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With international search report.

(54) Title: PROCESSES AND INTERMEDIATES IN THE SYNTHESIS OF 5-(3-[EXO-BICYCLO[2.2.1]HEPT-2-YLOXY]-4-METHOXYPHENYL)-3,4,5,6-TETRAHYDROPYRIMIDIN-2(1H)-ONE

(57) Abstract

This invention relates to novel processes for preparing the pharmaceutically active compound 5-(3-[(2S)-exo-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyphenyl)-3,4,5,6-tetrahydropyrimidin-2(1H)-one and its corresponding 2R enantiomer and for preparing certain intermediates used in the synthesis of these compounds. It also relates to novel intermediates used in the synthesis of such pharmaceutically active compounds and to other novel compounds that are related to such intermediates.

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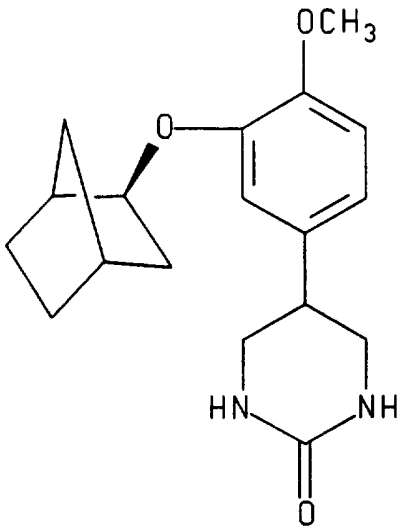
PROCESSES AND INTERMEDIATES IN THE SYNTHESIS OF 5-(3-[EXO-BICYCLO[2.2.1]HEPT-2-YLOXY]-4-METHOXYPHENYL)-3,4,5,6-TETRAHYDROPYRIMIDIN-2(1H)-ONE

Background of the Invention

This invention relates to novel processes for preparing the pharmaceutically active compound 5-(3-[(2S)-exo-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyphenyl)-3,4,5,6-tetrahydropyrimidin-2(1H)-one and its corresponding 2R enantiomer and for preparing certain intermediates used in the synthesis of these compounds. It also relates to novel intermediates used in the synthesis of such pharmaceutically active compounds and to other novel compounds that are related to such intermediates.

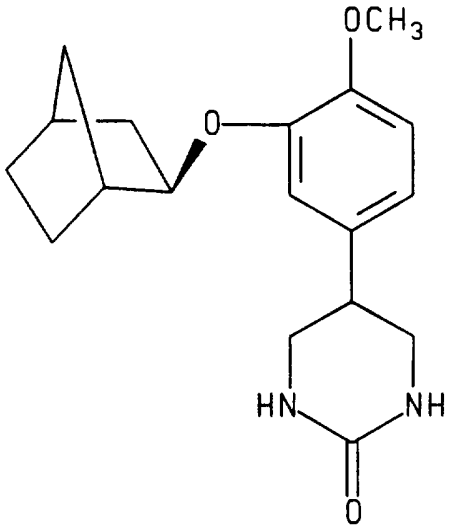
International Patent Application WO 87/06576, which was published on November 5, 1987, refers to 5-(3-[(2-exo-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyphenyl)-3,4,5,6-tetrahydropyrimidin-2(1H)-one, and states that it is useful as an antidepressant. International Patent Application WO 91/07178, which was published on May 30, 1991, refers to the utility of this compound in the treatment of asthma, inflammatory airway diseases and skin diseases.

United States Patent 5,270,206, which issued on December 14, 1993, refers to a process for preparing (+)-(2R)-endo-norborneol (also referred to as (2R)-endo-bicyclo[2.2.1]heptan-2-ol or (1S, 2R, 4R)-bicyclo[2.2.1]heptan-2-ol) and (-)-(2S)-endo-norborneol (also referred to as (2S)-endo-bicyclo[2.2.1]heptan-2-ol or (1R, 2S, 4S)-bicyclo[2.2.1]heptan-2-ol), and to their further conversion into the pharmaceutically active agents 5-(3-[(2S)-exo-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyphenyl)-3,4,5,6-tetrahydropyrimidin-2(1H)-one, depicted below,



VI

and 5-(3-[(2R)-exo-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyphenyl)-3,4,5,6-tetrahydropyrimidin-2(1H)-one, depicted below,

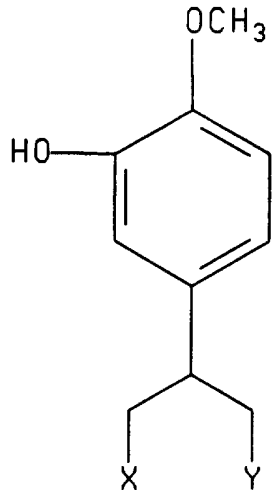


VI'

All documents cited herein, including the foregoing, are incorporated herein by reference in their entireties.

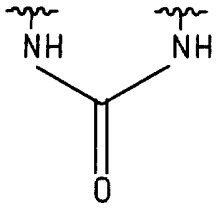
Summary of the Invention

This invention relates to a compound having the formula



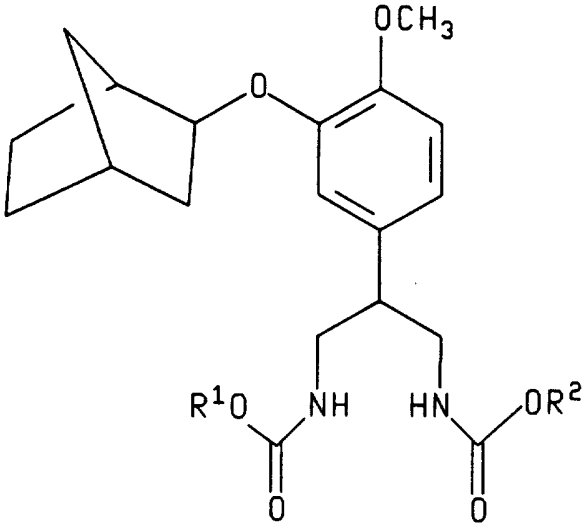
(II)

wherein X and Y are the same and are selected from -CN, $-CO_2(C_1-C_6)$alkyl, $-CONH_2$ and -CONHOH, or X and Y, taken together, form a group of the formula



(a)

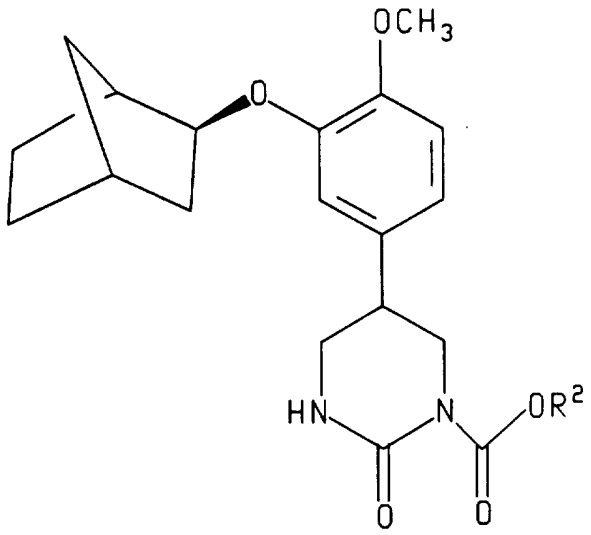
This invention also relates to a compound having the formula



(V)

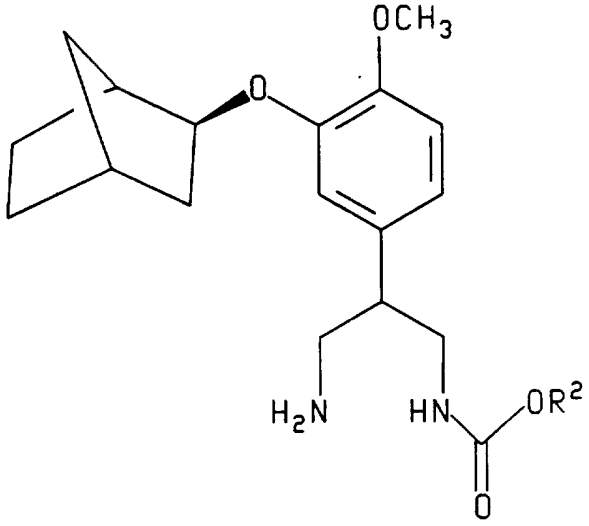
wherein R^1 and R^2 are independently selected from (C_1-C_6)alkyl and hydrogen.

This invention also relates to compounds of the formulae



(VIII)

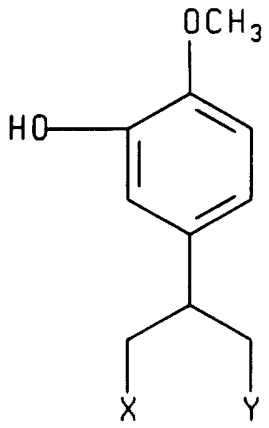
and



(VII)

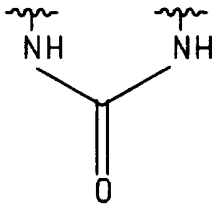
wherein each R^2 is independently selected from (C_1-C_6) alkyl.

This invention also relates to a process for preparing a compound of the formula



(II)

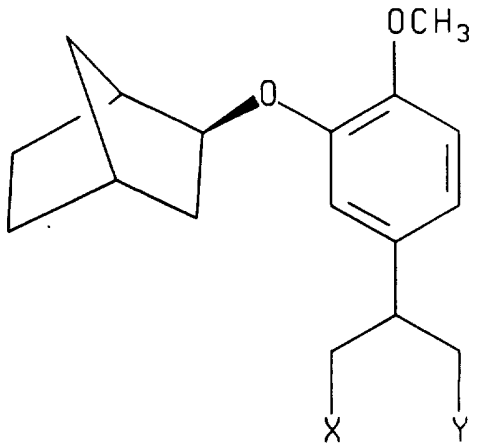
wherein X and Y are the same and are selected from -CN, $-CO_2(C_1-C_6)$alkyl, $-CONH_2$ and -CONHOH, or X and Y, taken together, form a group of the formula



(a)

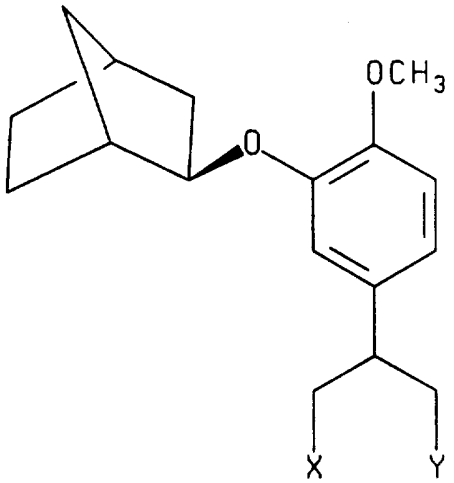
comprising: (1) reacting 3-hydroxy-4-methoxybenzaldehyde with a compound of the formula XCH_2CO_2H, wherein X is defined as above, in the presence of a base, preferably a tertiary amine, to yield a compound of the formula II wherein X and Y are both -CN, $-CO_2(C_1-C_6)$alkyl, $-CONH_2$ or -CONHOH; or (2) (a) reacting a compound of the formula II wherein X and Y are both -CN with hydrogen peroxide, preferably basic aqueous hydrogen peroxide, to form the corresponding bis-amide in which both -CN groups are replaced by $-CONH_2$; (b) subjecting the bis-amide formed in step (a) to a Hoffman rearrangement using an oxidizing agent (e.g., bis(acetoxy)iodobenzene, bis(trifluorocetoxy)iodobenzene, NaOCl, NaOBr or lead tetraacetate) to form the corresponding biscarbamate; and (c) reacting the biscarbamate formed in step (b) with a base (e.g., an alkali metal alkoxide containing from one to six carbon atoms or an alkali metal hydroxide), to form a cyclic urea wherein X and Y, taken together, form a group of the formula "a", as depicted above.

