

INSTRUCTIONS

(a) If Convention application insert "Convention"

convention (a)
AUSTRALIA 611984
Patents Act

APPLICATION FOR A (b) STANDARD/PETTY PATENT

(b) Delete one

☒ We (c) **MERRELL DOW PHARMACEUTICALS INC.**

(c) Insert FULL name(s) of applicant(s)

of (d) **2110 East Galbraith Road
Cincinnati, Ohio 45215
United States of America**

(d) Insert FULL address(es) of applicant(s)

(e) Delete one

hereby apply for the grant of a (e) Standard/Petty Patent for an invention entitled (f)

NOVEL SULFHYDRYL CONTAINING TRICYCLIC LACTAMS AND THEIR PHARMACOLOGICAL METHODS OF USE

(f) Insert TITLE of invention

which is described in the accompanying (g) complete specification.

(g) Insert "complete" or "provisional" or "petty patent"

(Note: The following applies only to Convention applications)

Details of basic application(s)

(h)	Application No.	Country	Filing Date
	139,485	United States of America	December 30, 1987

(h) Insert number, country and filing date for the/or each basic application

Address for Service:

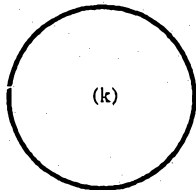
**PHILLIPS ORMONDE AND FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne, Australia 3000**

Dated (i) **October 14, 1988**

(i) Insert date of signing

(j) **MERRELL DOW PHARMACEUTICALS INC.**

(j) Signature of applicant(s) (For body corporate see headnote*)



By Gary D. Street
Gary D. Street
Managing Patent Counsel

(k) Corporate seal if any

Note: No legalization or other witness required

1267 AU

**PHILLIPS ORMONDE & FITZPATRICK
Patent and Trademark Attorneys
367 Collins Street
Melbourne, Australia**

AUSTRALIA

Patents Act

DECLARATION FOR A PATENT APPLICATION

INSTRUCTIONS

(a) Insert "Convention" if applicable

(b) Insert FULL name(s) of applicant(s)

(c) Insert "of addition" if applicable

(d) Insert TITLE of invention

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

In support of the (a) convention application made by

(b)

MERRELL DOW PHARMACEUTICALS INC.

(hereinafter called "applicant(s)" for a patent (c) for an invention entitled (d)

NOVEL SULFHYDRYL CONTAINING TRICYCLIC LACTAMS AND THEIR PHARMACOLOGICAL METHODS OF USE

I/~~We~~ (e)

Gary D. Street, Managing Patent Counsel
MERRELL DOW PHARMACEUTICALS INC.
2110 East Galbraith Road
Cincinnati, Ohio 45215, United States of America

do solemnly and sincerely declare as follows:

1. ~~I am/We are~~ the applicant(s).

(or, in the case of an application by a body corporate)

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

2. ~~I am/We are~~ the actual inventor(s) of the invention:

(or, where the applicant(s) is/are not the actual inventor(s))

2. (f) Gary A. Flynn
7121 Euclid Road
Cincinnati, Ohio 45243
United States of America

Douglas W. Beight
645 Glensprings Drive
Cincinnati, Ohio 45246
United States of America

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

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

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

(g) Applicant is the assignee of the above-entitled invention by virtue of a deed of Assignment from the actual inventors dated December 30, 1987

(Note: Paragraphs 3 and 4 apply only to Convention applications)

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

(h) United States of America - December 30, 1987

By: Gary A. Flynn and Douglas W. Beight

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

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

(k) Insert PLACE of signing

(l) Insert DATE of signing

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

Declared at (k) Cincinnati, Ohio, U.S.A.

Date (l) October 14, 1988

(m) MERRELL DOW PHARMACEUTICALS INC.

By


Gary D. Street
Managing Patent Counsel

To: The Commissioner of Patents

Note: No legalization or other witness required

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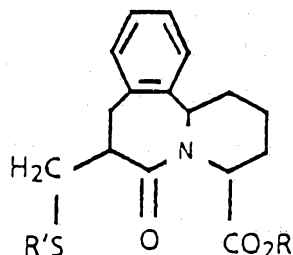
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(12) PATENT ABRIDGMENT (11) Document No. AU-B-27368/88
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 611984

- (54) Title
NOVEL SULFHYDRYL CONTAINING TRICYCLIC LACTAMS AND THEIR PHARMACOLOGICAL METHODS OF USE
- International Patent Classification(s)
(51)⁴ C07D 471/04 A61K 031/55
- (21) Application No. : 27368/88 (22) Application Date : 21.12.88
- (30) Priority Data
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139485 30.12.87 US UNITED STATES OF AMERICA
- (43) Publication Date : 06.07.89
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- (74) Attorney or Agent
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- (56) Prior Art Documents
AU 74022/87 C07D 471/04
- (57) Compounds are used for the treatment of hypertension, cardiotionia and ischaemia.

CLAIM

1. A compound of the formula

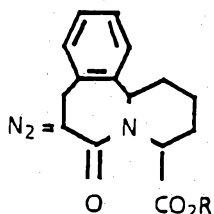


wherein

R is hydrogen; C₁-C₆ lower alkyl, or (C₆-C₁₂)aryl(C₁-C₆)lower alkyl; and

R' is hydrogen or -COR, wherein R is as defined above, and the pharmaceutically acceptable salts thereof.

6. A compound of the formula



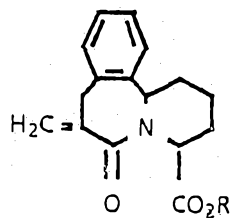
(11) AU-B-27368/88

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(10) 611984

wherein R is C₁-C₆ lower alkyl, or (C₆-C₁₂)aryl(C₁-C₆)lower alkyl.

7. A compound of the formula



wherein R is hydrogen, C₁-C₆ lower alkyl, or (C₆-C₁₂)aryl(C₁-C₆)lower alkyl.

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Patents Act

611984

COMPLETE SPECIFICATION
(ORIGINAL)

Application Number: Class Int. Class
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority

Related Art:

APPLICANT'S REFERENCE: M01267 AU

Name(s) of Applicant(s):

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UNITED STATES OF AMERICA.

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Complete Specification for the invention entitled:

NOVEL SULFHYDRYL CONTAINING TRICYCLIC LACTAMS AND THEIR PHARMACOLOGICAL
METHODS OF USE

Our Ref : 115727
POF Code: 1432/1432

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

NOVEL SULFHYDRYL CONTAINING TRICYCLIC LACTAMS AND THEIR
PHARMACOLOGICAL METHODS OF USE

BACKGROUND OF THE INVENTION

A need exists for compounds which inhibit angiotensin
5 converting enzyme (hereinafter ACE). The inhibition of
ACE blocks the conversion of the decapeptide angiotensin I
to angiotensin II. Angiotensin II is a potent pressor
substance, therefore blood pressure lowering can result
from inhibition of its biosynthesis, especially in animals
10 and humans whose hypertension is angiotensin II related.
Furthermore, ACE inhibition may also lower blood pressure
by potentiation of bradykinin. Although the relative
importance of these and other possible mechanisms remains
to be established, ACE inhibitors are effective
15 antihypertensive agents in a variety of animal models and
are useful clinically in treating human patients with
renovascular, malignant and essential hypertension. See,
e.g., D.W.Cushman, *et al.*, Biochemistry, 16, 5484 (1977).

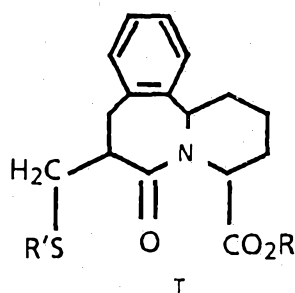
Additionally, a need exists for compounds which are
20 anti-ischemic agents useful in the treatment of
reperfusion injury. Reperfusion injury is that injury
which occurs when molecular oxygen is reintroduced into an
ischemic tissue. An ischemic tissue is one that is

deficient of blood due to a functional constriction or actual obstruction of a blood vessel. Ischemia (i.e., the deficiency of oxygenated blood in a tissue) can be caused by any means and in any tissue and includes ischemia to the heart or a portion of the heart resulting from a coronary thrombosis or any other blockage of the blood supply to the heart or a portion of the heart, ischemia surgically induced to the heart of a patient undergoing open-heart or coronary by-pass surgery, the ischemia which occurs to an organ or organ group such as a heart, heart-lung, liver, or kidney to be used in an organ transplant, ischemia occurring during circulatory shock, and ischemia which is caused by blockage of the arteries supplying the brain, i.e. stroke.

