INSTRUCTIONS

(a) If Convention application insert "Convention"

Convention (a) 72463/87

AUSTRALIA 596410

Patents Act

(b) Delete one

APPLICATION FOR A (b) STANDARD/~~PETTY~~ PATENT

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

~~I~~/We (c) MERRELL DOW PHARMACEUTICALS INC.
APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 20-2-90

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

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

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

(f) NOVEL DOPAMINE BETA HYDROXYLASE INHIBITORS

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

(Note: The following applies only to Convention applications)

Details of basic application(s)

	Application No.	Country	Filing Date
(h)	860,263	United States of America	May 6, 1986

FEE STAMP TO VALUE OF $325 ATTACHED
MAIL OFFICER

Address for Service:

LODGED AT SUB-OFFICE
- 4 MAY 1987
Melbourne

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

Dated (i) March 10, 1987

(i) MERRELL DOW PHARMACEUTICALS INC.

(j) By Gary D. Street
Gary D. Street
Managing Patent Counsel

(k) Corporate seal if any

(k)

Note: No legalization or other witness required

35073 AU

AUSTRALIA

Patents Act

DECLARATION FOR A PATENT APPLICATION

▼ **INSTRUCTIONS**
(a) Insert "Convention" if applicable
(b) Insert FULL name(s) of applicant(s)

In support of the (a) convention application made by (b)

MERRELL DOW PHARMACEUTICALS INC.

(c) Insert "of addition" if applicable
(d) Insert TITLE of invention

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

NOVEL DOPAMINE BETA HYDROXYLASE INHIBITORS

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

I/~~We~~ (e) Gary D. Street
of 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))

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

2. (f) Donald P. Matthews, 1250 Meadowbrook Drive, Indianapolis, Indiana 46240 James R. McCarthy, 1100 Maxwell Lane, Zionsville, Indiana 46077; Jeffrey P. Whitten, 9302 East 180 South, Zionsville, Indiana 46077; and Robert J. Broersma, Jr., 1233 Willow Way, Noblesville, Indiana 46060; all of the United States of America

(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 May 5, 1986

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

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

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

(h) United States of America - May 6, 1986
By: Donald P. Matthews, James R. McCarthy, Jeffrey P. Whitten and Robert J. Broersma, Jr.

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

(k) Insert PLACE of signing

(l) Insert DATE of signing

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

Note: No legalization or other witness required

Declared at (k) Cincinnati, Ohio

Dated (l) March 10, 1987

(m) MERRELL DOW PHARMACEUTICALS INC.

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

To: The Commissioner of Patents

35073 AU

P18/10/83

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(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 596410

(54) Title
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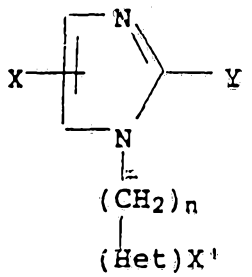
PHILLIPS,ORMONDE & FITZPATRICK

(57) Claim

1. A compound of the formula



I

including the 2-thione tautomers thereof, and the non-toxic pharmaceutically acceptable salts thereof, wherein n is zero or 1-4, X is hydrogen, cyano, C_{1-6} lower alkyl, ~~halogeno~~ Cl, Br, phenyl, or benzyl, z-substituted phenyl and benzyl with Z being C_{1-6} lower alkyl or halogeno, Y is ~~hydrogen,~~ aminomethyl, amido, alpha keto acid and their C_{1-6} esters, thioamido, amidino, aminoethylthio, or sulfhydryl, with the proviso that when Y is sulfhydryl or aminoethylthio, then X is hydrogen, (Het)X' is a

heterocycle of the group consisting of thienyl, furyl, ~~pyridyl~~, pyrimidinyl, pyrazolyl, pyrrolyl, thiazolyl and imidazol-2-yl, optionally substituted with either a halogen or a C_{1-6} lower alkyl with the proviso that when Y is SH and Het is 2-thienyl, then n is other than one.