This invention also relates to a process for preparing a compound of the formula



(III)

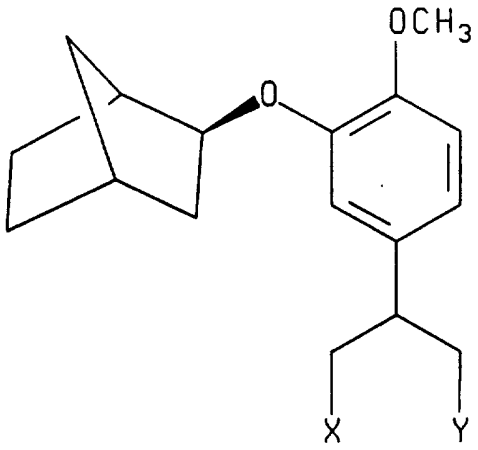
or



(III')

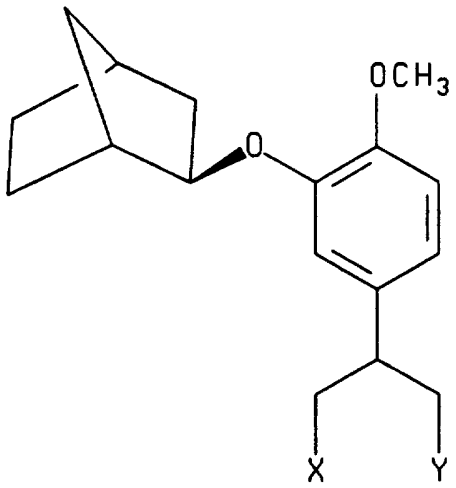
wherein X and Y are defined as for formula II above, comprising reacting a compound of formula II, as defined above, with, respectively, R-(+)-endo-norborneol or S-(-)-endo-norborneol, a triaryl or trialkyl phosphine and an azo dicarboxylate.

This invention also relates to a process for preparing a compound of the formula



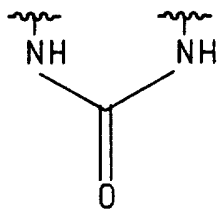
(III)

or



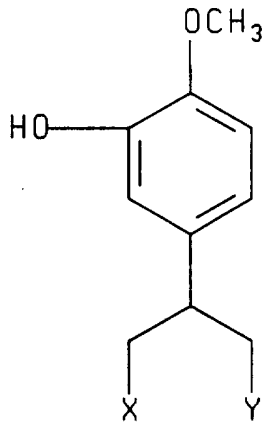
(III')

wherein X and Y are the same and are selected from -CN, -$CONH_2$, $CO_2(C_1$-$C_6)$alkyl and -CONHOH, or X and Y, taken together, form a group of the formula



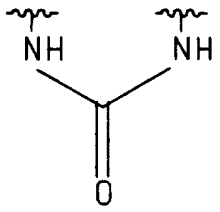
(a)

comprising: (1) reacting 3-hydroxy-4-methoxybenzaldehyde with a compound of the formula XCH_2CO_2H, wherein X is -CN, -$CO_2(C_1$-$C_6)$alkyl, -$CONH_2$ or -CONHOH, in the presence of a base, preferably a tertiary amine, to form a compound of the formula



(II)

wherein X and Y are the same and are selected from -CN, -$CONH_2$, -$CO(C_1$-$C_6)$alkyl and -CONHOH; or (2) (a) reacting a compound of the formula II wherein X and Y are both -CN with hydrogen peroxide to form the corresponding bis-amide in which both -CN groups are replaced by -$CONH_2$; (b) subjecting the bis-amide formed in step (a) to a Hoffman rearrangement using an oxidizing agent (e.g., bis(acetoxy)iodobenzene, bis(trifluorocetoxy)iodobenzene, NaOCl, NaOBr or lead tetraacetate) to form the corresponding biscarbamate; and (c) reacting the biscarbamate formed in step (b) with a base (e.g., an alkali metal alkoxide containing from one to six carbon atoms), to form a cyclic area wherein X and Y, taken together, form a group of the formula

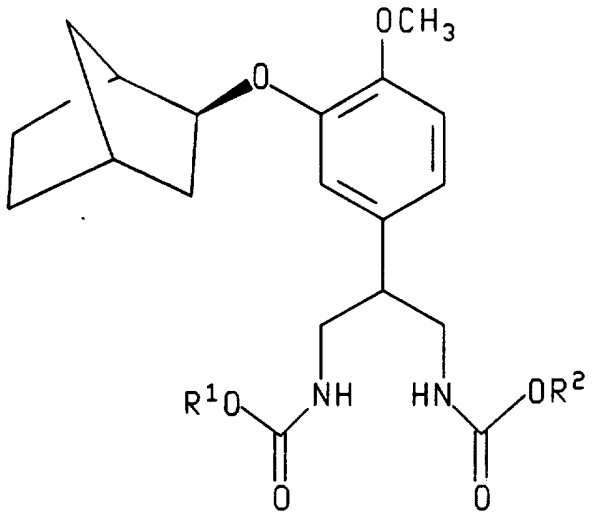


(a)

;

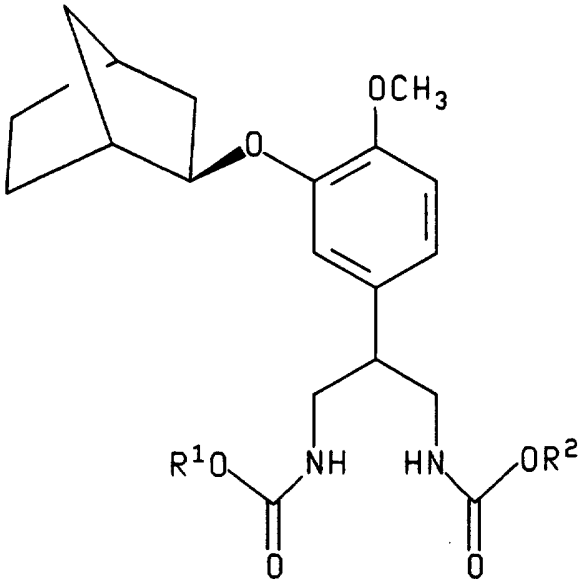
and then (3) reacting said compound of formula II so formed in step 1 or 2 above with, respectively, R-(+)-endo-norborneol or S-(-)-endo-norborneol, a triaryl or trialkyl phosphine and an azo dicarboxylate.

This invention also relates to a process for preparing a compound of the formula



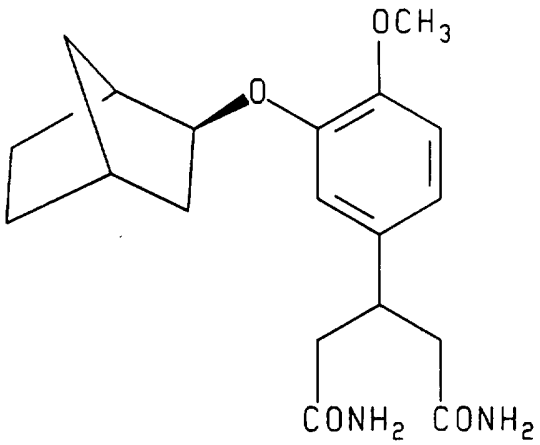
(V)

or



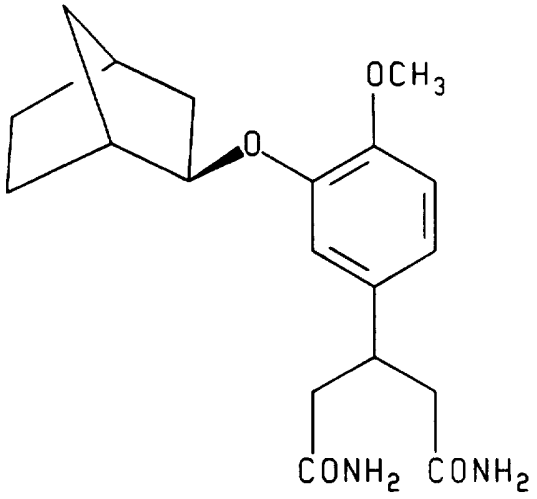
(V')

wherein R^1 and R^2 are independently selected from hydrogen and $(C_1\text{-}C_6)$alkyl, comprising reacting, respectively, a compound of the formula



(IV)

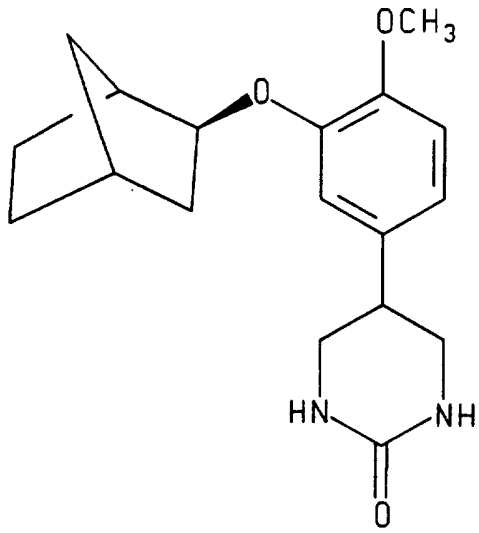
or



(IV')

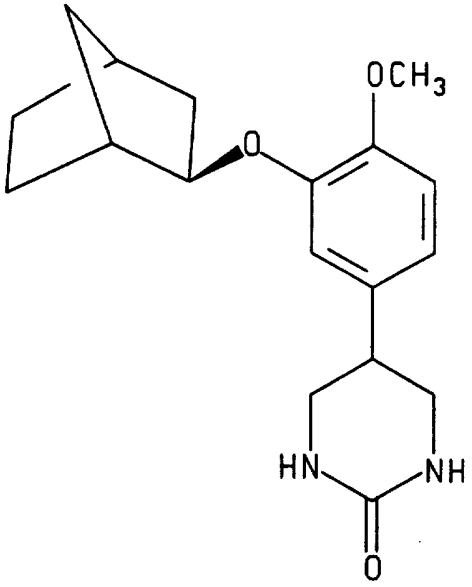
with diacetoxyiodobenzene, NaOZ and Z'OH, wherein Z and Z' are independently selected from hydrogen and (C_1-C_6)alkyl.

This invention also relates to a process for preparing a compound of the formula



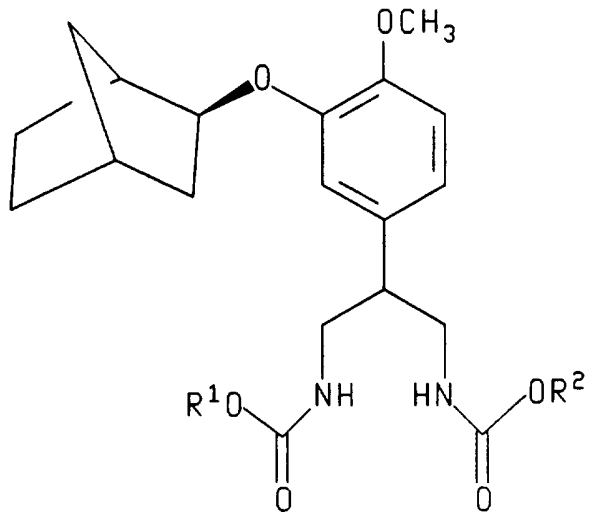
(VI)

or



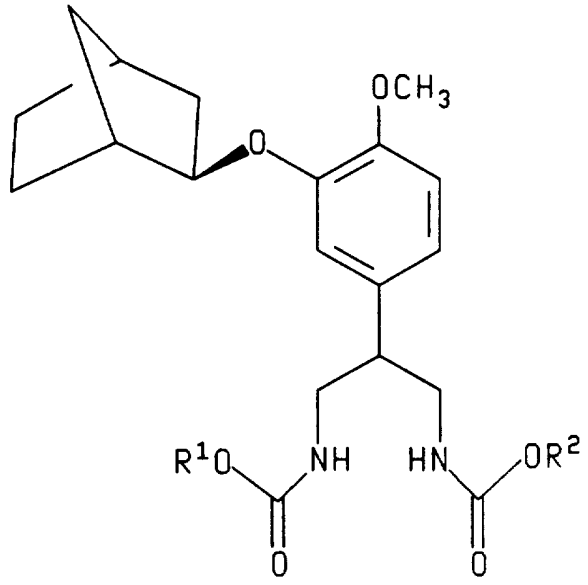
(VI')

comprising reacting, respectively, a compound of the formula



(V)