Likewise, a need exists for compounds that exert a strenghtening effect on the heart tissue of patients who have suffered heart failure. Heart failure, or cardiotionia, is the clinical condition resulting from the inablilty of the myocardium of the ventricles to maintain an adequate flow of blood to all the tissues of the body and includes backward heart-failure, congestive heart-failure, forward heart-failure, and left and right ventricular heart-failure. A cardi tonic agent is an agent which strenghtens the heart's action. The compounds effective in treatment of heart-failure function by strengthening the heart muscle by virtue of their ability to enhance myocardial contractile force and by reducing work load by virtue of their vasodilator activity.

DESCRIPTION OF THE INVENTION

This invention relates to certain conformationally rigid sulphhydryl containing fused tricyclic lactams of the formula



wherein

R is hydrogen, C₁-C₆ lower alkyl, or (C₆-C₁₂)aryl(C₁-C₆)lower alkyl; and

R' is hydrogen or -COR, wherein R is as defined above,
10 and to the pharmaceutically-acceptable salts thereof. The invention also concerns the intermediates and processes useful for their preparation, and to their pharmacological effect and use in the treatment of hypertension (i.e. to inhibit angiotensin converting enzyme), ischemia (i.e. to treat injury occurring during the reperfusion of ischemic
15 tissue), and cardiotionia (i.e. to enhance myocardial contractile force and to treat heart failure).

As used herein, ^{and in the claims} the term "C₁-C₆ lower alkyl" and the "C₁-C₆ lower alkyl" portion of the aryl groups means
20 straight or branched chain alkyl groups having from one to six carbon atoms and includes such groups as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, and the like, as well as vinyl, propargyl, butenyl, and the like. The term "C₆-C₁₂ aryl" refers to
25 aryl groups containing six to twelve carbon atoms and includes such groups as phenyl, naphthyl, indenyl,



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biphenyl and benzofused cycloalkyl groups such as, for example, indanyl and 1,2,3,4,-tetrahydronaphthyl.

Illustrative examples of the compounds of this invention include:

5 [4S-(4 alpha,7 alpha,12b beta)]-1,2,3,4,6,7,8,12b-octahydro-7-(mercaptomethyl)-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid

10 [4S-(4 alpha,7 alpha,12b beta)]-1,2,3,4,6,7,8,12b-octahydro-7-[(acetylthio)methyl]-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid

[4S-(4 alpha,7 alpha,12b beta)]-1,2,3,4,6,7,8,12b-octahydro-7-[(benzoylthio)methyl]-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid

15 [4S-(4 alpha,7 alpha,12b beta)]-1,2,3,4,6,7,8,12b-octahydro-7-(mercaptomethyl)-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid methyl ester

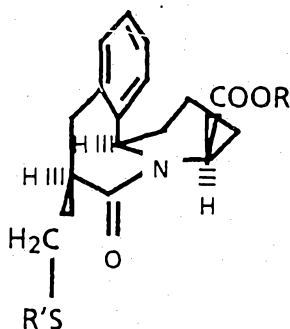
20 [4S-(4 alpha,7 alpha,12b beta)]-1,2,3,4,6,7,8,12b-octahydro-7-(mercaptomethyl)-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid diphenylmethyl ester

[4S-(4 alpha,7 alpha,12b beta)]-1,2,3,4,6,7,8,12b-octahydro-7-[(benzoylthio)methyl]-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid methyl ester

25 [4S-(4 alpha,7 alpha,12b beta)]-1,2,3,4,6,7,8,12b-octahydro-7-[(benzoylthio)methyl]-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid diphenylmethyl ester.

As is true for most classes of therapeutically effective compounds, certain subclasses and certain species which are especially effective are preferred over others. In this instance, those compounds of Formula I
5 wherein R and R' are both hydrogen are preferred.

Also preferred are those compounds having the diastereomeric configuration represented by the structure:

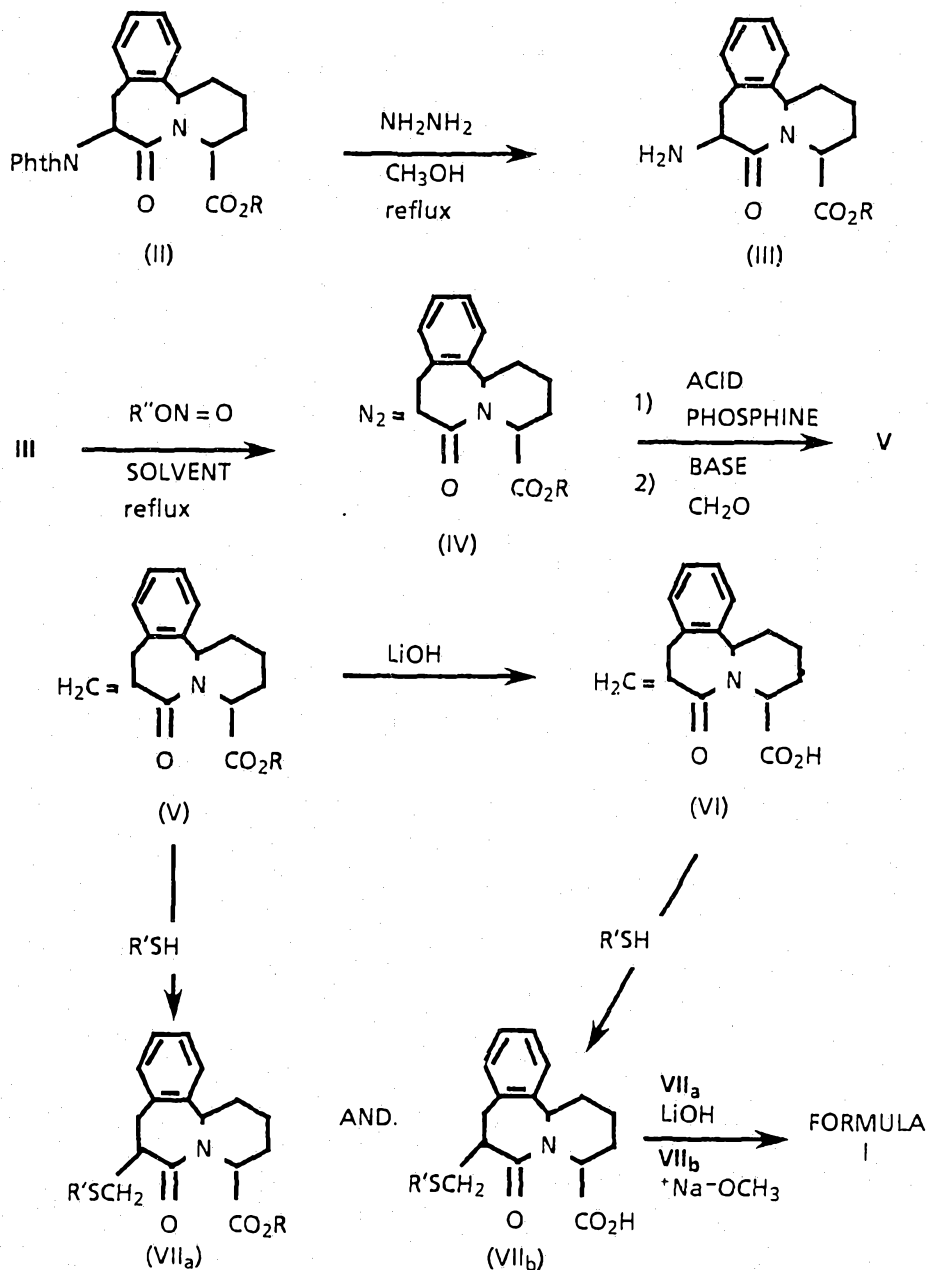


10 wherein R, and R' are as defined in Formula I and wherein the stereochemistry is 4(S), 7(S), and 12b(R), the preferred R, and R' groups being as described above.