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COMPLETE SPECIFICATION
(ORIGINAL)

Class Int. Class

Application Number:
Lodged: 72463/87

Complete Specification Lodged:
Accepted:
Published:

Priority

Related Art:

This document contains the amendments made under Section 49 and is correct for printing.

APPLICANT'S REFERENCE: C-35,073 AU

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Complete Specification for the invention entitled:

NOVEL DOPAMINE BETA HYDROXYLASE INHIBITORS

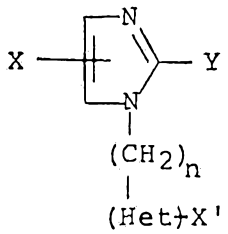
Our Ref : 52191
POF Code: 1432/1432

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

NOVEL DOPAMINE BETA HYDROXYLASE INHIBITORS

This invention relates to novel derivatives of 1-substituted imidazoles, to the processes and intermediates useful for their preparation, to the pharmaceutical compositions containing said imidazoles, to their dopamine beta-hydroxylase inhibiting pharmacological activity and to their applied use in the treatment of hypertension.

More specifically, this invention relates to novel 1-imidazole derivatives of the formula



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including the 2-thione tautomers thereof, and the non-toxic pharmaceutically acceptable salts thereof, wherein n is zero or 1-4, X is hydrogen, cyano, C_{1-6} lower alkyl, chloro, bromo, phenyl, or benzyl, Z-substituted phenyl and benzyl with Z being C_{1-6} lower alkyl or halogeno, Y is ~~hydrogen,~~ aminomethyl, amido, alpha-keto acid and their

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C_{1-6} esters, thioamido, amidino, aminoethylthio, or sulfhydryl, with the proviso that when Y is sulfhydryl or aminoethylthio, then X is hydrogen, (Het)X' is a heterocycle of the group consisting of thienyl, furyl, pyrazolyl, pyrimidinyl, pyrrolyl, thiazolyl and imidazol-2-yl, optionally substituted with either a halogen or a C_{1-6} lower alkyl, said compounds having a dopamine beta-hydroxylase inhibiting property and which are useful in the treatment of hypertension.

As used herein the term "lower alkyl" includes straight, branched-chain or cyclized hydrocarbyl radicals having up to six carbon atoms, preferably methyl, ethyl and propyl; halogeno preferably includes chloro, fluoro or bromo; Z substituted phenyl or benzyl includes those substituents at the ortho or meta positions, but preferably are located at the para- position. "Aminomethyl" includes those moieties of the formula $-CH_2NR_1R_2$, "amido" includes those moieties of the formula $-CONHR_1$; thioamido includes those moieties having the structure $-CSNHR_1$; "amidino" includes those moieties of the formula $R_3N=C-NR_1R_2$ with R_3 being H or OH, "sulfhydryl" includes $-SR_1$; alpha-keto acid and esters include $-COCOOR_1$, "aminoethylthio" includes those moieties of the formula $-SCH_2CH_2NR_1R_2$, wherein, in each of the foregoing instances, R_1 and R_2 independently represent hydrogen or C_{1-6} lower alkyl. The terms represented by "Het" of formula I embraces those named heterocyclics wherein "thienyl" includes its 2- and 3- position isomers, "furyl" includes its 2- and 3- position isomers, pyrimidinyl includes its 2-, 4- and 5- position isomers, "pyrrolyl" includes its 2- and 3- position isomers and their 2,5-dihydro 1H-pyrrolyl analogs, "pyrazolyl" includes its 3-, 4- and 5- isomers and its 4,5-dihydro analogs. The heterocyclic moieties may also contain halogeno or lower alkyl substituents at any of their open

alkyl substituents at any of their open positions, i.e., X' is hydrogen, halogeno or C_{1-6} lower alkyl. In those instances wherein n is zero, the heterocyclic moiety is attached directly to the nitrogen atom of the imidazole moiety, otherwise, it is separated by an alkylene bridging moiety having up to four carbon atoms, preferably one or three, i.e., methylene or propylene.