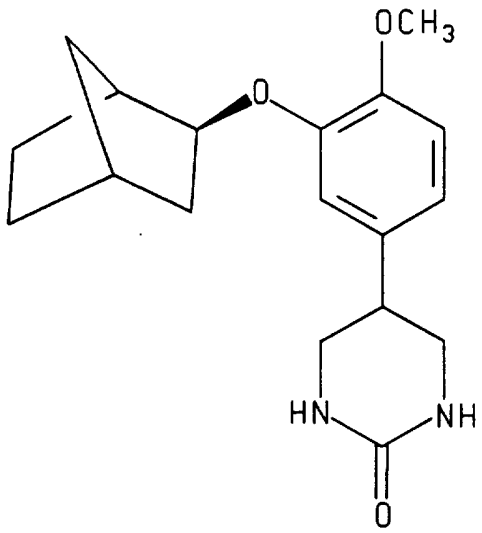
or



(V′)

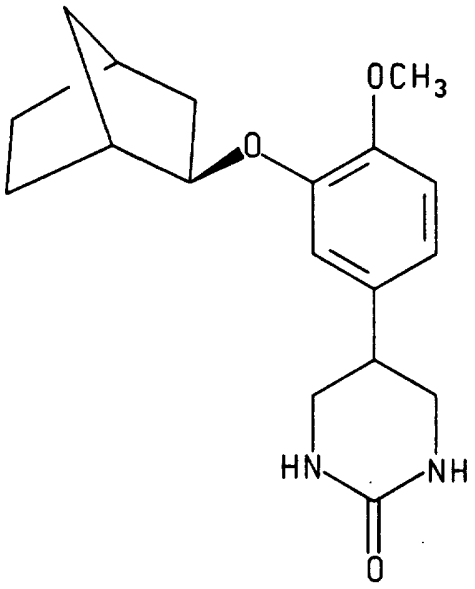
wherein R^1 and R^2 are independently selected from hydrogen and $(C_1\text{-}C_6)$alkyl with compounds of the formulae NaOZ and Z′OH, wherein Z and Z′ are independently selected from hydrogen and $(C_1\text{-}C_6)$alkyl.

This invention also relates to a process for preparing a compound of the formula



(VI)

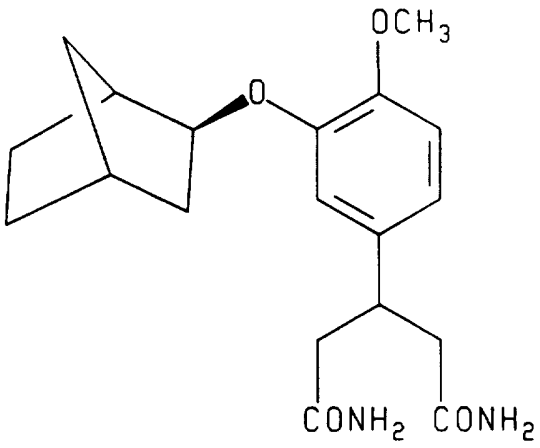
or



(VI')

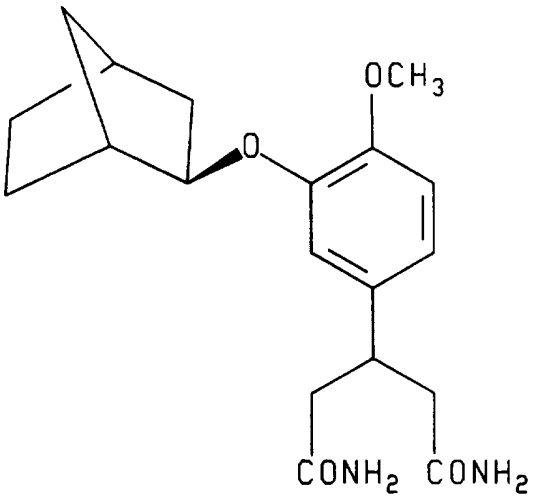
comprising:

reacting, respectively, a compound of the formula



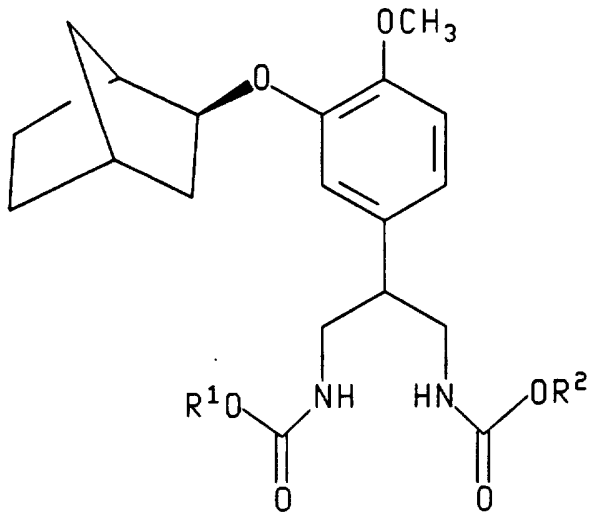
(IV)

or



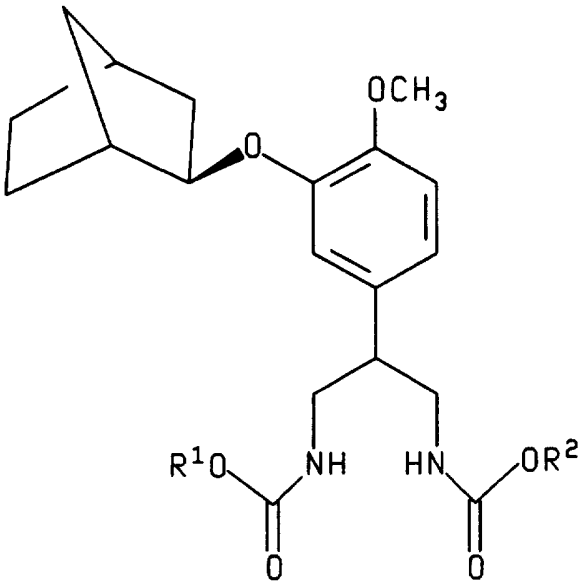
(IV')

with diacetoxyiodobenzene, NaOZ and Z'OH, wherein Z and Z' are independently selected from hydrogen and (C_1-C_6)alkyl, to form an intermediate of the formula



(V)

or



(V')

wherein R^1 and R^2 are independently selected from hydrogen and (C_1-C_6)alkyl; and then either

(b1) isolating said intermediate of formula V or V' and reacting it with compounds of the formulae NaOZ and Z'OH, wherein Z and Z' are defined as above; or

(b2) reacting said intermediate of formula V or V' in situ with compounds of the formula NaOZ and Z'OH, wherein Z and Z' are defined as above.

As used herein, the expression "reaction inert solvent" refers to a solvent which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product or products.

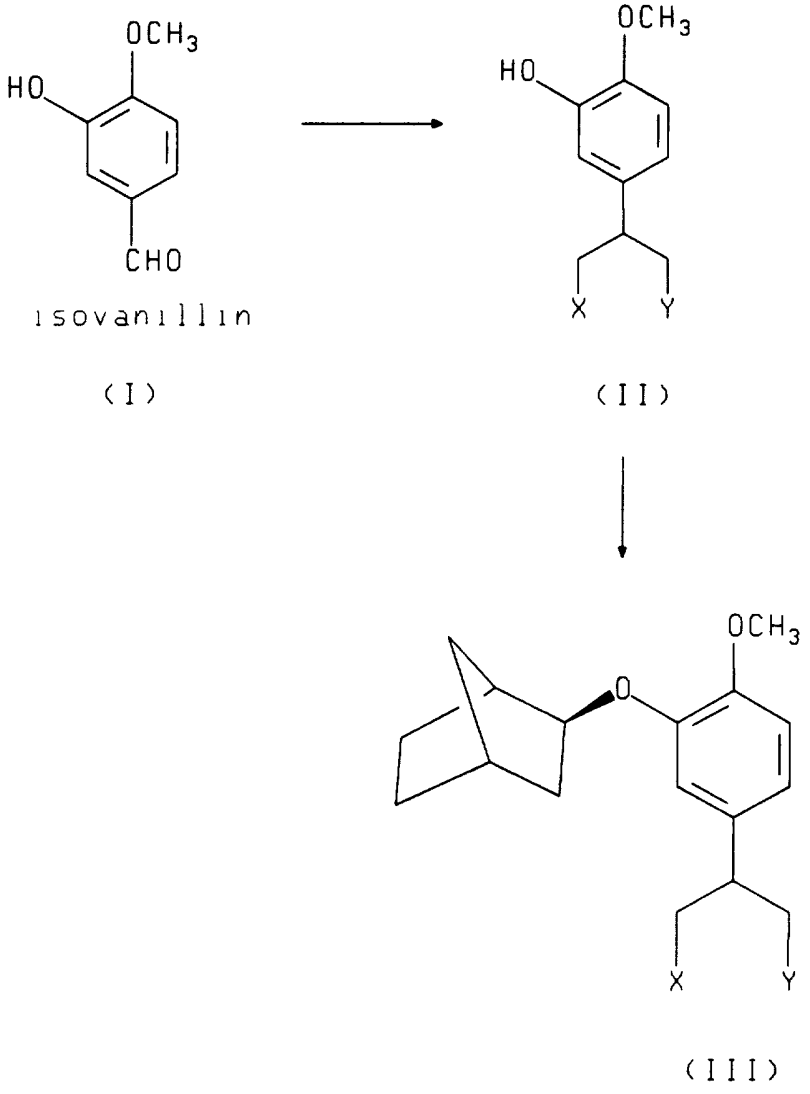
The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

Formulae II, and V and V′ above include compounds identical to those depicted but for the fact that one or more hydrogen, carbon, nitrogen or oxygen atoms are replaced by radioactive or stable isotopes thereof. Such radiolabelled compounds are useful as research and diagnostic tools in metabolism pharmacokinetic studies and in binding assays.

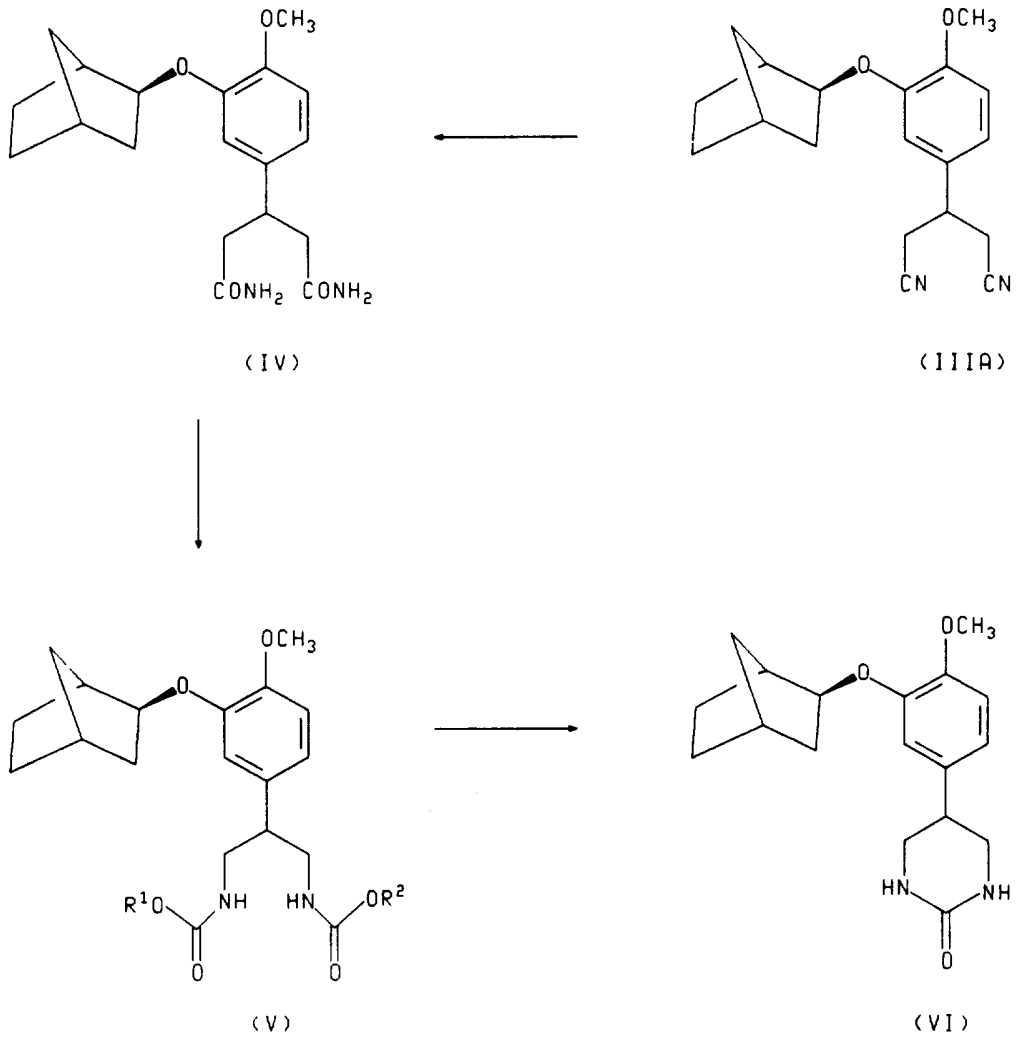
Detailed Description of the Invention

The processes of the this invention and methods of preparing the novel compounds of this invention are described in the following reaction schemes and discussion. Unless otherwise indicated, the substituents X, Y, R, R^1, R^2, R^3, and R^4, group "(a)" and formulae II, III, III′, IV, IV′, V, V′, VI and VI′ in the reaction schemes and discussion that follow are defined as above.