All enantiomeric isomers and diastereomeric isomers and mixtures thereof of the compounds of Formula I are
15 encompassed within the scope of this invention. The separation of said isomeric mixtures can be accomplished by standard techniques known in the art.

The tricyclic lactams of this invention can readily be prepared by the reactions depicted in Reaction Scheme I:

REACTION SCHEME I



wherein R and R' are as defined above except they must be other than H, and R'' is isoamyl or n-propyl.

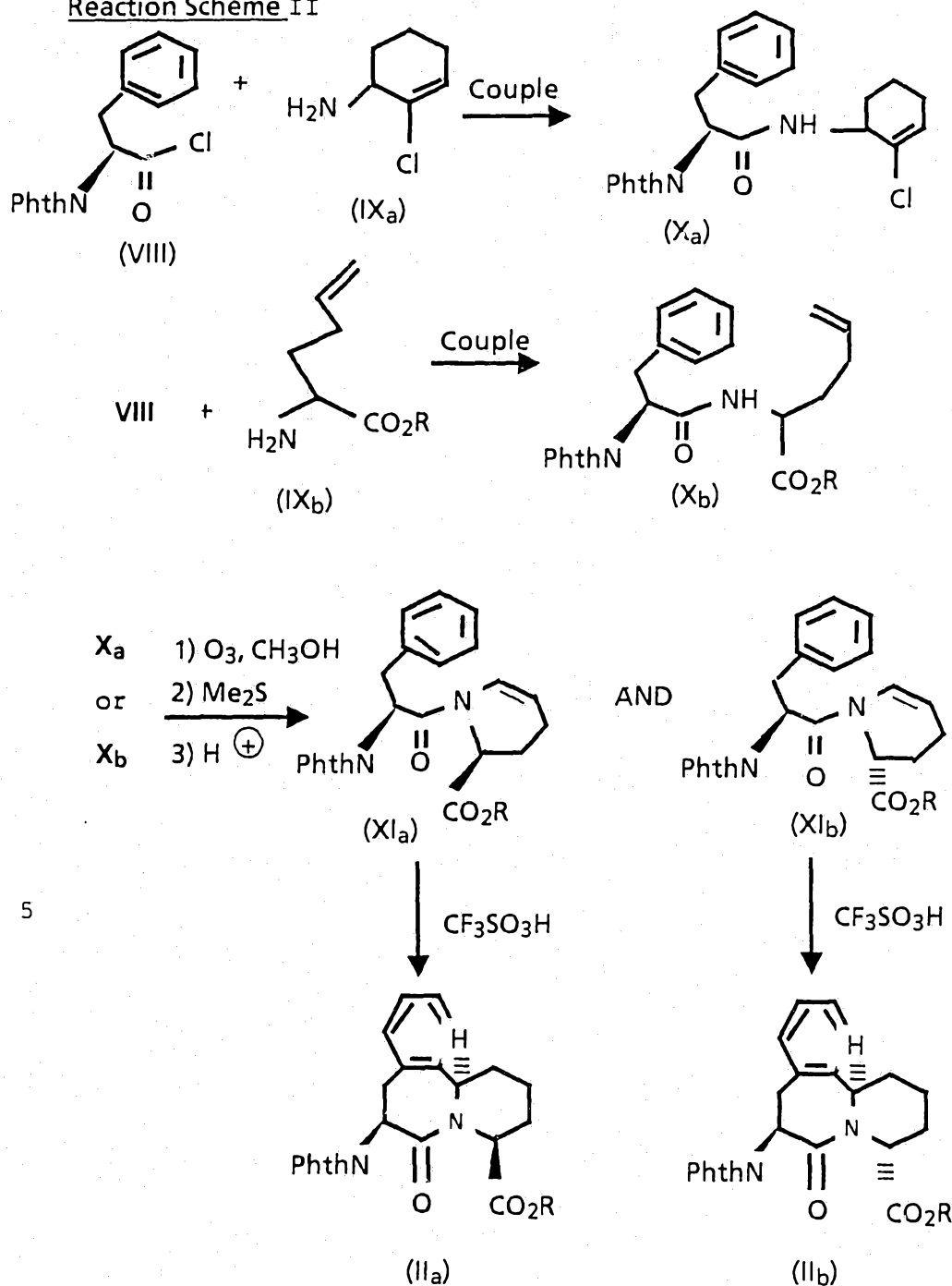
In essence, Reaction Scheme I illustrates that the tricyclic lactams of Formula I can be prepared by converting the phthalamide starting material II (wherein "Phth" is a nitrogen protecting phthalimide group), to the amine III by reacting it with excess hydrazine hydrate (NH_2NH_2) in an appropriate organic solvent such as methanol (CH_3OH) under nitrogen and under reflux conditions. The resulting amine III is then treated with an equivalent amount of alkyl nitrite ($\text{R}^*\text{ON}=\text{O}$) such as isoamyl nitrite or propyl nitrite, in the presence of acetic acid and an inert solvent such as dichloromethane or chloroform under nitrogen and under reflux conditions to produce the diazoamide intermediate IV. The diazo compound IV is first reacted with a mixture of two equivalents of a strong acid such as methanesulfonic acid or trifluoromethanesulfonic acid and an excess of a phosphine such as triphenylphosphine or tributylphosphine under nitrogen, at a temperature of from about -70°C to about 50°C , preferably at about -40°C to about -20°C , and the resulting mixture subsequently reacted with two equivalents of a strong base, such as potassium carbonate, and excess formaldehyde (CH_2O) to yield the olefinated lactam V. The olefinic lactam (V) can be coupled with an appropriate thioester ($\text{R}'\text{SH}$) by means of a Michael reaction using a base to yield the thioester VII_a, and then subjected to lithium hydroxide (LiOH) saponification to yield the compounds of Formula I (where the product containing R as hydrogen, or R as other than hydrogen is dependent on the duration of the reaction). Or alternatively, V can be hydrolyzed with lithium hydroxide (LiOH), when R is other than hydrogen, to produce the olefinic acid VI. VI can then be coupled with an appropriate thioester ($\text{R}'\text{SH}$) by means of a Michael reaction using a base to produce the thioester VII_b, which, in a suitable deoxygenated solvent such as

methanol, can be subjected to sodium methoxide ($^+Na^-OCH_3$) cleavage, yielding the sulfur containing tricyclic lactams of Formula I.

5 The intermediate compounds of Formulas IV and V are useful in the synthesis of the compounds of Formula I.

Preparation of the starting material (II) is illustrated by Reaction Scheme II below. In preparation of the methyl ester (II), it is generally preferred to initiate the sequence of reaction steps by utilizing N-protected phenylalanine which, when converted to its acid chloride (VIII, wherein Phth is a nitrogen protecting phthalamide group), is coupled by treatment with an aminovinyl chloride (IX_a) or an -OH protected vinyl amino acid (IX_b) according to the well-known Schott-Baumann
10 reaction. In this reaction, the reactants are coupled in the presence of sodium carbonate/acetone and water, preferably at room temperature and then subjected to an acidification step to produce intermediate compounds (X_a and X_b). These intermediates are treated with ozone (O_3)
15 in methylene chloride containing an alcohol such as methanol (CH_3OH) at $-78^\circ C$, quenched with dimethylsulfide (Me_2S) and pyridine, and the isolated products treated with trifluoroacetic acid/methylene chloride (H^+) at reflux temperatures to produce further intermediates (XI_a and
20 XI_b). These subsequent intermediates are then treated with trifluoromethanesulfonic acid (CF_3SO_3H) according to the well-known Friedel-Crafts cyclization procedure to produce the compound of Formula II.

Reaction Scheme II



wherein R is as defined above.

The following specific examples are presented to illustrate the synthesis of the compounds of this invention, but they should not be construed as limiting the scope of this invention in any way.