The most preferred compound is a compound of formula I where Y is SH, X is H, n is 2 and (Het)X' is 2-thienyl.

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~~alkyl substituents at any of their open positions, i.e., X'~~ is hydrogen, halogeno or C_{1-6} lower alkyl. In those instances wherein n is zero, the heterocyclic moiety is attached directly to the nitrogen atom of the imidazole moiety, otherwise, it is separated by an alkylene bridging moiety having up to four carbon atoms, preferably one or ~~three, i.e., methylene or propylene.~~

The compounds of formula I are useful in the free base form and, except in those instances wherein Y is SH, in the form of their acid addition salts; both forms being within the purview of this invention. The acid addition salts are simply a more convenient form for use and, in practice, use of the salt amounts to use of the free base. The acids which can be used include those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are relatively innocuous to the animal organism in pharmaceutical doses of the salts. In practice, it is convenient to form sulfate, phosphate, methansulfonate or lactate salts. Others are those derived from mineral acids (e.g., hydrochloric), and organic acids such as acetic acid, citric acid, tartaric acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like. The acid salts are prepared by standard techniques such as by dissolving the free base in aqueous or aqueous-alcohol solution or other suitable solvents containing the appropriate acid and isolating by evaporating the solution, or by reacting the free base and in an organic solvent in which case the salt separates directly or can be obtained by concentration of the solution.

In the preparation of the compounds of this invention it is quite obvious that the specific compound sought to be prepared will have a bearing of the particular process path

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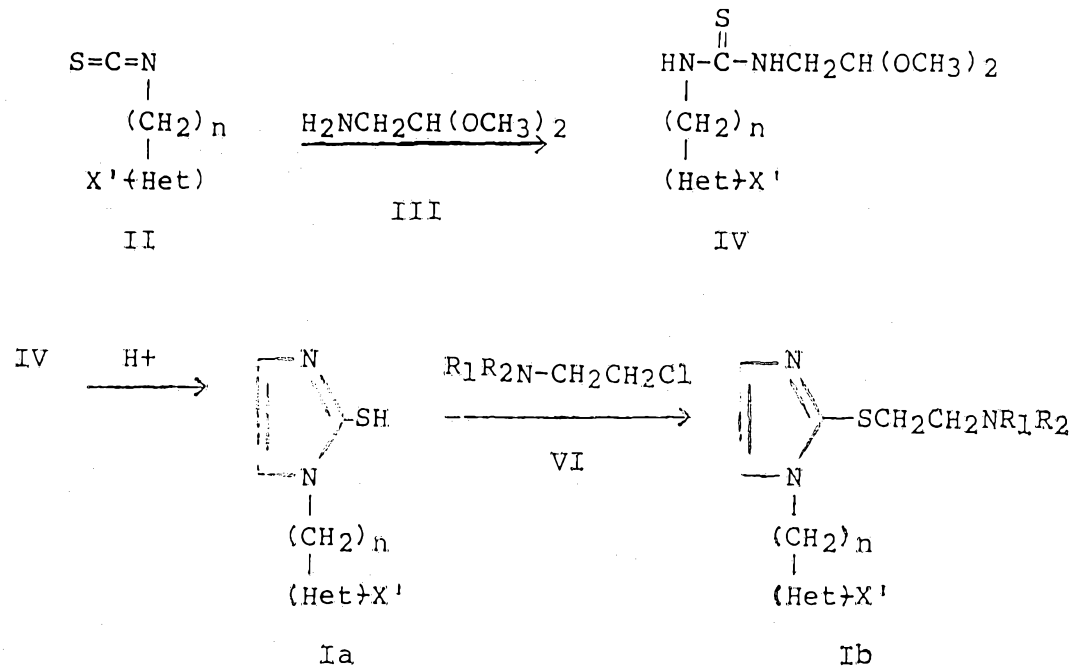
to be utilized. Such factors as the specific X, X', Z and/or Y substituents, the presence or absence of an alkylene bridge between the imidazolyl moiety and its attached heterocycle, and ready availability of the starting materials all play a role in choosing the specific path to be followed in the preparation of the compounds of this invention. Those factors are readily appreciated by one of ordinary skill in the art. However, in general, the compounds of this invention may be prepared by standard techniques and processes analogously known in the art.