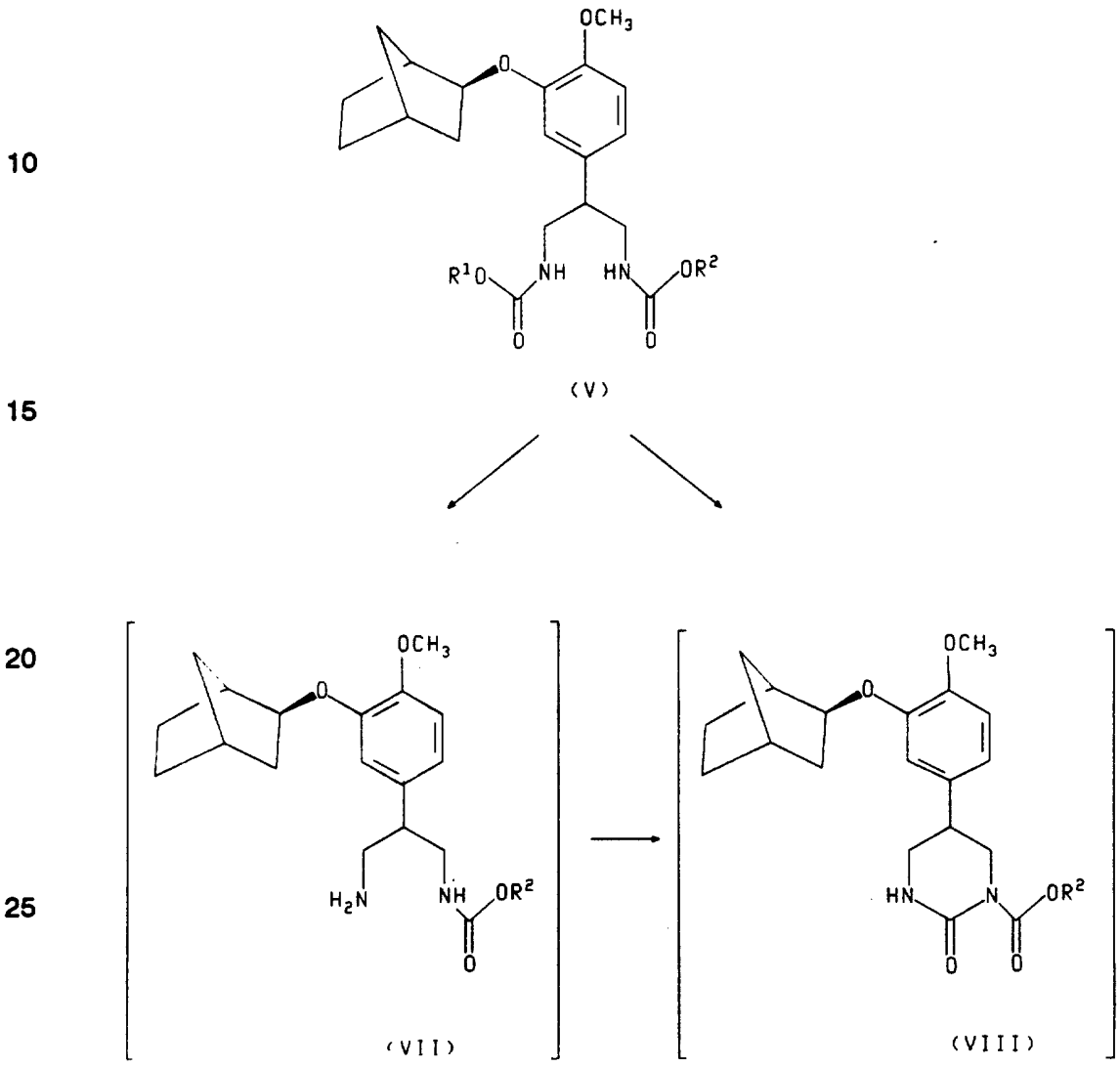
SCHEME 1



SCHEME 2

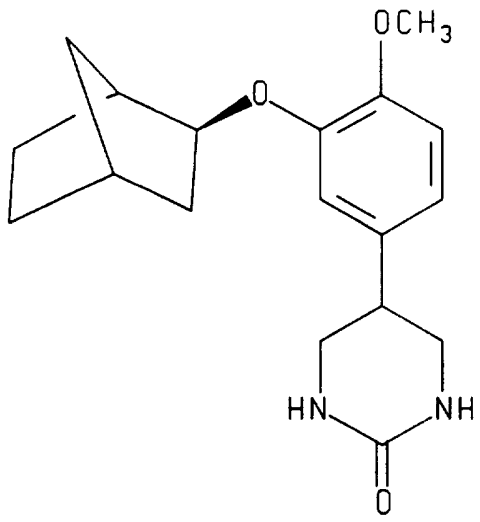

OCH3
O
CONH2 CONH2
(IV)
OCH3
O
CN CN
(IIIA)
OCH3
O
R1O NH HN OR2
O O
(V)
OCH3
O
HN NH
O
(VI)

SCHEME 2A


OCH3
O
R1O
NH
HN
OR2
O
O
(V)
OCH3
O
H2N
NH
OR2
O
(VII)
OCH3
O
HN
N
OR2
O
O
(VIII)

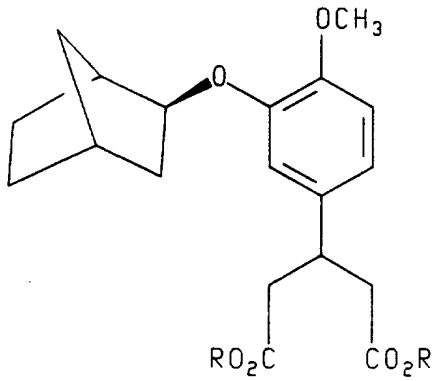
SCHEME 2A cont'd

(VII) (VIII)



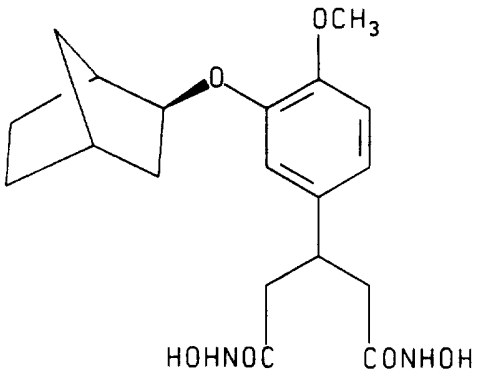
(VI)

SCHEME 3



(R=(C_1-C_6)alkyl)

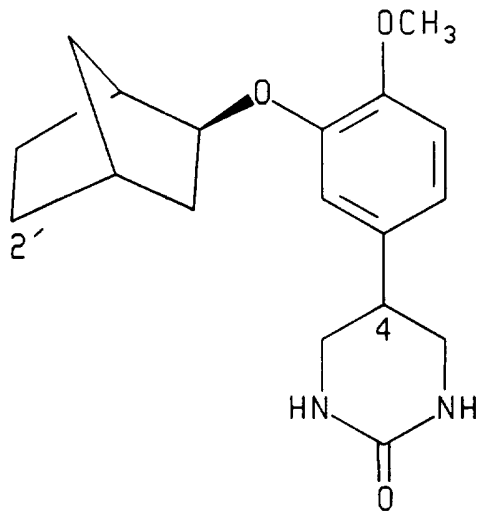
(IIIB)



(IIIC)

SCHEME 3 cont'd

(IIIC)



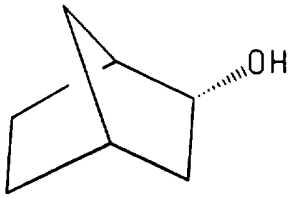
(VI)

Scheme 1 illustrates the preparation of compounds of the formulae II and III. Scheme 2 illustrates the preparation of compounds of the formula V and also the preparation of 5-(3-[(2S)-exo-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyphenyl)-3,4,5,6-tetrahydropyrimidin-2-(1H)-one (compound VI) from the compound of formula III wherein X and Y are both -CN. (Such compound of formula III wherein X and Y are both -CN is referred to in scheme 2 and hereinafter as the compound of formula IIIA.) Scheme 3 illustrates the preparation of compound VI from compounds of the formula III wherein X and Y are both $-CO_2(C_1-C_6)$alkyl or -CONHOH. (The compound of formula III wherein X and Y are both $-CO_2(C_1-C_6)$alkyl or -CONHOH are referred to in scheme 3 and hereinafter, respectively, as the compound of formula IIIB or IIIC).

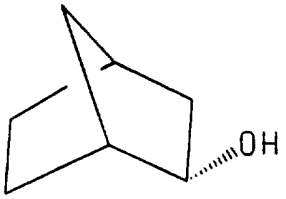
Referring to scheme 1, isovanillin (compound I) is condensed with two molar equivalents of a compound of the formula XCH_2CO_2H, wherein X is -CN, $-CO_2(C_1-C_6)$alkyl, $-CONH_2$ or -CONHOH, in a sequential Knoevenagel-Michael sense with accompanying decarboxylation, to yield a compound of the formula II, wherein X and Y are the same and are selected from the values given in the above definition of X, in a reaction inert solvent in the presence of a base, preferably a tertiary amine. This reaction may be conducted at a temperature ranging from about 10°C to about 130°C. It is preferably conducted at about the reflux temperature. Suitable solvents include but are not limited to N-methylmorpholine, triethylamine, pyridine, as well as non-basic reaction-inert solvents such as tetrahydrofuran (THF), dimethylformamide (DMF), acetonitrile and toluene. Preferably, a secondary amine (e.g., piperidine or pyrrolidine) is also added as a catalyst. In one preferred embodiment of the reaction, N-methylmorpholine is used as the solvent/base and piperidine is also added to the reaction mixture.

Compounds of the formula II wherein X and Y, taken together, form a group of the "a" (i.e., the cyclic urea) may be prepared by subjecting the compound of formula II wherein X and Y are both -CN to the series of reactions illustrated in scheme 2 and described later in this application.

The compound of formula II formed in the above reaction can be converted into the corresponding compound of the formula III by coupling it under Mitsunobu conditions with either R-(+)-endo-norborneol, depicted below,



or S-endo-norborneol, depicted below



to yield, respectively, the corresponding compound of formula III or III′ having the opposite stereochemistry as determined by the endo-norborneol reactant. Thus, if R-endo-norborneol is used, the product will be a compound of the formula III that has an "S" configuration, and if S-endo-norborneol is used, the product will be a compound of the formula III′ that has an "R" configuration.

This reaction is typically carried out in the presence of a triaryl or trialkyl phosphine such as triphenylphosphine or tributylphosphine and an azo dicarboxylate oxidizing agent. It is also generally carried out in an aprotic solvent such as tetrahydrofuran (THF) acetonitrile, methylene chloride, DMF, toluene and benzene, preferably THF, at a temperature from about 10°C to about 150°C, preferably at about the reflux temperature. Suitable azo compounds include diisopropylazodicarboxylate, azodicarbonyldipiperidine and diethylazodicarboxylate. Diisopropylazodicarboxylate and azodicarbonyldipiperidine are preferred.

