heterocycle containing from 3 to 5 carbon atoms or 2 to 4 carbon atoms and a sulfur atom,

R_6 is aryl having 6 to 10 carbon atoms, aryl-C_1-C_6 alkyl, aryl-C_2-C_6 alkenyl, or aryl-C_2-C_6 alkynyl, and

salts thereof with acids or bases, especially pharmaceutically acceptable acid and base salts.

2. A compound according to Claim 1 wherein R_1, R_2, R_3, R_4, R_5, R_7 and R_8 are independently alkyl, alkenyl, or alkynyl groups with hydroxy, C_1-C_6 alkoxy, thio, C_1-C_6 alkylmercapto, amino,

C_1 -C_6 alkylamino, di(C_1 -C_6 alkyl) amino, halogen, or nitro-groups;

or mono or polycyclic, fully saturated and partially unsaturated cycloalkyl groups substituted by halogen, hydroxy, C_1 -C_6 alkyl, C_1-C_6 alkoxy, amino C_1-C_6 alkylamino, di(C_1-C_6 alkyl)amino, thiol, C_1-C_6 alkylmercapto, nitro, or trifluoromethyl groups.

3. A compound according to Claim 1 wherein R_6 comprises an aryl group or an arylalkyl, arylalkenyl or arylalkynyl group wherein the aryl group is substituted by hydroxy, C_1 -C_6 alkoxy, amino, C_1-C_6 alkylamino, di(C_1-C_6 alkyl) amino, thiol, C_1-C_6 alkylmercapto, hydroxy-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, thio-C_1-C_8 alkyl, nitro, halogen, trifluoromethyl, methylenedioxy, ureido, or guanidino.

4. A compound according to Claim 1 wherein R and R_9 are independently hydroxy or C_1-C_6 alkoxy,

R_1 and R_2 are hydrogen or C_1 -C_6 alkyl, aryl-C_1 -C_6 alkyl having from 7 to 12 carbon atoms, or heterocyclic-C_1 -C_6 alkyl having from 6 to 12 carbon atoms,

R_3, R_4, R_5, R_7 and R_8 are hydrogen or C_1-C_6 alkyl,

R_6 is aryl or aryl-C_1 -C_6 alkyl, and the aryl group contains from 6 to 10 carbon atoms wherein the aryl groups can be substituted by C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2 -C_6 alkynyl, hydroxy, C_1 -C_6 alkoxy, amino, C_1 -C_6 alkylamino, di(C_1 -C_6 alkyl)amino, thiol, C_1 -C_6 alkylmercapto, hydroxy-C_1 -C_6 alkyl, amino-C_1-C_6 alkyl, thio-C_1-C_6 alkyl, nitro, halogen, trifluoromethyl, methylenedioxy, ureido and guanidino, and salts thereof especially pharmaceutically acceptable acid and base salts.

5. A compound according to any preceding Claim wherein R_1 is C_1 -C_6 alkyl or aryl-C_1 -C_6 alkyl, R_4 is C_1-C_6 alkyl, and R_2, R_3, R_5, R_7 and R_8 are hydrogen.

6. A compound according to Claim 5 wherein R and R_9 are hydroxy.

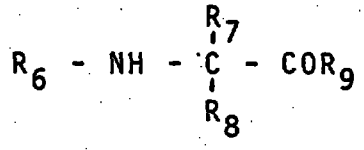
7. A compound according to Claim 5 wherein R is ethoxy and R_9 is hydroxy.

8. A compound according to Claim 7 wherein R_1 and R_4 are methyl.

9. A compound according to Claim 7 wherein R_1 is phenethyl and R_4 is methyl.

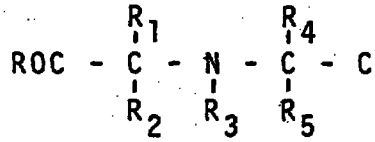
10. A compound according to any of Claims 1 to 9 wherein R_6 is p-tolyl.

11. The process of preparing a compound of formula I according to any one of the preceding Claims, which comprises reacting under amide-forming conditions of an amino compound of formula II



(II)

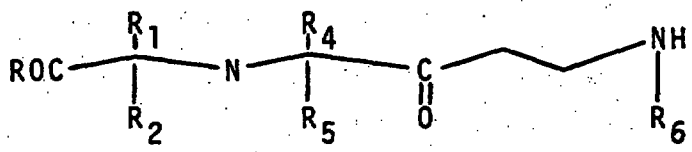
with an acylating derivative of an acid of formula III



(III)

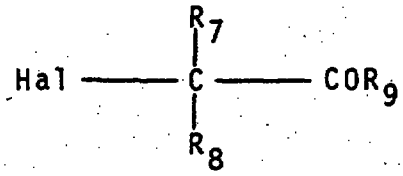
or reducing the corresponding imine; or by reaction

to eliminate hydrogen halide of a compound of formula VI



(VI)

with a halo compound of formula VII

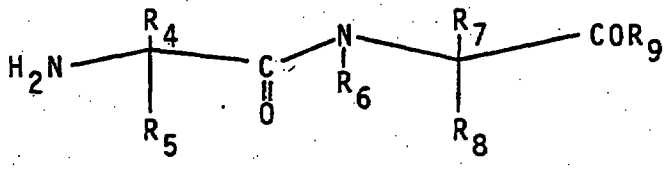


(VII)

and optionally by substitution or conversion reactions introducing various substituents into the said products; and

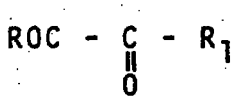
optionally forming salts thereof, especially pharmaceutically acceptable salts with acids and bases.

12. The process of preparing a compound of formula I, in which R_2 and R_3 are each H which comprises reacting a dipeptide of the structure



(IV)

with an α-keto acid or ester of the structure



(V)

to form the corresponding imine, and reducing the said imine.

13. Therapeutic composition which comprises a compound according to any of Claims 1 to 10, and a pharmaceutically acceptable excipient.

* C L M S *

14. A process according to Claim 11 and substantially as hereinbefore described with reference to any of Examples 1 to 6.