5

EXAMPLE 1

[2(S)]N-(2-Chloro-2-Cyclohexene-1-yl)-1,3-Dihydro-1,3-Dioxo-2H-Isoindole-2-(S)-(Phenylmethyl-2-Acetamide (Xa)

Step A. 2-(2-Chloro-2-Cyclohexen-1-yl)-1H-Isoindole-1,3(2H)-Dione

10 A solution of 11.0g (72.8 mmol) 1,6-dichlorocyclohexene, 20.0g (108 mmol) potassium phthalimide and 1.0 g (6.0 mmol) potassium iodide in 50 ml dry dimethylformamide was stirred 24 hours at 110°C under an atmosphere of nitrogen. The reaction mixture was allowed to cool then
15 poured into 30 ml diethyl ether. The dark mixture was filtered, then the ether and DMF removed *in vacuo*. The dark crystalline residue was dissolved in ethyl acetate then chromatographed on 500 g flash silica eluting with 10% to 20% ethyl acetate/hexane. Concentration of appropriate
20 fractions followed by recrystallization from ethyl acetate/hexane gave 14.0 g (73.5%) of the desired phthalimide, mp 99-103°C.

Step B. A solution of 6.0 g (120 mmol) of hydrazinehydrate and 26.1 g (100 mmol) of N-phthalimido-6-amino-1-chlorocyclohexene in 150 ml methanol was refluxed under N₂
25 for 3 hrs., cooled to 25°C and allowed to stir for 3 hrs. The mixture was filtered, concentrated, poured into 300 ml 1N HCl, and washed with 200 ml CH₂Cl₂. The aqueous layer was basified and extracted with three 500 ml portions of
30 CH₂Cl₂. The organics were dried over MgSO₄, filtered, and concentrated to give 9.25 g (70 mmol) of crude amine. The

neutral extract was concentrated to give 6.0 g of unreacted starting phthalimide. To a stirred solution of 21 g (71 mmol) of phthalimido-L-phenylalanine and 18.5 g (75 mmol) of N-carbethoxy-2-ethoxy-1,2-di-hydroquinoline in 200 ml CH₂Cl₂ at 25°C under N₂ was added 9.25 g (70 mmol) of the 6-amino-1-chlorocyclohexene in 20 ml CH₂Cl₂ over 30 min. After stirring for 18 hours, the reaction mixture was washed with two 200 ml portions of 10% HCl solution, 200 ml sat. NaHCO₃ solution, and brine. The organics were dried over MgSO₄, filtered and concentrated to give a solid. Recrystallization from CH₂Cl₂/hexane gave 26.1 g of a mixture of the desired 2-(S) diastereomeric amides (Xa) which were not separated at this point. (64% overall yield): IR(KBr) 3400, 1775, 1715, 1650, 1530, 1380, cm⁻¹; ¹H NMR δ 1.60 (m, 2H), 1.82 (m, 2H), 2.05 (m, 2H), 3.49 (s, 1H), 3.59 (s, 1H), 4.60 (m, 1H), 5.05 (dd, 1/2H, J_a=10Hz, J_b=2Hz), 5.17 (dd, 1/2H, J_a=10Hz, J_b=2Hz), 5.95 (t, 1H, J=7 Hz), 6.45 (m, 1H), 7.10 (s, 5H), 7.70 (m, 4H).

Anal. Calcd. for C₂₃H₂₁ClN₂O₃: C, 67.56; H, 5.18; N, 6.85.
Found: C, 67.40; H, 5.30; N, 6.80.

EXAMPLE 2

[S(R*,R*)]-1-[2-(1,3-Dihydro-1,3-Dioxo-2H-Isoindol-2-yl)-1-Oxo-3-Phenylpropyl]-1,2,3,4-Tetrahydro-2-Pyridine-Carboxylicacid, Methyl Ester (XIa)

A solution of 12.2 g (30 mmol) of the vinyl chloride from Example 1 in 300 ml CH₂Cl₂ containing 20 ml absolute methanol was cooled to -70°C and stirred while a stream of ozone in oxygen (generated by a Welsbach Ozonator) was passed into the solution *via* a glass frit. When the solution turned blue, excess ozone was removed by passing dry N₂ into the solution. . The reaction mixture was treated with 20 ml methyl sulfide and 4 ml pyridine, then allowed to gradually warm to 25°C and stir for 20 hours.

The solution was poured into 200 ml 10% HCl solution and the organics were separated, washed well with H₂O, dried over MgSO₄ and concentrated to give 13.0 g of an amber oil. The crude ozonolysis product was dissolved in 200 ml CH₂Cl₂ containing 0.5 ml trifluoroacetic acid and refluxed under N₂ for 3 hours. The cooled solution was washed with saturated NaHCO₃ solution, dried over MgSO₄ and concentrated to give 12.2 g of an amber oil. Preparative HPLC separation using 50% ethyl acetate/hexane (Waters Prep-500 one recycle) gave 4.3 g (10.1 mmol) of each diastereomeric acylenamine XIa and XIb, (68% overall yield). Isomer XIa was recrystallized from CH₂Cl₂/hexane to give a fine white crystalline powder: mp 146-147°C; $[\alpha]_D^{25} = -320.1^\circ$ (c=1.1, CHCl₃); IR (KBr) 1770, 1740, 1720, 1670, 1650, 1390, 1220, 722 cm⁻¹; ¹H NMR δ 1.85 (m, 2H), 2.30 (m, 2H), 3.50 (d, 2H, J=7 Hz), 3.72 (s, 3H), 4.71 (m, 1H), 5.20 (m, 1H), 5.27 (t, 1H, J=7 Hz), 6.45 (d, 1H, J=9 Hz), 7.12 (s, 5H), 7.71 (m, 4H).

Anal. Calcd. for C₂₃C₂₂N₂O₅: C, 68.89; H, 5.30; N, 6.69.
Found: C, 68.61; H, 5.26; N, 6.56.

EXAMPLE 3

[4S-(4a,7a,12bβ)]-7-(1,3-Dihydro-1,3-Dioxo-2H-Isoindo-2-yl)-1,2,3,4,-6,7,8,12b-Octahydro-6-Oxopyrido[2,1-a][2]Benzazepine-4-Carboxylic Acid, Diphenylmethyl Ester (IIa)

To a stirred solution of 4.20 g (10.0 mmol) of desired acylenamine from Example 2 in 20 ml CH₂Cl₂ under N₂ atmosphere was added 6 ml CF₃SO₃H. After stirring at 20°C for 18 hours, the solution was poured onto ice and extracted into 200 ml ethyl acetate. The organics were washed well with water, dried over MgSO₄ and concentrated. The residue was dissolved in CH₂Cl₂ and treated with 2.2 g diazodiphenylmethane and allowed to stand for 12 hours. The solution was concentrated and the residue was flash

chromatographed on 400 ml silica using 33% ethyl acetate/hexane to give 4.5 g (7.7 mmol, 77% yield) of the title benzhydrylester (R=CHPh₂) as a foam. Recrystallization from CH₂Cl₂/hexane was slow but gave 4.3 g (75%
5 yield) of pure transparent plates: mp. 156-157°C; [α]_D^{Amb}= -87.6°C (c=0.6, CHCl₃); IR 1780, 1717, 1643, 1450, 1379 cm⁻¹; ¹H NMR δ 1.8-2.1 (m, 4H), 2.38 (m, 2H); 3.23 (dd, 1H, J_a=18 Hz, J_b=16 Hz), 4.38 (dd, 1H, J_a=19 Hz, J_b=12 Hz), 5.30 (dd, 1H, J_a=6 Hz, J_b=2 Hz), 5.42 (dd, 1H, J_a=6 Hz, J_b=4 Hz), 6.05
10 (dd, 1H, J_a=12 Hz, J_b=6 Hz), 6.30 (s, 1H), 6.61 (d, 1H, J=7 Hz), 6.9-7.4 (m, 13 H), 7.75 (m, 2H), 7.92 (m, 2H).

Anal. Calcd. for C₃₆H₃₀N₂O₅: C, 75.77; H, 5.30; N, 4.91.
Found: C, 75.79; H, 5.46; N, 4.77.