The stereochemistry of the compound of formula III or III′ formed in the above step is retained in all subsequent steps shown in schemes 2 and 3.

As indicated above, scheme 2 illustrates the conversion of compounds of the formula IIIA into compounds of the formula VI. Referring to scheme 2, a compound of the formula IIIA is hydrolyzed with hydrogen peroxide, preferably basic aqueous hydrogen peroxide, to form the bis-amide of formula IV. This reaction is typically conducted in a polar solvent such as acetone, ethanol, isopropanol or methyl ethyl ketone, with acetone being preferred, at a temperature from about 0°C to about 100°C, with about room temperature being preferred. Sodium carbonate or another inorganic salt of similar basicity may be added to the reaction mixture to accelerate the reaction.

The compound of formula IV so formed is then subjected to a Hoffman rearrangement reaction in which both carboxamide groups are converted, with migration of nitrogen, into the carbamate groups of formula V. Suitable oxidizing reagents include bis(acetoxy)iodobenzene, bis(trifluoroacetoxy)iodobenzene, NaOCl, NaOBr and lead tetracetate may be used. Bis(acetoxy)iodobenzene is preferred. This reaction is typically carried out in the presence of a base. When diacetoxyiodobenzene is used, acceptable bases include alkali metal hydroxides and (C_1-C_6)alkoxides. The reaction temperature may range from about -20°C to about 100°C, with from about 0°C to about 25°C being preferred. Examples of appropriate reaction-inert solvents are (C_1-C_6)alkanols, THF, DMF and acetonitrile.

The final step in the sequence is the base catalyzed closure of the biscarbamate of formula V to form the symmetrical pyrimidin-2-one of formula VI. This reaction may be carried out from about 0°C to about 100°C, and is preferably carried out at the reflux temperature. Suitable solvents include but are not limited to lower alcohols, with methanol being preferred. Suitable bases include alkali metal alkoxides containing from one to six carbon atoms. The preferred base is sodium methoxide.

Alternatively, the last two steps of the sequence may be accomplished in a combined fashion without the isolation of the bis-carbamate V. This modification is essentially identical to the previous description of the Hoffman rearrangement. It is preferable to conduct the reaction at the reflux temperature of the solvent. It is also preferable to add additional base to the reaction mixture. The range of acceptable oxidizing agents, bases and solvents is the same as described previously. The preferred reaction utilizes diacetoxyiodobenzene, sodium methoxide and methanol.

The reaction of compounds of the formula V to form compounds of the formula VI, as described above, may proceed through one or both of the intermediates of formulae VII and VIII shown in scheme 2A.

The compound of formula III wherein X and Y are both -$CONH_2$ is the same as the compound of formula IV, and therefore it can be converted into compound (VI) using the methods illustrated in scheme 2.

Compounds of the formula III wherein X and Y are both -CONHOH or -CO_2(C_1-C_6)alkyl may be converted into compound VI using the methods illustrated in scheme 3.

Referring to scheme 3, the diester of formula IIIB is reacted with hydroxylamine hydrochloride in the presence of a base, e.g., a tertiary amine base, to form the hydroxamic acid of formula IIIC. This reaction can be conducted in a variety of reaction-inert solvents that do not have a strong nucleophilic character, including but not limited to lower alcohols, cyclic and acyclic ethers (e.g., ethyl ether or THF), neutral aromatic compounds such as benzene and toluene, DMF, dimethylacetamide, ethyl acetate, acetonitrile and water, at a temperature from about 0°C to about 100°C, preferably at about 20°C.

The hydroxamic acid of formula IIIC can then be converted into compound VI via a Loessen rearrangement using conditions or a reagent having the ability to dehydrate an alcohol, at a temperature from about 0°C to about 100°C, preferably at about 20°C. The preferred reagent is p-toluenesulfonylchloride. Alternatively, one can form a different ester of the hydroxamic acid, optionally in situ, and then convert that ester via heat and/or acid treatment into the compound of formula VI, using methods well known in the art.

The preparation of other compounds of the present invention not specifically described in the foregoing experimental section can be accomplished using combinations of the reactions described above that will be apparent to those skilled in the art.

In each of the reactions discussed or illustrated in the scheme above, pressure is not critical unless otherwise indicated. Pressures from about 0.5 atmospheres to about 3 atmospheres are generally acceptable, and ambient pressure, i.e., about 1 atmosphere, is preferred as a matter of convenience.

The processes and products of this invention are useful in the synthesis of the pharmaceutically active compounds VI and VI'. Compounds VI and VI', as well as racemic mixtures of these compounds (hereinafter referred to, collectively as "the active compounds") are useful in the treatment of depression, asthma, inflammatory airway disorders and skin disorders (e.g., psoriasis and atopic dermatitis).

The active compounds are calcium independent c-AMP phosphodiesterase inhibitors. The ability of such compounds to inhibit c-AMP phosphodiesterase may be determined by the method of Davis, Biochimica et Biophysica. Acta., 797, 354-362 (1984).

The antidepressant activity of the active compounds may be determined by the behavioral despair paradigm described by Porsult et al., Arch. Int. Pharmacodyn., 227, 327-336 (1977) and by the procedure described by Roe et al., J. Pharmacol. Exp. Therap., 226, 686-700 (1983) for determining the ability of a test drug to counteract reserpine hypothermia in mice.

When used for the treatment of depression the active compounds are used as is or in the form of pharmaceutical compositions comprising an active compound and pharmaceutically-acceptable carriers or diluents. For oral administration, the preferred route for administering the active compounds, suitable pharmaceutical carriers include inert diluents or fillers, thereby forming dosage forms such as tablets, powders, capsules, and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. For example, tablets containing various excipients, such as sodium citrate, are employed, together with various disintegrants such as starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. preferred materials therefor include lactose or milk sugar and high molecular weight polyethylene glycols.

For oral administration, the daily dose of active agent is from about 0.1 mg to about 10 mg, and for parenteral administration, preferably i.v. or i.m., from about 0.01 mg. to about 5 mg. The prescribing physician, of course, will ultimately determine the appropriate dose for a given human subject dependent upon factors such as the severity of the patient's symptoms and the patient's response to the particular drug.

In vitro and in vivo tests relevant to the utility of the active compounds in treating asthma and skin disorders are discussed in International Patent Application WO 91/07178, referred to above and incorporated herein by reference in its entirety, on pages 4 and 5 of the specification and in Examples 1-3.

In the systemic treatment of asthma or inflammatory skin diseases with one of the active compounds, the dosage is generally from about 0.01 to 2 mg/kg/day (0.5-100 mg/day in a typical human weighing 50 kg) in single or divided doses, regardless of the route of administration. Of course, depending upon the exact compound and the exact nature of the individual illness, doses outside this range will be prescribed at the

discretion of the attending physician. In the treatment of asthma, intranasal (drops or spray), inhalation of an aerosol through the mouth, and conventional oral administration are generally preferred. However, if the patient is unable to swallow, or oral absorption is otherwise impaired, the preferred systemic route of administration will be parenteral (i.m., i.v.). In the treatment of inflammatory skin diseases, the preferred route of administration is oral or topical. In the treatment of inflammatory airway diseases, the preferred route of administration is intranasal or oral.

The active compounds are generally administered in the form of pharmaceutical compositions comprising one of said compounds together with a pharmaceutically acceptable vehicle or diluent. Such compositions are generally formulated in a conventional manner utilizing solid or liquid vehicles or diluents as appropriate to the mode of desired administration: for oral administration, in the form of tablets, hard or soft gelatin capsules, suspensions, granules, powders and the like; for parenteral administration, in the form of injectable solutions or suspensions, and the like; for topical administration, in the form of solutions, lotions, ointments, salves and the like, in general containing from about 0.1 to 1% (w/v) of the active ingredient; and for intranasal or inhaler administration, generally as 0.1 to 1% (w/v) solution.

The present invention is illustrated by the following examples. It will be understood, however, that the invention is not limited to the specific details of these examples.

EXAMPLE 1

3-(3-Hydroxy-4-methoxyphenyl)-pentane-1,5-dinitrile

To a 500 mL flask containing isovanillin (30.4 gm, 200 mmol) and cyanoacetic acid (68.0 gm, 800 mmol) was charged a solution consisting of 3.0 mL (30 mmol) piperidine and 151 mL N-methylmorpholine. The initially formed yellow slurry was warmed to mild reflux for 21 hours and then cooled to room temperature and concentrated on a rotary evaporator. The resulting brown oil was dissolved in 430 mL ethyl acetate (EtOAc), washed sequentially with water (H_2O), five normal hydrochloric acid (5N HCl) and H_2O and the combined aqueous washes back extracted with dichloroethane. Combination of the organic layers followed by solvent removal led to a thick orange oil which was crystallized from ethyl acetate/methylene chloride ($EtOAc/CH_2Cl_2$) to yield 38.3 gm of orange solids after filtration and drying.

Recrystallization from EtOAc/diisopropyl ether gave 35.3 gm (82%) of light yellow solid, m.p. 90-92°C.

EXAMPLE 2

3-(3-[(2S)-exo-Bicyclo[2.2.1]hept-2-yloxy]-4-methoxyphenyl)-1,5-pentanedinitrile

To a tetrahydrofuran (THF) solution (20 mL) containing R-(+)-endo-norborneol (1.12 gm, 10.0 mmol), 3-(3-hydroxy-4-methoxyphenyl)-pentane-1,5-dinitrile (4.33 gm, 20 mmol) and triphenylphosphine (TPP) (3.93 gm, 15 mmol) was added 1,1'-(azodicarbonyl)-dipiperidine (ADDP) (3.78 gm, 15 mmol) at room temperature. The resulting brown slurry was heated at reflux for 12 hours, and then diluted with 10 mL THF and 30 mL toluene, cooled to room temperature and granulated for 30 minutes. After filtration to remove the reduced ADDP, the filtrate was washed 2X with 20 ml 1N sodium hydroxide (NaOH) and the remaining organic phase stirred with 0.2 gm activated charcoal and 20 gm sodium sulfate (Na_2SO_4), filtered and concentrated to a thick, dark brown oil. Recrystallization from isopropanol/hexanes gave 2.34 gm (75%) of an off-white solid, m.p. 126-127°C.

EXAMPLE 3

3-(3-[(2S)-exo-Bicyclo[2.2.1]hept-2-yloxy]-4-methoxyphenyl)-pentane-1,5-dinitrile

To a refluxing solution of THF (30 mL) containing norborneol (2.243 gm, 20.00 mmol) and triphenylphosphine (5.272 gm, 20.10 mmol) was added a second THF solution of 3-(3-hydroxy-4-methoxyphenyl)-pentane-1,5-dinitrile (4.350 gm, 20.10 mmol) and diisopropyl azodicarboxylate (DIAD) (4.044 gm, 21.00 mmol). The mixture was heated at reflux for 18 hours, cooled and concentrated on the rotary evaporator, and then redissolved in 60 mL toluene. The resulting brown toluene solution was washed 2 times with 1N NaOH, dried over Na_2SO_4, and filtered and concentrated to yield 18 gm of beige solid. Recrystallization from 1/1 isopropanol/hexanes gave 4.26 gm (69%) of white solid, m.p. 127-128°C.

EXAMPLE 4

3-(3-[(2S)-exo-Bicyclo[2.2.1]hept-2-yloxy]-4-methoxyphenyl)glutaramide

To a cooled (6°C) acetone solution (46 mL) of 3-(3-[(2S)-exo-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyphenyl)-pentane-1,5-dinitrile (2.29 gm, 7.38 mmol) was added 24 mL of 10% aqueous sodium carbonate (Na_2CO_3) (23 mmol) followed by 5.2 mL of 30% hydrogen pyroxide (H_2O_2). The resulting slurry was stirred at room temperature for 4 days, treated with an additional 1.7 mL 30% H_2O_2 and then stirred for two more days.

The excess peroxide was decomposed by the addition of 4 equivalents of sodium bisulfite ($NaHSO_3$) and the volume was reduced to about 80 mL on the rotary evaporator. The thick slurry was then acidified using 6.5 mL of concentrated HCl, neutralized with concentrated ammonium hydroxide (NH_4OH) and condensed to about 50 mL of volume. Filtration and vacuum drying provided 2.20 gm (86%) of white solids, m.p. 161-163°C.