In those instances wherein the compounds sought to be prepared contain a sulfhydryl substituent on the imidazole ring moiety, and n is either zero or an alkylene bridge, it is convenient to react an isothiocyanate derivative (II) with an appropriate acetal (III) to form a reaction product (IV), which is subjected to a cyclization reaction to form the imidazole ring bearing the sulfhydryl substituent (Ia). The sulfhydryl substituent may readily be converted to its aminoethylthio derivative (Ib) by reaction with an aminoethylchloride. These reactions are depicted in Reaction Scheme A.

REACTION SCHEME A:



wherein Het, n, X, X', R_1 and R_2 are as defined in formula I.

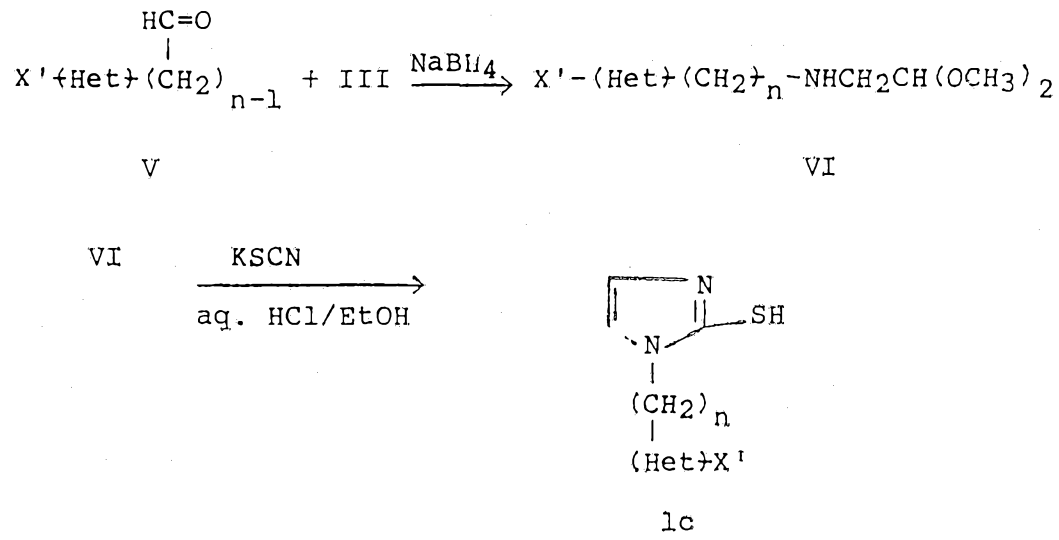
Of course, in those instances wherein the desired product contains an X substituent other than halogen, the acetal (III) bears the appropriate substituent. In those instances wherein it is desired to prepare a halogenated derivative, i.e., X is halogeno, then the thione (Ia) is appropriately protected and halogenated according to procedures well known in the art.

The reaction of the isothiocyanate derivatives (II) with the acetal (III) is a simple condensation reaction, preferably effected by heating the reactants under reflux conditions using inert solvents, e.g., toluene or DMF at 80°C, to form the thiourea (IV) intermediates. These intermediates are subjected to cyclization by treatment

with acid, preferably by refluxing the intermediates with aqueous hydrochloric acid in ethanol to produce the desired 1-substituted-2-imidazole bearing a sulfhydryl substituent (Ia). The sulfhydryl moiety of the compounds may be converted to its aminoethylthio analog (Ib) by treatment with the appropriate aminoethyl halide, as its hydrohalic salts, preferably by admixture at room temperature in the presence of a solvent. Alternatively, the sulfhydryl moiety may be chemically removed by catalytic reduction, preferably utilizing Raney nickel or dilute nitric acid at 80°C to 90°C or other equivalently functional systems. In this instance, the chemically reduced product may be converted to its 2-cyanoimidazole derivative by sequential treatment with cyanogen chloride and a base according to standard procedures well known in the art.