EXAMPLE 4

15 [4S-(4a,7a,12bβ)]-7-(1,3-Dihydro-1,3-Dioxo-2H-Isoindol-2-yl)-1,2,3,4,6,7,8,~12b-Octahydro-6-Oxopyrido[1-a][2]Benzazepine-4-Carboxylic Acid, Methyl Ester (II_b)

Alternatively the cyclization product could be treated
20 with diazomethane to give the methyl ester from Example 3 (R=CH₃): mp 138-149°C [α]_D^{Amb}= -122.4° (c=0.97, EtOH); IR 1778, 1720, 1655, 1620, 1375 cm⁻¹; ¹H NMR δ 1.7-2.2 (m, 4H), 2.43 (m, 2H), 3.10 (s, 3H), 3.44 (dd, 1H, J_a=17 Hz, J_b=6 Hz), 4.42 (dd, 1H, J_a=17 Hz, J_b=12 Hz), 5.23 (dd, 1H, J_a=6 Hz, J_b=2 Hz), 5.47 (dd, 1H, J_a=6 Hz, J_b=4 Hz), 6.08 (dd, 1H, J_a=12 Hz, J_b=6 Hz), 7.23 (m, 4H), 7.77 (m, 2H), 7.89 (m, 2H).
25

Anal. Calcd. for C₂₄H₂₂N₂O₅: C, 68.89; H, 5.30; N, 6.69.
Found: C, 68.98; H, 5.83; N, 6.63.

EXAMPLE 5

[4S-(4a,7a,12b β)]-7-Amino-1,2,3,4,6,7,8,12b-Octahydro-6-Oxo-Pyrido[2,1-a][2]Benzazepine-4-Carboxylic Acid Methyl Ester (III)

5 Twenty ml (20 mmol) 1M hydrazine hydrate in methanol was added to a mixture of 4.18 g (10.0 mmol) methyl ester of Example 4 in 30 ml methanol. The mixture was allowed to stir at ambient temperature under an atmosphere of nitrogen for 18 hr. The mixture was then filtered through
10 Celite, washed thoroughly with methanol, and concentrated *in vacuo*. The resulting oil was partitioned between methylene chloride and water, and the methylene chloride portion was washed with an additional 20 ml of water. The solution was dried over anhydrous magnesium sulfate,
15 filtered and concentrated *in vacuo* to yield 3.05 g (106%) of the title ester. The product was recrystallized from methylene chloride/hexane to give analytically pure amine as a partial hydrate.

¹H NMR (CDCl₃): 7.15 (m, 4H); 5.46 (m, 1H); 5.34 (m, 1H)
20 4.69 (dd, J_a=11Hz, J_b=5Hz, 1H); 2.98 (s, 3H); 2.94 (dd, J_a=17Hz, J_b=14Hz); 2.43 (m, 2H); 2.08-1.70 (complex, 1.82 (s, 2H). Calc. for C₁₆H₂₀N₂O₃·0.3 H₂O: C, 65.42; H, 6.45; N, 9.54; Found: C, 65.39; H, 7.18; N, 9.58.

EXAMPLE 6

25 4S-trans-1,2,3,4,6,7,8,12b-Octahydro-7-Methylene-6-Oxo-Pyrido[2,1-a][2]Benzazepine-4-Carboxylic Acid Methyl Ester (V)

Isoamyl nitrite (1.13 g, 4.8mmol) was added to a solution of 1.17 g (4.0 mmol) of the title ester of
30 Example 5 and 44 microliters (0.8 mmol) of acetic acid in 20 ml of dry dichloromethane. The solution was refluxed under nitrogen for 85 min. and allowed to cool. The solution was extracted once with 20 ml of 5% aqueous

sulfuric acid, washed with water, and shaken with 20 ml saturated sodium bicarbonate (NaHCO_3) solution. The acidic extract was made basic and back extracted with ethyl acetate to recover approximately 300 mg unreacted starting amine. The dichloromethane fraction was dried over sodium sulfate (Na_2SO_4) and concentrated to give 616 mg of 4S-trans-7-diazo-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid methyl ester (IV) (51.4% yield). The diazo compound (616 mg, 2.1 mmol) was dissolved in 10 ml methylene chloride (CH_2Cl_2) and added dropwise over 13 min. to a stirred solution of 2.16 g (8.23 mmol) of triphenylphosphine and 0.33 ml (4.1 mmol) of trifluoromethanesulfonic acid at -40°C under an atmosphere of nitrogen. Stirring was continued for 2.5 hr. at -20°C . The solution was concentrated *in vacuo* and the resulting oil was dissolved in 25 ml 95% ethyl alcohol. To this stirred solution was added a solution of 0.59 g (4.2 mmol) of potassium carbonate (K_2CO_3) in 6 ml water followed immediately by 4 ml of 37% formaldehyde solution. After stirring for 23 min. at 25°C , the reaction mixture was quenched with 4 ml 1N HCl, filtered, and the solid washed with 10 ml 50% alcohol/water. The filtrate was concentrated *in vacuo*, the residue dissolved in ethyl acetate, and dried over MgSO_4 and concentrated *in vacuo*. Flash chromatography on silica gel using 40% ethyl acetate in hexane afforded 197mg (17.3% overall yield) of the title compound.

^1H NMR δ (CDCl_3): 7.1-7.3 (m, 4H); 5.70 (s, 1H); 5.42 (s, 1H); 5.3-5.4 (m, 2H); 4.02 (d, $J=20$ Hz, 1H); 3.95 (d, $J=20$ Hz, 1H); 3.05 (s, 3H); 2.3-2.5 (m, 2H); 1.6-2.1 (m, 4H).

EXAMPLE 7

4S-trans-1,2,3,4,6,7,8,12b-Octahydro-7-Methylene-6-Oxo-Pyrido[2,1-a][2]Benzazepine-4-Carboxylic Acid (VI)

One molar lithium hydroxide (0.22 ml, 0.22 mmol) was
5 added to a solution of 32 mg (0.11 mmol) of the title
compound of Example 6 in 1 ml methanol. The solution was
allowed to stir at ambient temperature under an atmosphere
of nitrogen for 20 hr. The mixture was then diluted with
10 ml water, and extracted once with 10 ml ethyl acetate.
10 The resulting aqueous solution was acidified with 1N HCl,
then extracted with three portions of 7 ml methylene
chloride. The methylene chloride portions were combined,
dried over anhydrous magnesium sulfate, then concentrated
in vacuo to yield 20 mg (66%) of the title compound.

15 ¹H NMR δ (CDCl₃) 7.40-7.10 (complex, 4H); 5.75 (s,
1H); 5.45 (s, 1H); 5.30 (t, 5 = 3 Hz, 1H); 5.20 (dd, J_a =
4 Hz, J_b = 2 Hz); 3.98 (d, J = 15 Hz, 1H); 3.85 (d, J = 15
Hz, 1H); 2.5-2.3 (complex, 2H); 2.0-1.7 (complex, 4H); ¹³C
NMR δ (CDCl₃); 17.77, 17.94, 24.43, 25.18, 38.11, 50.84,
20 52.40, 120.12, 124.73, 126.09, 127.90, 129.32, 137.03,
138.03, 142.74, 171.34, 174.45.

EXAMPLE 8

[4S-(4a,7a,12b β)]-7-[(benzoylthio)methyl]-
1,2,3,4,6,7,8,12b-Octahydro-6-Oxo-Pyrido[2,1-
25 a][2]Benzazepine-4-Carboxylic Acid (VII_b)

Thiolbenzoic acid (59 mg, 0.42 mmol) and 65 micro-
liters (0.47 mmol) triethylamine were added to a solution
of 115 mg (0.42 mmol) of the title compound of Example 7
in 7 ml methanol at ambient temperature under an
30 atmosphere of nitrogen. After stirring 24 hr., while the
reaction was still incomplete, the solution was
concentrated to 1 ml, then an additional 60 microliters

(0.43) triethylamine and 7 drops thiolbenzoic acid were added. After stirring an additional 24 hr., the reaction was quenched with excess 1N HCl then extracted into ethyl acetate. The ethyl acetate solution was washed once with
5 brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Some thiolbenzoic acid was removed by Kugelrohr distillation (60 °C/0.7 torr). The residue was allowed to cool yielding 190 mg (110%) of the crude title compound. The compound was purified by HPLC (7.5
10 mm x 250 mm 10 micron μ -porosil column; 0.5% acetic acid, 5% isopropanol, 94.5% hexane as eluant; 4 ml per min. flow rate), to yield 35 mg of the title compound (20%).