EXAMPLE 5

5-(3-[(2S)-exo-Bicyclo[2.2.1]hept-2-yloxy]-4-methoxyphenyl)-3,4,5,6-tetrahydropyrinidin-2(1H)-one

To a cooled (2°) methanol (MeOH) (40 mL) suspension of diacetoxyiodobenzene (43.60 gm, 133 mmol) was added 152 mL of 25% sodium methoxide (NaOMe) in MeOH solution over 10 minutes. After stirring for 20 minutes at 3°C, 3-(3-[(2S)-exo-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyphenyl)glutaramide (22.98 gm, 66.5 mmol) was added as a precooled slurry in 45 mL MeOH and the reaction was allowed to warm to room temperature over 3 hours followed by 45 minutes of heating at reflux. The slurry was cooled to room temperature, treated with 152 mL of 25% NaOMe in MeOH solution and heated to reflux for 16 hours. The condenser was then replaced with a distillation head and 350 mL of MeOH was removed. The resulting slurry was cooled to 12°C, diluted with 200 mL CH_2Cl_2 and 100 ml H_2O and neutralized with concentrated HCl. Separation of the layers and extraction of the aqueous layer 2X with CH_2Cl_2 provided 3 organic layers which were combined, dried over sodium sulfate (Na_2SO_4), filtered and then concentrated to yield 39 gm of pale orange solid. Reslurry in refluxing EtOAc gave 15.48 gm of white solid (77%) m.p. 199-200°C.

EXAMPLE 6

N,N'-Dimethoxycarbonyl-2-(3-[(2S)-exo-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyphenyl)-1,3-propanediamine

To a cooled (0°C) suspension of 3-(3-[(2S)-exo-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyphenyl)-glutaramide (0.346 gm, 1.00 mmol) in 1.75 ml of MeOH was added 0.140 gm of potassium hydroxide (KOH) (2.50 mmol) followed by 0.657 gm (3.0 mmol) diacetoxyiodobenzene. The resulting hazy yellow solution was allowed to warm to room temperature, stir for 80 minutes and was then concentrated on the rotary evaporator to a paste. The material was transferred to a separatory funnel with water

and extracted two times with CH_2Cl_2. The combined organic layers dried over Na_2SO_4, filtered and concentrated to provide 0.506 gm (125%) of the desired bis-carbamate as an impure yellow foam. Thin layer chromatography (TLC): R_f = 0.74 in 9:1 CH_2Cl_2/MeOH. Gas chromatography - mass spectrometry showed the major peak with a molecular ion of 406 which is the molecular weight of the title compound.

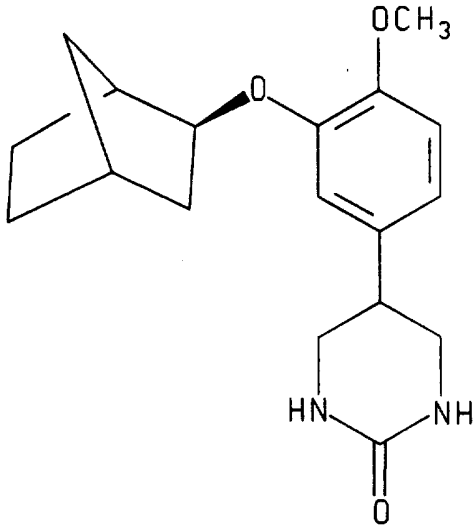
EXAMPLE 7

5-(3[(2R)-exo-bicyclo[2.2.1]hept-2-yloxy]-4-methoxyphenyl)-3,4,5,6-tetrahydropyrimidin-2(1H)-one

The crude bis-carbamate foam from Example 6 (98 mg, 0.2 mmol) was dissolved in MeOH (0.5 mL), treated with 0.5 mL of 25% NaOMe in MeOH, and refluxed for 18 hours. After removal of the solvent, the resulting solid was dissolved in water, extracted two times with CH_2Cl_2 and the combined organic layers dried over magnesium sulfate ($MgSO_4$). Filtration and concentration of the filtrate gave 48 mg (75%) of the desired urea as a yellow solid. Thin layer chromatography (TLC): R_f = 0.57 in 9:1 CH_2Cl_2/MeOH.

CLAIMS

1. A process for preparing a compound of the formula



(VI)

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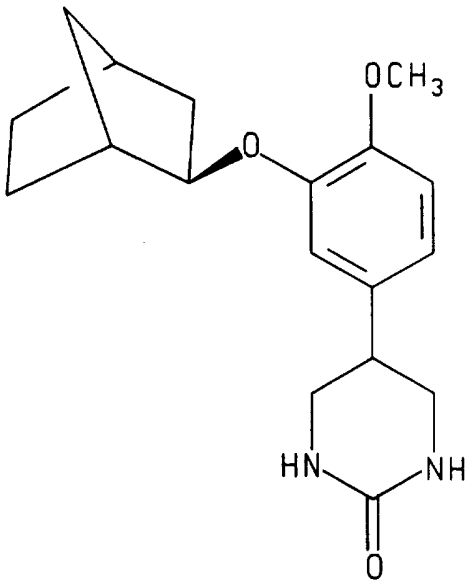
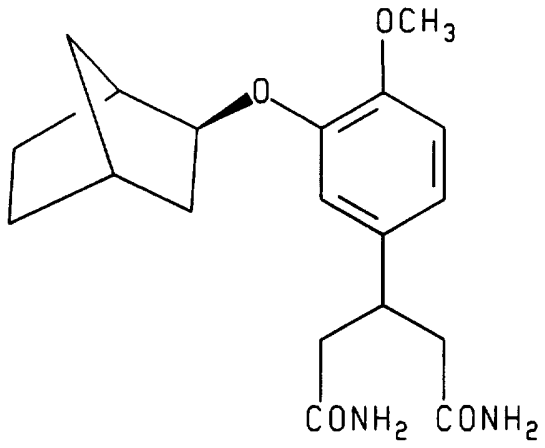


(VI')

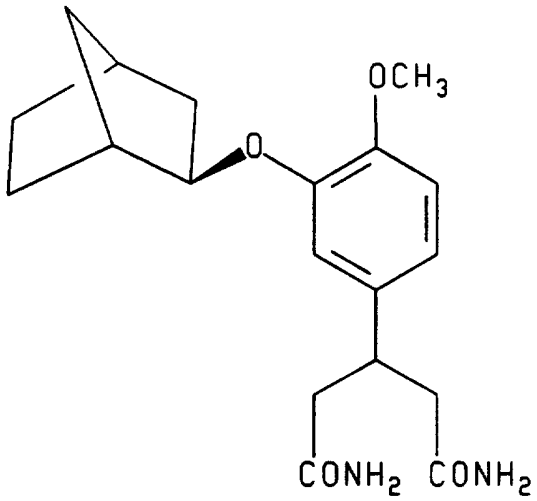
comprising:

(a) reacting, respectively, a compound of the formula



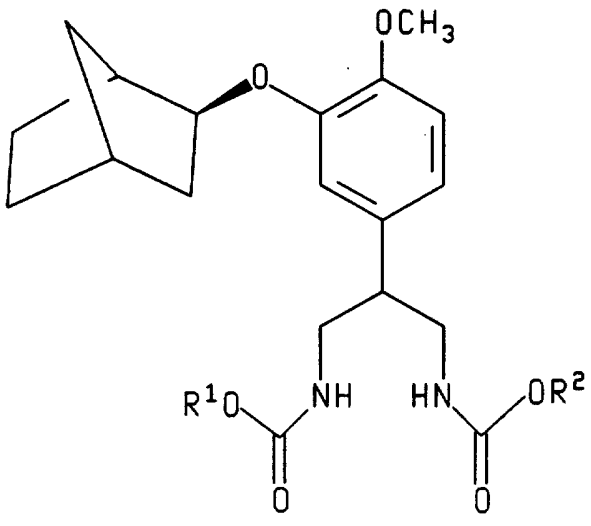
(IV)

or



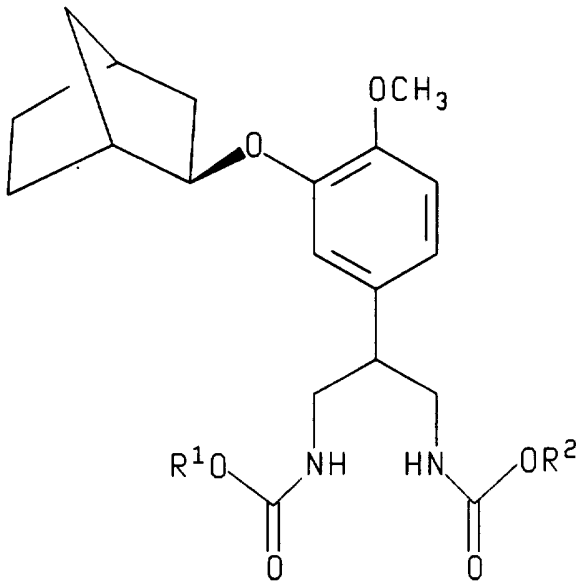
(IV')

with diacetoxyiodobenzene, NaOZ and Z'OH, wherein Z and Z' are independently selected from hydrogen and (C_1-C_6)alkyl, to form an intermediate of the formula



(V)

or



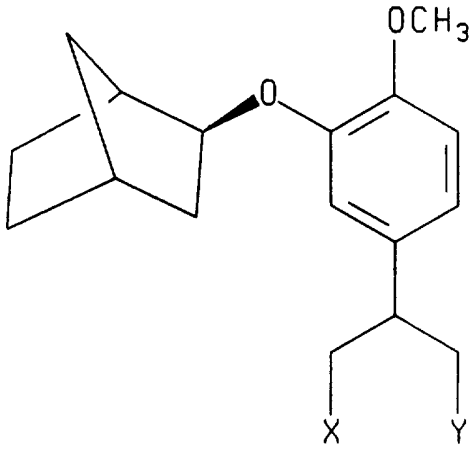
(V′)

wherein R^1 and R^2 are independently selected from hydrogen and (C_1-C_6)alkyl; and then either:

(b1) isolating said intermediate of formula V or V′ and reacting it with compounds of the formulae NaOZ and Z′OH, wherein Z and Z′ are defined as above; or

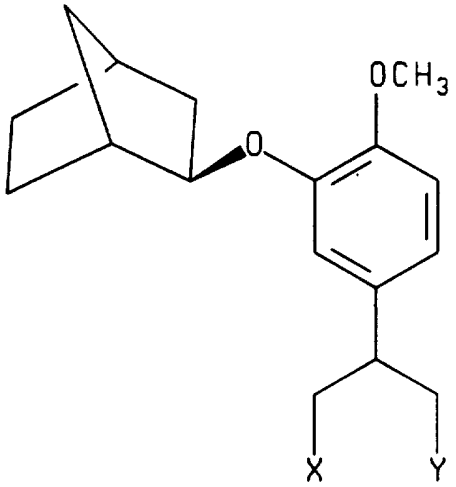
(b2) reacting said intermediate of formula V or V′ in situ with compounds of the formula NaOZ and Z′OH, wherein Z and Z′ are defined as above.

2. A process for preparing a compound of the formula



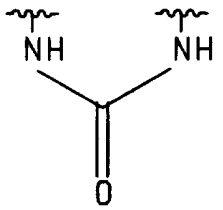
(III)

or



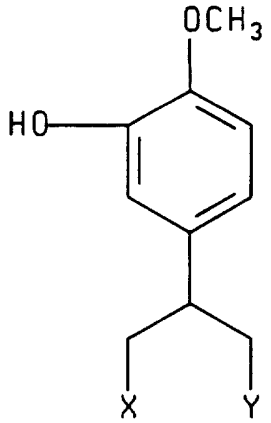
(III')

wherein X and Y are the same and are selected from -CN_1, -$CONH_2$, -$CO_2(C_1$-$C_6)$alkyl and -CONHOH, or X and Y, taken together, form a group of the formula



(a)

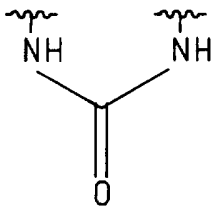
comprising: (1) reacting 3-hydroxy-4-methoxybenzaldehyde with a compound of the formula XCH_2CO_2H, wherein X is -CN, -$CO_2(C_1$-$C_6)$alkyl, -$CONH_2$ or -CONHOH, in the presence of a base, to form a compound of the formula



(II)

wherein X and Y are the same and are selected from -CN, -$CONH_2$, -$CO_2(C_1$-$C_6)$alkyl and -CONHOH; or (2) (a) reacting a compound of the formula II wherein X and Y are both -CN with hydrogen peroxide to form the corresponding bis-amide in which both -CN groups are replaced by -$CONH_2$; (b) subjecting the bis-amide formed in step (a) to

a Hoffman rearrangement using an oxidizing agent to form the corresponding biscarbamate; and (c) reacting the biscarbamate formed in step (b) with a base to form a cyclic area wherein X and Y, taken together, form a group of the formula



(a)

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and then (3) reacting said compound of formula II formed in step 1 or 2 above with a triaryl or trialkylphosphine, an azo dicarboxylate, and either R-(+)-endo-norborneol or S-(-)-endo-norborneol, respectively.