Alternatively, in those instances wherein n is other than zero, the 1-hetero-2-imidazoles (Ic) may be prepared by treating a heteroaldehyde derivative (V) with the aforementioned acetals (III) to form a Schiff base which is reduced to form an intermediate (VI) which is subjected to a cyclization reaction by treatment with aqueous HCl in ethanol in the presence of an alkali metal isothiocyanate preferably KSCN. These reactions may be depicted by the following reaction scheme.

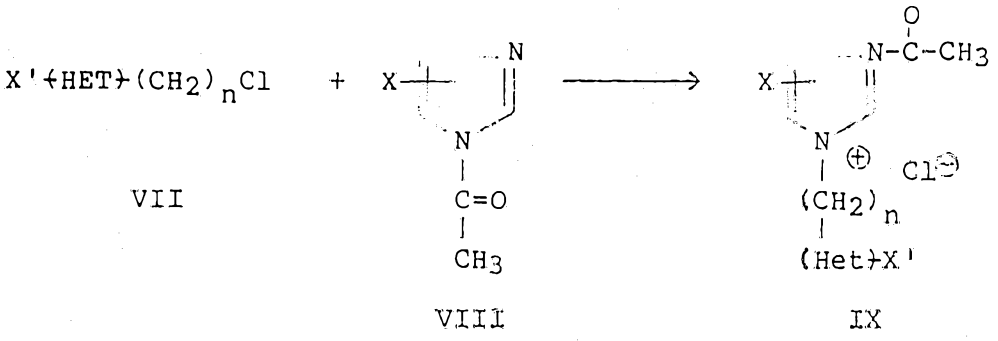
REACTION SCHEME B:



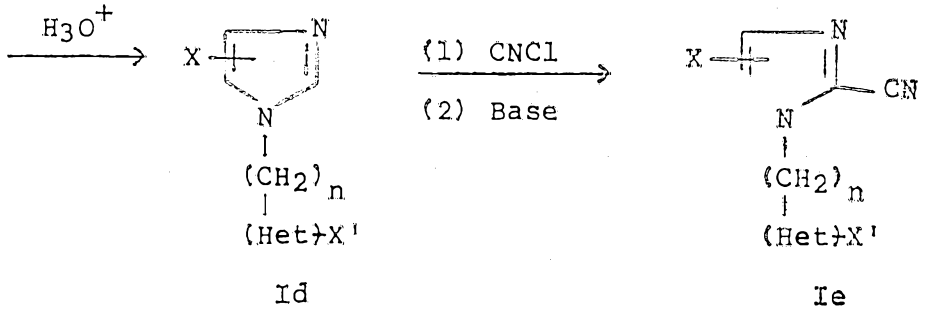
wherein (Het)X', is as previously defined and n is other than zero.

Still another alternate method for preparing compounds of Formula I is by reacting a halo derivative of an appropriate heterocycle with an X-substituted imidazole to form a X'(het)$(CH_2)_n$ substituted-X-substituted-imidazole. In one illustration of this type reaction the imidazole is first acylated and then the N-acylated imidazole is treated with a halo derivative of an appropriate heterocyclic to form an intermediate N'-acylated-N^3-imidazolium cation which is hydrolized to form the appropriately X-substituted analogs of Id. In another illustration the alkali metal derivatives of an X-substituted imidazole may be reacted with a halo derivative of an appropriate heterocycle to produce the desired 1-(2-heterocycle)-X-substituted imidazole; the reaction being effected according to standard and well-known conditions. These reactions are depicted by the following reaction scheme.