NMR δ (CDCl₃): 8.00 (d, J = 7 Hz, 2H); 7.60 (m, 1H);
7.45 (m, 2H); 7.25-7.05 (complex m, 4H); 5.55 (m, 1H);
15 5.25 (m, 1H); 3.90 (m, 1H); 3.50-3.35 (complex m, 3H);
2.95 (dd, J_a = 17 Hz, J_b = 13 Hz, 1H); 2.50 (complex d, J =
10 Hz, 1H); 2.35 (complex d, J = 10 Hz, 1H); 2.00 (complex
m, 2H); 1.80 (complex m, 2H).

The following compound can be prepared by substituting
20 thiolacetic acid for thiolbenzoic acid above, and following the procedure of Example 8: [4S-(4 α ,7 α ,12b β)]-1,2,3,4,6,7,8,12b-octahydro-7-[(acetylthio)methyl]-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid.

The following compound can be prepared by substituting
25 the unsaturated methyl ester title compound of Example 5 for the title compound of Example 7 and following the procedure of Example 8: [4S-(4 α ,7 α ,12b β)]-1,2,3,4,6,-7,8,12b-octahydro-7-[(benzoylthio)methyl]-6-oxo-pyrido-[2,1-a][2]benzazepine-4-carboxylic acid methyl ester.

30 Further treatment of the product just named above with an excess of sodium methoxide in degassed methyl alcohol for a short period of time under an atmosphere of nitrogen, and isolation by chromatography yields:

[4S-(4a,7a,12b β)]-1,2,3,4,6,7,8,12b-octahydro-7-(mercaptomethyl)-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid methyl ester.

The following compound can be prepared by treating the title compound of Example 8 with diazodiphenylmethane and isolating by chromatography: [4S-(4a,7a,12b β)]-1,2,3,4,6,7,8,12b-octahydro-7-[(benzoylthio)methyl]-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid diphenylmethyl ester.

Further treatment of the product just named above with an excess of sodium methoxide in degassed methyl alcohol for a short period of time under an atmosphere of nitrogen, and isolation by chromatography yields: [4S-(4a,7a,12b β)]-1,2,3,4,6,7,8,12b-octahydro-7-(mercaptomethyl)-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid diphenylmethyl ester.

EXAMPLE 9

[4S-(4a,7a,12b β)]-1,2,3,4,6,7,8,12b-Octahydro-7-(mercaptomethyl)-6-Oxo-Pyrido[2,1-a][2]Benzazepine-4-Carboxylic Acid (VII_a)

One molar sodium methoxide (350 microliters) was added to a solution of 27 mg (66 micromoles) of the title compound of Example 6 in 7 ml methanol deoxygenated with argon at ambient temperature under an atmosphere of argon. After stirring for 2 hr., the solution was made acidic with excess 1N HCl, saturated with sodium chloride, then extracted into ethyl acetate. The ethyl acetate solution was concentrated *in vacuo* yielding the title compound, which was purified by HPLC (7.5 mm x 250 mm 10 micron μ -Porisil column; 0.5% acetic acid, 5% isopropanol, 94.5% hexane as eluant; 4 ml per min. flow rate). The yield of the purified title compound was 10 mg (50%).

¹H NMR δ (CDCl₃): 7.25-7.00 (m, 4H); 5.55 (m, 1H);
5.20 (m, 1H); 5.75 (m, 1H); 3.30 (dd, J_a = 18 Hz, J_b = 8
Hz, 1H); 3.10 (dt, J_d = 13 Hz, J_t = 8 Hz, 1H); 2.85 (dd,
J_a = 14 Hz, J_b = J_b = 18 Hz, 1H); 2.50 (complex m, 2H);
5 2.35 (broad d, J = 10 Hz, 1H); 2.05-1.90 (complex, 2H);
1.85 (dd, J_a = 8 Hz, J_b = 10 Hz, 1H); 1.80-1.65 (complex,
2N). ¹³C NMR δ (CDCl₃): 175.26, 173.42, 136.90, 136.28,
130.68, 127.61, 125.71, 125.06, 50.92, 50.59, 44.78,
35.77, 26.50, 25.15, 25.11, 16.97.

10 The compounds of this invention are useful both in the
free carboxylate form and as salts. The expression
"pharmaceutically-acceptable salt" means any organic or
inorganic addition salt of the carboxylate compounds of
Formula I. These salts are included within the scope of
15 this invention. Such salts include ammonium salts; alkali
metal salts, such as sodium and potassium salts; alkaline
earth metal salts, such as the calcium and magnesium
salts; salts with organic bases such as, for instance,
dicyclohexylamine salts, N-methyl-D-glucamine, and salts
20 with amino acids such as arginine and lysine; and the
like. The non-toxic, physiologically acceptable salts are
preferred, although other salts are also useful, for, for
example, isolating or purifying the product.

The salts can be formed by conventional means such as
25 by reacting the free acid forms of the product with one or
more equivalents of the appropriate base in a solvent or
medium in which the salt is insoluble, or in a solvent
such as water which is then removed *in vacuo* or by freeze-
drying, or by exchanging the cations of an existing salt
30 for another cation on a suitable ion exchange resin.

The utility of the compounds of this invention as
antihypertensive agents can be determined by the
evaluation of ACE inhibition in *in vitro* enzyme inhibition

assays. For example, a useful method of evaluation is that of Y. Piquilloud, A. Reinharz and M. Roth, Biochem. Biophys. Acta, 206, N36 (1970), in which the hydrolysis of cardobenzylxyphenylalanylhistidinyl-leucine is measured.

5 *In vivo* evaluations may be made, for example, in normotensive rats challenged with angiotensin I by the technique of J. R. Weeks and J. A. Jones, Proc. Spc. Exp. Biol. Med., 104, 646 (1960), or in a high renin rat model such as that of S. Koletsky, *et al.*, Proc. Soc. Exp. Biol. Med., 125, 96 (1967).

10

The following Table indicates the activity of a compound of this invention as an ACE inhibitor as determined by a standard and well known procedure for assaying the enzyme-enhanced conversion of a substrate

15 into product as an indication of enzyme activity. This procedure utilizes a continuous, spectrophotometric method for following the pre-equilibrium interaction of ACE with the substrate/product complex as set forth by Holmquist, *et al.*, in Analytical Biochemistry, 95, (1979) 540-548.

20 Substrate, 1mM 2-furanacryloyl-L-Phe-Gly-Gly, and inhibitor, at the indicated concentration, were thermally equilibrated in 2 ml of buffer to 25 °C in the chamber of a Cary 210 spectrophotometer, then rabbit lung ACE was added to complete the assay mixture, and the reaction

25 monitored and recorded by computer. Captopril, a known ACE inhibitor, was used as a positive control for the assay. The significantly reduced amount of product formed when the reaction is run in the presence of the compound of this invention demonstrates the compound's usefulness

30 as an ACE inhibitor as illustrated in Table I.

TABLE I

Concentration of inhibitor	Time	Concentration of end product
5 Captopril, 10nM (positive control)	8 min.	160nM
Compound 1*, 10nM	8 min.	95nM
Compound 1*, 5nM	8 min.	148nM

*Compound 1 is [4S-(4 alpha,7 alpha,12b beta)]-
1,2,3,4,6,7,8,12b-octahydro-7-(mercaptomethyl)-6-oxo-
10 pyrido[2,1-a][2]benzazepine-4-carboxylic acid; i.e. where
R and R' are both hydrogen.

The amount of the active ingredient to be administered
to a patient for the treatment of hypertension can vary
widely according to such considerations as the particular
15 dosage unit employed, the period of treatment, the age and
sex of the patient treated, and the nature and extent of
the disorder treated. The total amount of the active
ingredient to be administered will generally range from
about 0.1 mg/kg to 100 mg/kg and preferably from 0.3 mg/kg
20 to 30 mg/kg. A unit dosage may contain from 25 to 525 mg
of active ingredient, and can be taken one or more times
per day. The compound of Formula I can be administered
with a pharmaceutical carrier using conventional dosage
unit forms either orally, parenterally, topically, or the
25 like, as described below.