3. A process according to claim 2 wherein said base is a tertiary amine.

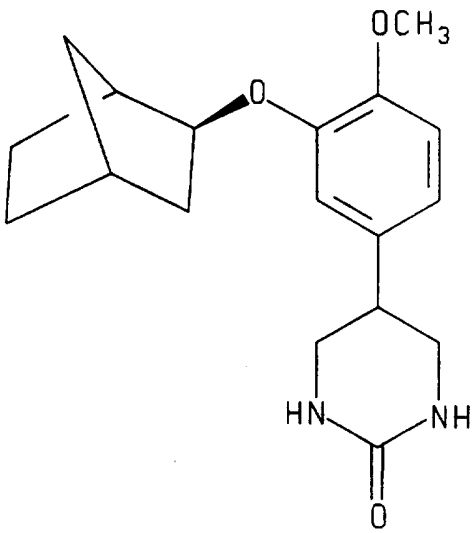
4. A process according to claim 2 wherein both a tertiary amine and a secondary amine are added to the reaction mixture.

5. A process according to claim 4 wherein the tertiary amine is selected from N-methylmorpholine, triethylamine, pyridine and diisopropyl amine and the secondary amine is selected from piperidine and pyrrolidine.

6. A process according to claim 2 wherein the azo dicarboxylate is selected from diisopropylazadicarboxylate and azodicarbonyldipiperidine.

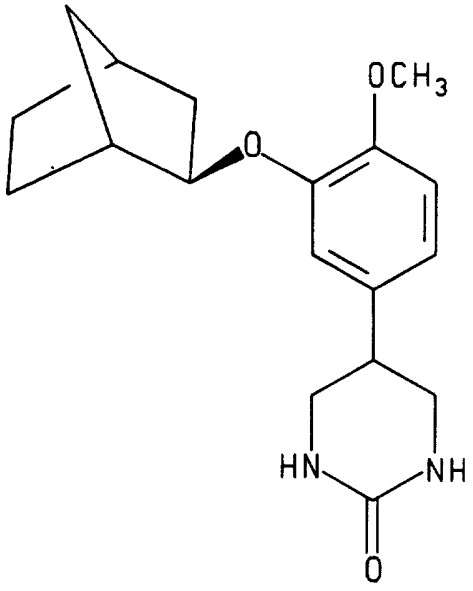
7. A process according to claim 2 wherein the triarylphosphine is triphenylphosphine.

8. A process for preparing a compound of the formula



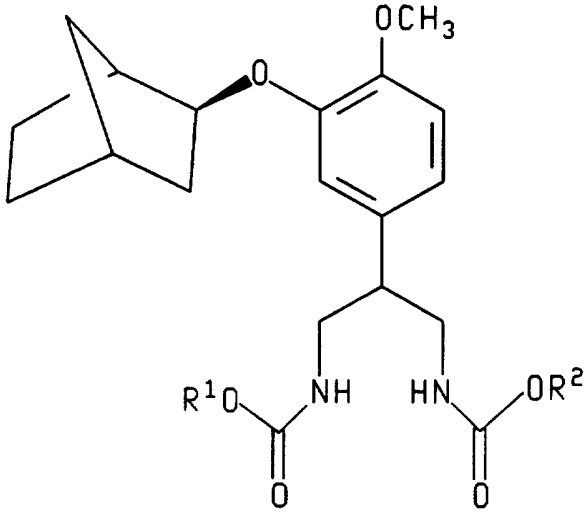
(VI)

or



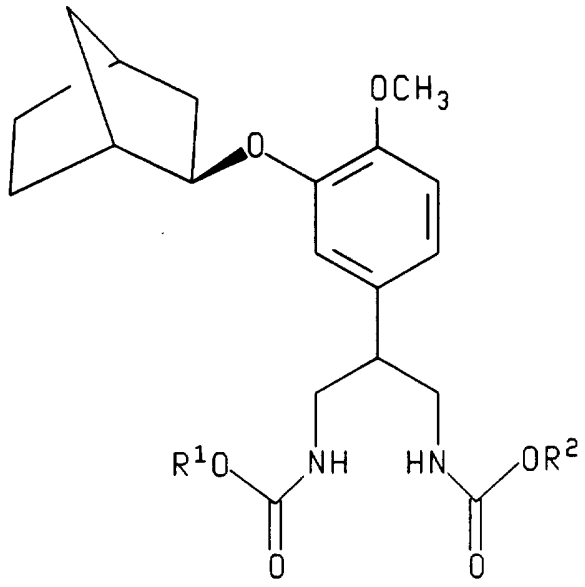
(VI')

comprising reacting, respectively, a compound of the formula



(V)

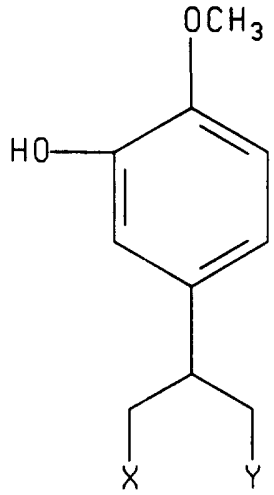
or



(V′)

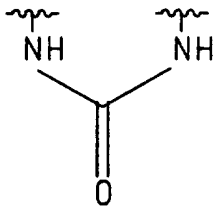
wherein R^1 and R^2 are independently selected from hydrogen and $(C_1\text{-}C_6)$alkyl, with compounds of the formulae NaOZ and Z′OH, wherein Z and Z′ are independently selected from hydrogen and $(C_1\text{-}C_6)$alkyl.

9. A compound having the formula



(II)

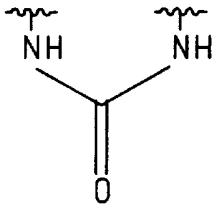
wherein X an Y are the same and are selected from $-CO_2(C_1\text{-}C_6)$alkyl, $-CONH_2$ and -CONHOH, or X and Y, taken together, form a group of the formula



(a)

10. A compound according to claim 9 wherein X and Y are both $-CONH_2$.

11. A compound according to claim 9 wherein X and Y, taken together, form a group of the formula

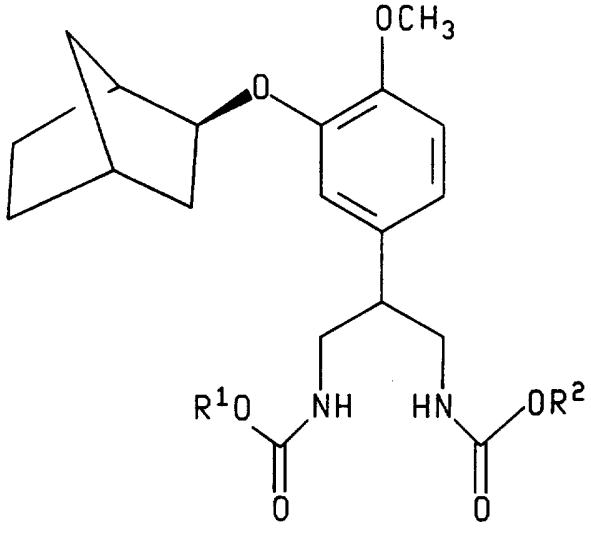


(a)

12. A compound according to claim 9 wherein X and Y are both $-CO_2(C_1-C_6)$alkyl.

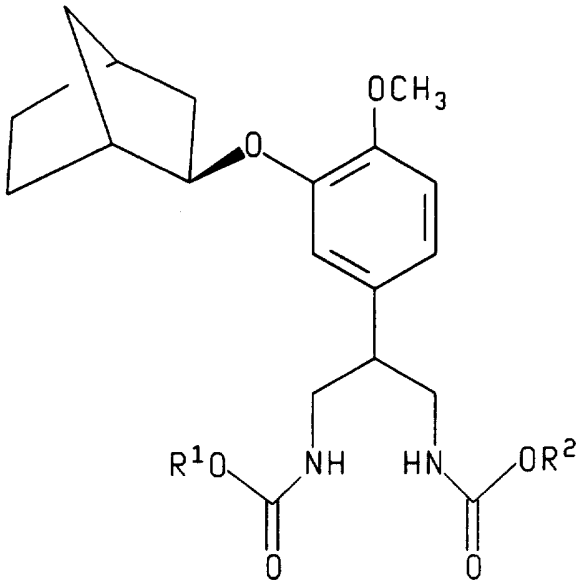
13. A compound according to claim 9 wherein X and Y are both -CONHOH.

14. A compound having the formula



(V)

or



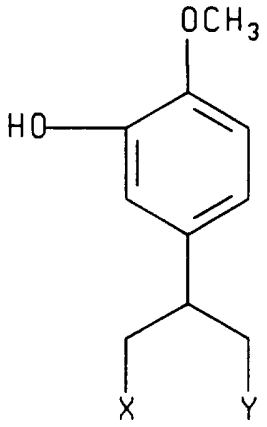
(V')

wherein R^1 and R^2 are independently selected from $(C_1\text{-}C_6)$alkyl and hydrogen.

15. A compound according to claim 14 wherein both R^1 and R^2 are selected from $(C_1\text{-}C_6)$alkyl.

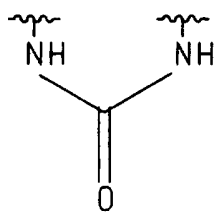
16. A compound according to claim 14 wherein both R^1 and R^2 are hydrogen.

17. A process for preparing a compound of the formula



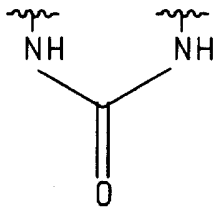
(II)

wherein X and Y are the same and are selected from $-CO_2(C_1\text{-}C_6)$alkyl, $-CONH_2$ and -CONHOH, or X and Y, taken together, form a group of the formula



(a)

comprising: (1) reacting 3-hydroxy-4-methoxybenzaldehyde with a compound of the formula XCH_2CO_2H, wherein X is selected from $-CO_2(C_1-C_6)$alkyl, $-CONH_2$ and -CONHOH, in the presence of a base, to yield a compound of the formula II wherein X and Y are both $-CO_2(C_1-C_6)$alkyl, $-CONH_2$ or -CONHOH; or (2) (a) reacting a compound of the formula II wherein X and Y are both -CN with hydrogen peroxide to form the corresponding bis-amide in which both -CN groups are replaced by $-CONH_2$; (b) subjecting the bis-amide formed in step (a) to a Hoffman rearrangement using an oxidizing agent to form the corresponding biscarbamate; and (c) reacting the biscarbamate formed in step (b) with a base to form a cyclic urea wherein X and Y, taken together, form a group of the formula



(a)

18. A process according to claim 17, wherein 3-hydroxy-4-methoxybenzaldehyde is reacted with $HOOCCH_2CONHOH$.

19. A process according to claim 17, wherein 3-hydroxy-4-methoxybenzaldehyde is reacted with $HOOCCH_2CONH_2$.

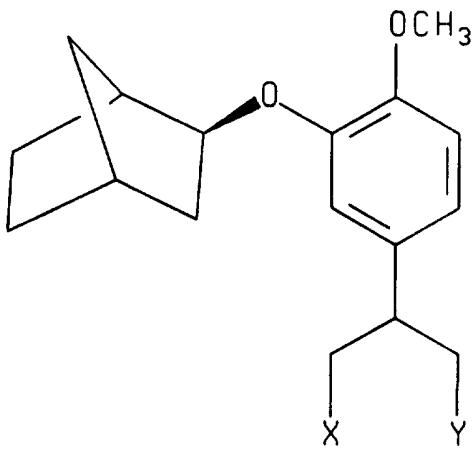
20. A process according to claim 17, wherein 3-hydroxy-4-methoxybenzaldehyde is reacted with $HOOCCCH_2CO_2(C_1-C_6)$alkyl.