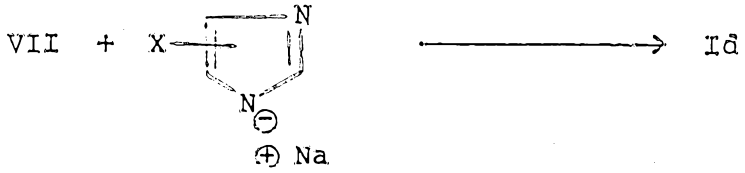
REACTION SCHEME C:



VII VIII IX



Id Ie



X

wherein the X', X and n moieties are as previously defined.

Useful references for some of the foregoing reactions are J. Med. Chem. 28, 1405-1413 (1985); J. Med. Chem. 10, 1409 (1985); J. Med. Chem. 18, 833 (1975) and Chem. Rev. 390 (1944).

The compounds prepared by the foregoing reaction schemes may readily be converted to the desired 2-Y'-X-substituted-2H-imidazole (Y' being as defined for Y except that the $-SR_1$ and $-SCH_2CH_2R_1R_2$ moieties are excluded), by standard procedures well known in the art. In effecting these transformations it is convenient to utilize the 2-cyano derivative of the imidazoles of formula Id as starting materials for the initiation of these conversions.

The cyano derivatives may readily be prepared by reacting the imidazole (Id) with cyanogen chloride, in a nitrogen atmosphere, in an solvent, preferably acetonitrile or toluene, at room temperature and then treating the reaction product with a base, preferably triethylamine at below 0° C temperatures. These procedures are standard and well known in the art.

The cyano moiety may readily be converted to its aminomethyl derivatives by standard reduction procedures (i.e., $LiAlH_4$, or H_2/PtO_2, or $H_2/Pd/C/HCl$) well known reducing reagents for this conversion. Alkylation of the aminomethyl moiety ($-CH_2NH_2$) may be effected by use of the Borsch reduction in the presence of the appropriate aldehyde (i.e., reacting $RCHO/NaCNBH_3$ in ethanol at room temperature at pH 4.0-5.0). The imidate ester (Y is $HN=\underset{|}{C}-OR$) is prepared by reacting the appropriate alcohol with the cyano derivative. The imidate ester ($HN=\underset{|}{C}-OR$) is readily converted to its amidino derivative (Y is $HN=\underset{|}{C}-NR_1R_2$) by reaction with the appropriate amine in

acid, and to its hydroxy amidine (Y is HON=C(-NH$_2$)-) by reaction with hydroxylamine in the presence of 1 equivalent of acid in an alcoholic solvent. This derivative can be converted to its alkylated derivative (i.e., Y is HO-N=C(-NR$_1$R$_2$)-) by treatment with an amine in the presence of 1 equivalent of acid. Treatment of the amidine (Y is HN=C(-NH$_2$)- or HN=CNR$_1$R$_2$) with H_2S in pyridine (with warming) yields the corresponding thioamides (Y is S=C(-NH$_2$)- or S=C(-NR$_1$R$_2$)-). Alternatively the cyano moiety may be treated with H_2S in pyridine to yield the desired thioamide (Y is S=CNH$_2$). Acid catalysis of the nitrile yields the amide (Y is -CONH$_2$).

The following examples merely illustrate the various techniques and procedures utilized for the preparation of the compounds of this invention; it being understood that they are not meant to limit the scope of the compounds defined by this invention.

EXAMPLE 1

1,3-Dihydro-1-(2-thienylmethyl)-2H-imidazole-2-thione

A mixture of 33.6 g (0.3 mol) thiophene-2-carboxaldehyde, 39.9 g (0.3 mol) aminoacetaldehyde diethyl acetal, 0.3 g TsOH and 200 ml ethanol is placed in a 500 ml flask and heated to reflux. After 2 hrs., the reaction is concentrated and the residue dissolved in 250 ml ethanol. Solid $NaBH_4$ (12.5 g, 0.33 mol) is added in small portions. The reaction is refluxed for 1-1/2 hrs., cooled to room temperature and poured into cold water. The product is extracted into CH_2Cl_2 (2 X 250 ml). After drying (Na_2SO_4) and concentration 66.7 g crude product is obtained as a pale yellow oil. 22.9 g (0.1 mol) of the crude amine is placed in a 500 ml flask along with 11.7 g (0.12 mol) KSCN, 150 ml ethanol, 40 ml water and 15 ml concentrated hydrochloric acid. After

refluxing for 5 hrs., the reaction is poured onto 1 l ice water. The white crystals are collected and dried to give 12.0 g (61%) product, mp 128-130°C (EtOH).