The compounds of this invention can be administered as
the sole anti-hypertensive agent or in combination with
other anti-hypertensives and/or diuretics and/or calcium

entry blockers. For example, the compounds of this invention can be given in combination with such compounds as benzthiazide, clonidine, deserpidine, furosemide, hydralazine hydrochloride, indacrinone and variable ratios of its enantiomers, prazosin, propanolol, reserpine, and the like, as well as admixtures and combinations thereof.

Typically, the individual daily dosages for these combinations can range from about one fifth of the minimally recommended clinical dosages to the maximum recommended levels for the entities when they are given singly.

The ability of the compounds of this invention to reduce reperfusion injury can be demonstrated by their ability reduce myocardial stunning. Myocardial stunning is the prolonged loss of contractile function in the absence of necrosis following short periods of myocardial ischemia. (See, E. Braunwald and R. A. Kloner, Circ. 66, 1146-1149 (1982). Stunning has been implicated in a variety of disorders and conditions in which blood circulation has been temporarily cut off from the heart or in which a relatively high concentration of oxygen derived free radicals is known to be present.

In order to measure stunning, an anesthetized dog is instrumented to record blood pressure, heart rate electrocardiogram (ECG), cardiac contractile force, and left intraventricular systolic pressure and its derivative. Two crystal sets each with two crystals are implanted in the left myocardium to measure shortening of the myocardial segments between the crystals of each set. One set is placed toward the base and the other toward the apex. The apical crystal set is placed to be within the ischemic area during occlusion of the left anterior descending coronary artery (LAD) at the intermediate

point. The basal set of crystals are placed to be in the normal myocardium during ischemia. Following a control period, the LAD is occluded for 15 minutes followed by 3 hours of reperfusion. A short period of occlusion is used
5 to prevent any substantial necrosis. During the period of occlusion, the shortening of the myocardial segment between the apical crystals (ischemic myocardium) decreases and actually shows a lengthening during contraction in control dogs whereas the shortening between
10 the basal crystals (nonischemic myocardium) is maintained. When the occlusion period is ended and reperfusion of the ischemic myocardium has commenced, contractility of the previously ischemic area improves but does not recover during the 3 hour reperfusion period. This disparity in
15 contractility (reported as per cent shortening) between the normal and previously ischemic region is referred to as stunning and is reported below in Table 1. To avoid any possible effect on stunning by the positive inotropic activity of the compound of this invention, the positive
20 inotropic effect of the compound was allowed to dissipate at least 80% prior to occlusion of the LAD.

For use in the treatment of reperfusion injury (ischemia), the compound of Formula I will ideally be administered to the patient at the time of tissue
25 reperfusion and treatment therewith will continue until such time that reperfusion injury of the type being treated has normally ceased, which will typically be for about 2 to 3 days following substantial reperfusion of the tissue. For example, the compounds of Formula I could
30 conveniently be administered to a patient with a coronary thrombosis concurrently with the administration of a clot dissolving agent such as streptokinase or urokinase. Administration of compounds of Formula I prior to an
ischemia may be indicated in certain instances such as
35 where a patient has substantial risk of heart attack or

stroke and would continue until the risk of an ischemic event has substantially disappeared, for example, where the patient has recently suffered a heart attack or stroke, or where the patient is to undergo a surgical
5 procedure requiring a temporary, surgically-induced organ ischemia such as in open heart surgery or coronary by-pass surgery.

The amount of the active ingredient to be administered in the treatment of ischemia can vary widely according to
10 such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the disorder treated. The total amount of the active ingredient to be administered will
15 generally range from about 0.1 mg/kg to 100 mg/kg and preferably from 0.3 mg/kg to 30 mg/kg. A unit dosage may contain from 25 mg to 525 mg of active ingredient, and can be taken one or more times per day. The active compound of formula 1 can be administered with a pharmaceutical
20 carrier using conventional dosage unit forms either orally, parenterally, topically, or the like, as described below.

The utility of the compounds of Formula I as cardiogenic agents may be determined by administering the
25 test compound (0.1-100 mg/kg) intravenously, intraperitoneally, intraduodenally, or intragastrically in a suitable vehicle to a mongrel dog (either sex). The test dogs are anesthetized and prepared by isolating a suitable artery (e.g., femoral or common carotid) and vein
30 (e.g., femoral or external jugular) and introducing polyethylene catheters filled with 0.1% heparin-sodium to record arterial blood pressure and administer compounds, respectively. The chest is opened by splitting the sternum at the midline or by an incision at the left fifth

intercostal space, and a pericardial cradle is formed to support the heart. A Walton-Brodie strain gage is sutured to the right or left ventricle to monitor myocardial contractile force. An electromagnetic flow probe may be placed around the root of the ascending aorta for measuring cardiac output less coronary blood flow. A catheter may also be put into the left atrium or the left ventricle of the heart to record left atrial pressure or left ventricular pressure. Heart failure is induced by administering sodium pentobarbital (20 to 40 mg/kg) followed by a continuous infusion of 0.25 - 2 mg/kg/min. or propranolol hydrochloride (4 mg/kg) followed by a continuous infusion of 0.18 mg/kg/min. to the blood perfusing the heart. Following administration of either of the cardiac depressants, the right atrial pressure dramatically increases and cardiac output is severely depressed. Reversal of these effects by the test compound indicates cardiogenic activity.

The amount of the active ingredient to be administered to the patient for the treatment of cardiogenic shock can vary widely according to such considerations as the particular compound and dosage unit employed, the period of treatment, the age and sex of the patient treated, and the nature and extent of the disorder treated. The total amount of the active ingredient to be administered will generally range from about 0.1 mg/kg to 100 mg/kg and preferably from 0.3 mg/kg to 20 mg/kg. A unit dosage may contain from 25 mg to 500 mg of active ingredient, and can be taken one or more times per day. The compounds of Formula I can be administered with a pharmaceutical carrier using conventional dosage unit forms either orally, parenterally, topically, or the like, as described below.

The compounds of this invention can be utilized to achieve the desired pharmacological effect by

administration to a patient in need thereof in an appropriately formulated pharmaceutical composition. Therefore, the present invention includes pharmaceutical compositions which are comprised of a pharmaceutically-acceptable carrier and a pharmaceutically-effective amount of a compound of Formula I. A pharmaceutically-effective amount of compound is that amount which produces a result or exerts an influence on the particular condition being treated. The compounds of Formula I can be administered with a pharmaceutical carrier using conventional dosage unit forms either orally, parenterally, topically, or the like. A patient, for the purposes of this invention, is a mammal, including humans, in need of treatment for a particular condition, injury, or disease.

For oral administration the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions and may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms can be a capsule which can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and cornstarch. In another embodiment, the compounds of this invention can be tableted with conventional tablet bases such as lactose, sucrose, and cornstarch in combination with binders such as acacia, cornstarch, or gelatin, disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum, lubricants intended to improve the flow of tablet granulations and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example, talc, stearic acid, or magnesium, calcium, or

zinc stearate, dyes, coloring agents, and flavoring agents intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include
5 diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and the polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent.

The compounds of this invention may also be
10 administered parenterally, that is, subcutaneously, intravenously, intramuscularly, or interperitoneally, as injectable dosages of the compound in a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid or mixture of liquids such as water,
15 saline, aqueous dextrose and related sugar solutions, an alcohol such as ethanol, isopropanol, or hexadecyl alcohol, glycols such as propylene glycol or polyethylene glycol, glycerol ketals such as 2,2-dimethyl-1,3-dioxolane-4-methanol, ethers such as poly(ethyleneglycol)
20 400, an oil, a fatty acid, a fatty acid ester or glyceride, or an acetylated fatty acid glyceride with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as pectin, carbomers, methylcellulose,
25 hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutically adjuvants. Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example,
30 peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum, and mineral oil. Suitable fatty acids include oleic acid, stearic acid, and isostearic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable
35 soaps include fatty alkali metal, ammonium, and

triethanolamine salts and suitable detergents include cationic detergents, for example, dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamines acetates; anionic detergents, for example, alkyl, aryl, 5 and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates; nonionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylenepolypropylene copolymers; and amphoteric detergents, for example, alkyl- 10 beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures. The parenteral compositions of this invention will typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used 15 advantageously. In order to minimize or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulations ranges from 20 about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB. Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty 25 acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The pharmaceutical compositions may be in the form of 30 sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethyl-cellulose, methylcellulose, hydroxypropylmethyl-cellulose, 35 sodium alginate, polyvinylpyrrolidone, gum tragacanth and

gum acacia; dispersing or wetting agents which may be a naturally-occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a
5 condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadecaethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol such as polyoxyethylene sorbitol
10 monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example, polyoxyethylene sorbitan monooleate.