21. A process according to claim 17, wherein said base is a tertiary amine.

22. A process according to claim 17, wherein both a tertiary amine and a secondary amine are added to the reaction mixture.

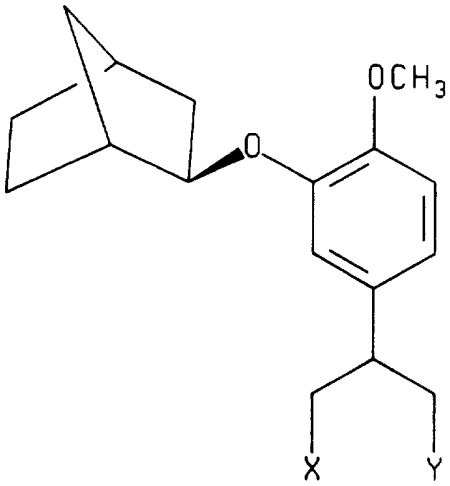
23. A process according to claim 22, wherein said secondary amine is piperidine or pyrrolidine.

24. A process for preparing a compound of the formula



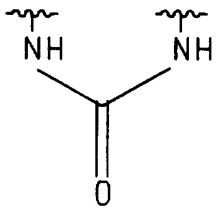
(III)

or



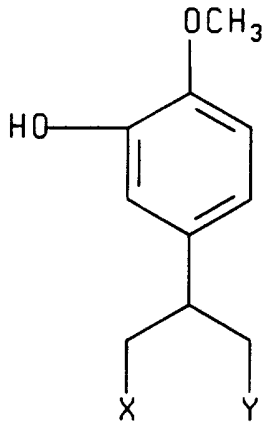
(III')

wherein X and Y are the same and are selected from -CN_1-$CONH_2$, $CO_2(C_1$-$C_6)$alkyl and -CONHOH, or X and Y, taken together, form a group of the formula



(a)

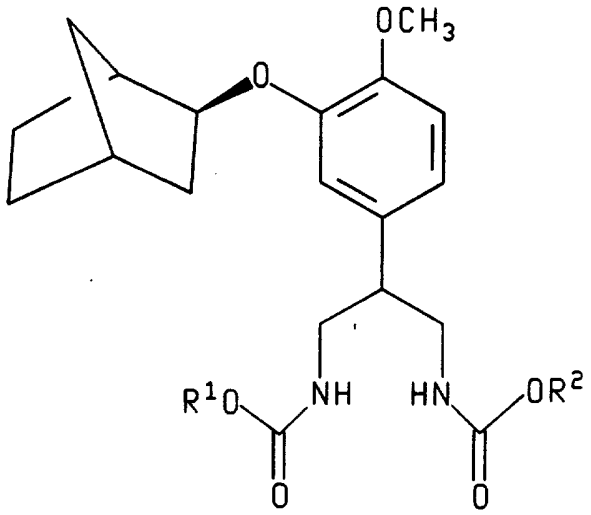
comprising reacting a compound of the formula



(II)

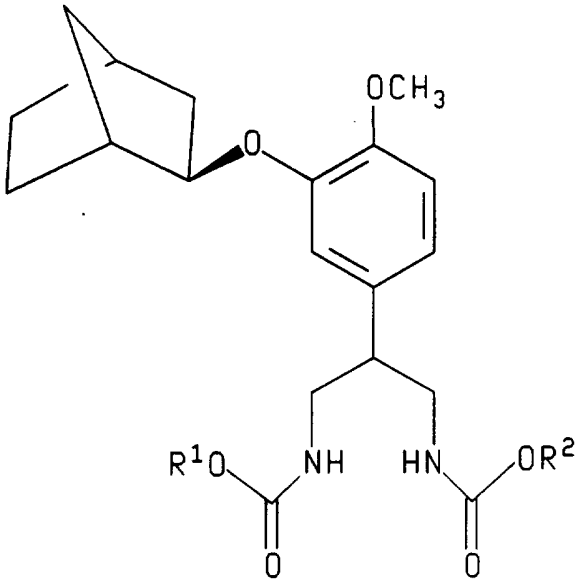
wherein X and Y are the same and are defined as above, with a triaryl or trialkylphosphine, an azo dicarboxylate and either R(+)-endo-norborneol or S-(-)-endo-norborneol, respectively.

25. A process for preparing a compound of the formula



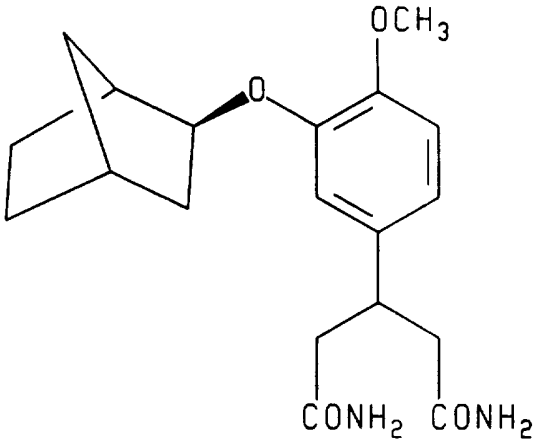
(V)

or



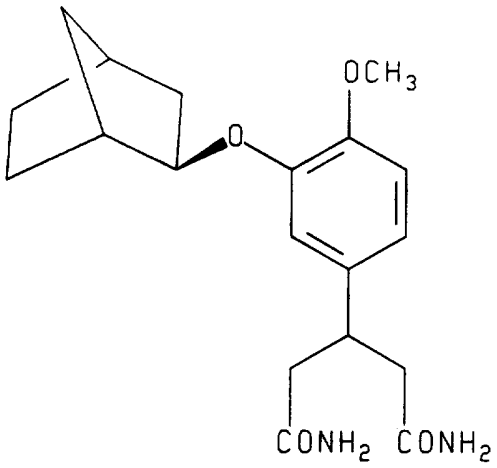
(V')

wherein R^1 and R^2 are independently selected from hydrogen and (C_1-C_6)alkyl, comprising reacting, respectively, a compound of the formula



(IV)

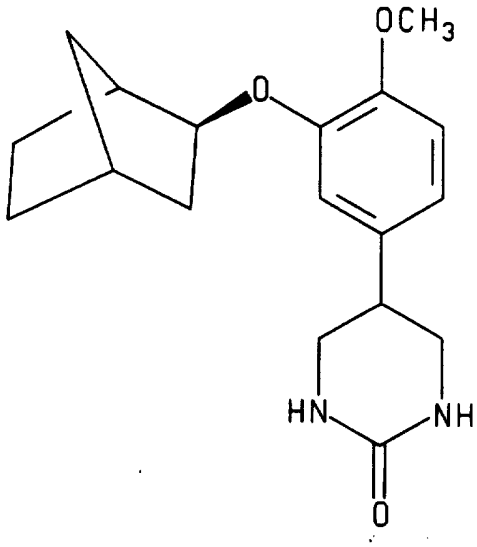
or



(IV′)

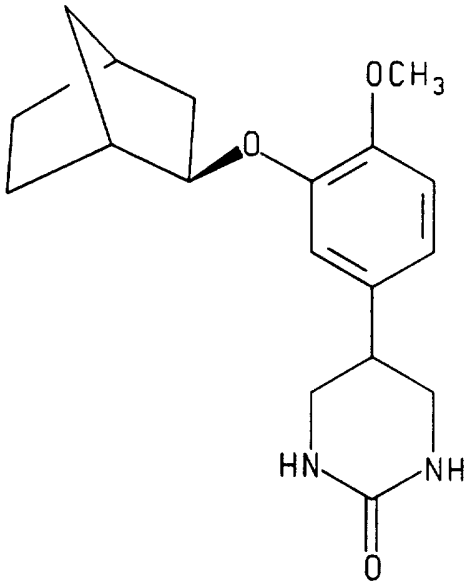
with diacetoxyiodobenzene, NaOZ and Z′OH, wherein Z and Z′ are independently selected from hydrogen and (C_1-C_6)alkyl.

26. A process according to claim 25, further comprising reacting said compound of formula V or V′ with compounds of the formulae ZONa and Z′OH, wherein Z and Z′ are defined as in claim 25, to yield, respectively, a compound of the formula



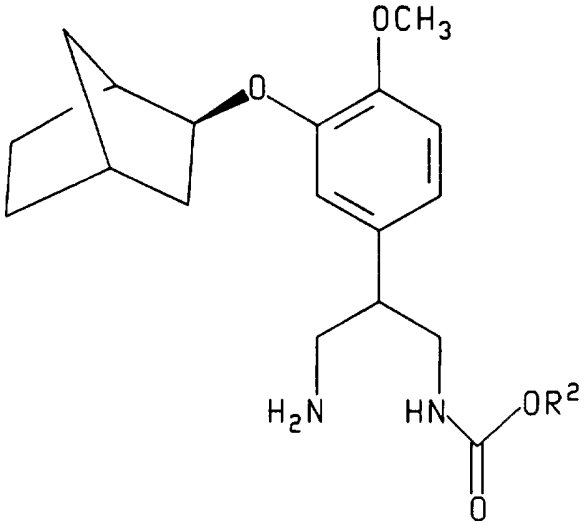
(VI)

or



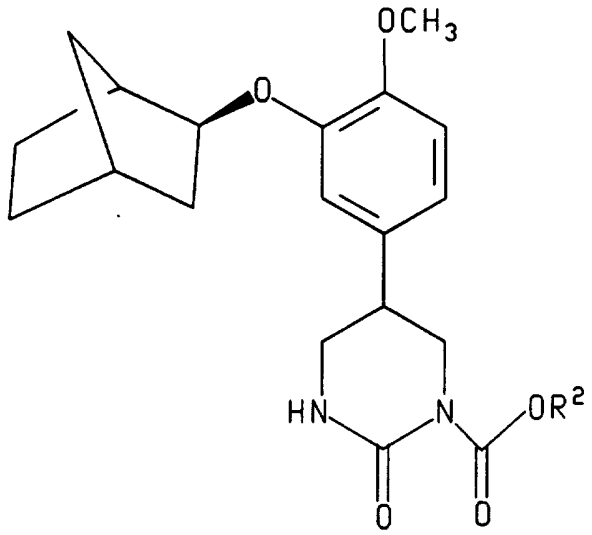
(VI')

27. A compound of the formula



(VII)

or



(VIII)

wherein each R^2 is independently selected from $(C_1\text{-}C_6)$alkyl.

INTERNATIONAL SEARCH REPORT

Intern. nal Application No
PCT/IB 95/00319

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D239/10 C07C235/34 C07C259/06 C07C69/734

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 12461 (PFIZER) 9 June 1994 see page 41 - page 42; claims; examples 21,22	1,9,24
A	WO,A,87 06576 (PFIZER) 5 November 1987 cited in the application see claims 1,17,58,59	1,2

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 June 1995	07.07.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Francois, J

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INTERNATIONAL SEARCH REPORT

Intern. nal Application No
PCT/IB 95/00319

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 92, no. 13, 1980, Columbus, Ohio, US; abstract no. 110633r, V.ASKAM ET AL. 'COMPOUNDS HAVING ANTITREMORINE ACTIVITY,BICAEBAMATES DERIVATIVES OF 1,3-DIAMINO-2-PHENYLPROPANES.' page 626 ; see abstract	1,25,26
A	& J.CHEM.RES. SYNOP., vol.7, 1979, ENGL. page 234	1,25,26

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inten nal Application No
PCT/IB 95/00319

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9412461	09-06-94	AU-B-	5539694	22-06-94
		CN-A-	1094028	26-10-94
		FI-A-	935379	03-06-94
		HU-A-	65928	28-07-94
WO-A-8706576	05-11-87	CA-A-	1331606	23-08-94
		DE-D-	3789164	07-04-94
		DE-T-	3789164	09-06-94
		EP-A-	0247725	02-12-87
		ES-T-	2061492	16-12-94
		FI-B-	94341	15-05-95
		JP-B-	6045602	15-06-94
		JP-A-	62281864	07-12-87
		SU-A-	1646488	30-04-91
		SU-A-	1653542	30-05-91
		US-A-	5294730	15-03-94