EXAMPLE 2

1,3-Dihydro-1-(1-methylpyrrol-2-ylmethyl)-2H-imidazole-2-thione

Procedure: Reflux a mixture of 10.9 g (0.1 mol) 1-methyl-2-pyrrolecarboxaldehyde, 13.1 g (0.1 mol) aminoacetaldehyde diethylacetal 0.1 g $TsOH \cdot H_2O$ and 200 ml ethanol for 2 hrs. Cool and concentrate the resulting mixture to obtain a tan oil. Dissolve the residue in 200 ml ethanol and slowly add 4.2 g (0.11 mol) solid $NaBH_4$. After addition is completed, reflux the reaction mixture for 2 hrs., pour the cooled reaction mixture into 1 l water. Extract the product into CH_2Cl_2 (2X 200 ml), dry (Na_2SO_4) and concentrate to obtain 24.2 g of crude acetal derivative. Mix the acetal derivative (22.6 g) (0.01 mol) with 11.6 g (0.12 mol) KSCN, 150 ml ethanol, 40 ml H_2O and 15 ml concentrated hydrochloric acid, reflux the mixture for 6 hrs. and pour the resulting mixture into 1 l ice water. Collect and dry the resulting crystals.

EXAMPLE 3

1,3-Dihydro-1-(4-pyrazolylmethyl)-2H-imidazole-2-thione

Under reflux conditions, heat a mixture of 9 g (0.14 mol) 4-pyrazolylcarboxaldehyde, 0.1 g TsOH, 18.6 g (0.14 mol) aminoacetaldehyde diethylacetal and 150 ml ethanol for 1-1/2 hours. Cool and concentrate reaction mixture, re-dissolve residue in 200 ml ethanol. Slowly add 5.7 g (0.15 mol) solid $NaBH_4$ and reflux the resulting mixture for 3 hrs., pour the mixture into water. Extract the intermediate aminoacetal derivative into CH_2Cl_2 (2x 150 ml). Dry (over Na_2SO_4) and concentrate the resulting mixture to give 32.1 g of a tan residue. Dissolve the entire residue in 150 ml ethanol and further add 15.5 g

(0.16 mol) KSCN, 40 ml H_2O and 15 ml concentrated HCl. Reflux the mixture for 5 hrs., allow the mixture to cool and pour into 1 l of ice water and neutralize with dilute NaOH. Collect and dry the resulting crystals.

EXAMPLE 4

1,3-Dihydro-1-(4-pyrimidinylmethyl)-2H-imidazole-2-thione

A mixture of 10.8 g (0.1 mol) 4-pyrimidinecarboxaldehyde, 13.1 g (0.1 mol) amino acetaldehyde diethylacetal, 0.1 g TsOH and 300 ml ethanol is placed in a 500 ml round bottomed flask. The reaction is refluxed for 2 hrs. then concentrated to give the crude imine. The imine is dissolved in 250 ml ethanol and 3.8 g (0.1 mol) solid $NaBH_4$ added slowly. After addition is completed, the mixture is refluxed 2 hrs. The reaction is diluted with H_2O to a total volume of 1 l and the amine derivative extracted into CH_2Cl_2 (2 X 250 ml). After drying (Na_2SO_4) and concentration, the amine is obtained as an orange oil. Without further purification, the amine is dissolved in 200 ml ethanol and 11.6 g (0.12 mol) KSCN, 40 ml water and 15 ml concentrated hydrochloric acid added. The reaction is gently refluxed for 6 hrs, cooled and poured onto ice. The desired product, as a crystalline solid is collected and dried in a vacuum oven.