The suspensions may also contain one or more
15 preservatives, for example, ethyl or n-propyl p-hydroxybenzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the
20 active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin or cetyl alcohol. The sterile
25 injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, and isotonic sodium chloride solution. In
30 addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables.

A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating
5 excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are, for example, cocoa butter and polyethylene glycol.

For topical use, a cream, ointment, jelly, solution,
10 suspension, or the like, which contains a composition of this invention, can be employed.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the
15 active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example those
20 sweetening, flavoring, and coloring agents described above, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a
25 mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally-occurring gums such as gum acacia and gum tragacanth, (2) naturally-occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived from fatty acids and hexitol anhydrides, for
30 example, sorbitan monooleate, (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening
35 agents such as, for example, glycerol, propylene glycol,

sorbitol or sucrose. Such formulations may also contain a demulcent, and preservative and flavoring and coloring agents.

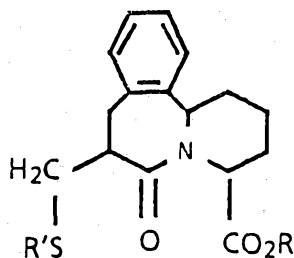
For administration, the compositions of the invention
5 can also contain other conventional pharmaceutically acceptable compounding ingredients as necessary or desired. For example, the compositions may include such ingredients generally referred to as carriers or diluents. These compositions may also be preserved by the addition
10 of an antioxidant such as ascorbic acid or other suitable preservative.

Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized. Whatever the dosage form, it will contain a
15 pharmaceutically effective amount of the compound of this invention.

It should be apparent to one of ordinary skill in the art that changes and modifications can be made to this invention without departing from the spirit or scope of
20 the invention as it is set forth herein.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

- 1 1. A compound of the formula



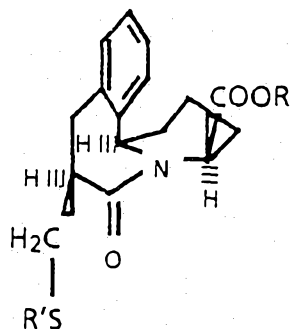
3 wherein

4 R is hydrogen; C₁-C₆ lower alkyl, or (C₆-C₁₂)aryl(C₁-
5 C₆)lower alkyl; and

6 R' is hydrogen or -COR, wherein R is as defined above,
7 and the pharmaceutically acceptable salts thereof.

- 1 2. All enantiomeric isomers and diastereomeric isomers
2 and mixtures thereof of a compound of Claim 1.

- 1 3. A compound of either one of Claims 1 or 2 of the diastereomeric
2 configuration:

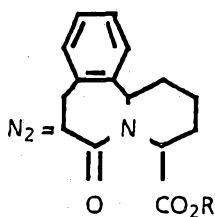


4 wherein the stereochemistry is 4(S), 7(S), 12b(R).

1 4. A compound of Claim 3 wherein R and R' are both
2 hydrogen.

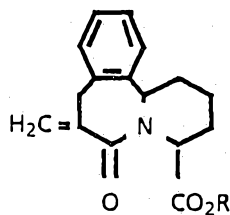
1 5. A compound of Claim 3 wherein R is methyl and R' is
2 hydrogen.

1 6. A compound of the formula



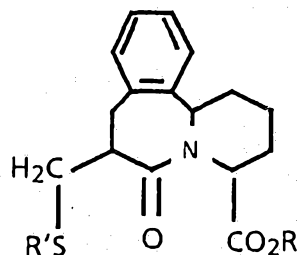
3 wherein R is C_1-C_6 lower alkyl, or (C_6-
4 C_{12})aryl(C_1-C_6)lower alkyl.

1 7. A compound of the formula



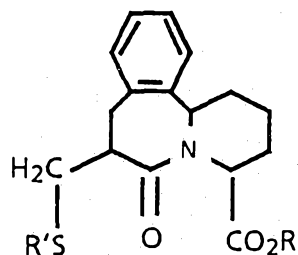
3 wherein R is hydrogen, C_1-C_6 lower alkyl, or
4 (C_6-C_{12})aryl(C_1-C_6)lower alkyl.

1 8. A method of treating hypertension which comprises
2 administering to a patient in need thereof a compound of
3 the formula



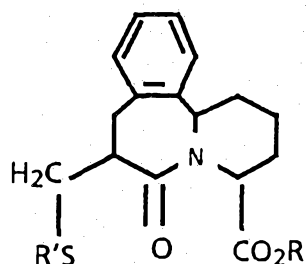
5 wherein R is hydrogen, C₁-C₆ lower alkyl, or (C₆-
 6 C₁₂)aryl(C₁-C₆)lower alkyl; and
 7 R' is hydrogen or -COR, wherein R is as defined above,
 8 or the pharmaceutically-acceptable salts thereof, in an
 9 amount necessary to effect an antihypertensive result.

1 9. A method of treating cardiotionia which comprises
 2 administering to a patient in need thereof a compound of
 3 the formula



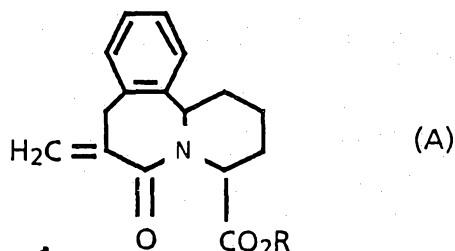
5 wherein R is hydrogen, C₁-C₆ lower alkyl, or (C₆-
 6 C₁₂)aryl(C₁-C₆)lower alkyl; and
 7 R' is hydrogen or -COR, wherein R is as defined above,
 8 or the pharmaceutically-acceptable salts thereof, in an
 9 amount necessary to effect an enhancement of myocardial
 10 contractile force.

1 10. A method of treating ischemia which comprises
 2 administering to a patient in need thereof a compound of
 3 the formula

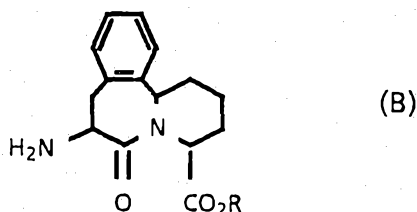


6 wherein R is hydrogen, C₁-C₆ lower alkyl, or (C₆-
 7 C₁₂)aryl(C₁-C₆)lower alkyl; and
 8 R' is hydrogen or -COR, wherein R is as defined above,
 9 or the pharmaceutically-acceptable salts thereof, in a
 quantity necessary to effect an anti-ischemic result.

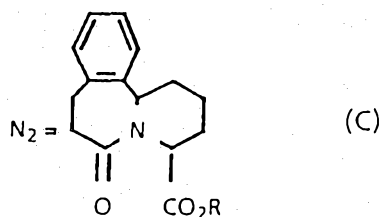
1 11. A process for preparing a compound of the formula



4 wherein R is hydrogen, C₁-C₆ lower alkyl, or (C₆-
 5 C₁₂)aryl(C₁-C₆)lower alkyl,
 which comprises reacting a compound of the formula



8 wherein R is as defined above
 9 with an alkyl nitrite of the formula R''ON=O, wherein R'' is
 10 isoamyl or n-propyl, in the presence of acetic acid and an
 11 inert solvent under reflux conditions, to produce an
 intermediate compound of the formula



and sequentially treating C first with strong acid and a phosphine selected from the group consisting of tributylphosphine or triphenylphosphine, at a temperature of about -70°C to about 50°C, and then with a strong base and formaldehyde to produce the compound of Formula A.

12. A compound as claimed in any one of claims 1, 6 or 7 substantially as hereinbefore described with reference to any one of the examples.

13. A method as claimed in any one of claims 8 to 10 substantially as hereinbefore described with reference to any one of the examples.

14. A process as claimed in claim 11 substantially as hereinbefore described with reference to any one of the examples.

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