EXAMPLE 5

1,3-Dihydro-1-(2-(5-methylimidazolyl)methyl)-2H-imidazole-2-thione

A mixture of 11.0 g (0.1 mol) 4(5)-methyl-2-imidazolecarboxaldehyde, 13.3 g (0.1 mol) aminoacetaldehyde diethylacetal, 0.2 g TsOH and 200 ml ethanol is heated to reflux. After 1 hr., the reaction is cooled and concentrated. The residue is dissolved in 200 ml ethanol and 3.8 g (0.1 mol), solid $NaBH_4$ added in small portions. The reaction is then refluxed for 2 hrs.,

poured onto 1.2 L H_2O and the product extracted into CH_2Cl_2 (2 X 200 ml). The CH_2Cl_2 solution is dried (Na_2SO_4) and concentrated to give a tan oil. The oil is dissolved in 200 ml ethanol and 11.6 g (0.12 mol) KSCN, 40 ml H_2O and 15 ml concentrated hydrochloric acid added. The reaction is refluxed for 6 hrs. After cooling, the reaction is poured onto 1 L ice. The product, tan crystals, is collected by vacuum filtration and dried.

EXAMPLE 6

1,3-Dihydro-1-(2-furanylmethyl)-2H-imidazole-2-thione

A 500 ml flask is charged with 38.4 g (0.4 mol) furan-2-carboxaldehyde, 53.2 g (0.4 mol) aminoacetaldehyde diethylacetal and 100 ml ethanol. The solution is refluxed for 1-1/2 hrs. then concentrated under vacuum to give an orange oil. This oil is dissolved in 150 ml ethanol and 17 g (0.45 mol) $NaBH_4$ is added slowly. This mixture is refluxed 1-1/2 hrs., cooled and diluted with water. A little glacial acetic acid is added to destroy the excess $NaBH_4$. The product is extracted into EtOAc (2 X 300 ml). After drying ($NaSO_4$) and concentration, 70.3 g amino derivative is obtained; 21.3 (0.1 mol) amino derivative is placed in a 500 ml flask and 11.7 g (0.12 mol) KSCN, 150 ml ethanol, 40 ml water and 15 ml concentrated hydrochloric acid is added. The reaction is refluxed for 5 hrs. The cooled reaction is diluted with water and the product extracted into EtOAc. Drying (Na_2SO_4) and concentration gives 14.7 g crude product. Purification by flash chromotography (4% MeOH/CH_2Cl_2) yields 4.75 (26%) desired product mp 105.5-108°C (EtOAc).

EXAMPLE 7

1,3-Dihydro-1-(thienylmethyl)-2H-imidazole-2-thione

Under a blanket of nitrogen, 11.3 g (0.1 mol) 2-aminomethylthiophene is added to 19.6 g (0.11 mol) 1,1'-thiocarbonyldiimidazole in 200 ml anhydrous toluene at

0°C. The reaction is held at 0°C for 4 hrs. Then 10.5 g (0.1 mol) aminoacetaldehyde dimethyl acetal is added and the reaction is warmed at 80°C for 2 hrs. The toluene is removed and the residue dissolved in 100 ml ethanol, 15 ml water and 15 ml concentrated HCl. The mixture is refluxed 5 hrs., cooled and poured onto 1 L ice. After recrystallization (1/1 EtOH/H_2O) the desired product is obtained as white shiny crystals, mp 128-130°C.

EXAMPLE 8

1,3-Dihydro-1-(4-pyridyl)-2H)-imidazole-2-thione

Under a blanket of nitrogen, 14.1 g (0.15 mol) 4-aminopyridine is added to 28.5 g (0.16 mol) 1,1-thiocarbonyldiimidazole in 300 ml anhydrous DMF at 0°C. The reaction is held at 0°C for 4 hrs. To the 4-isothiocyanatopyridine formed 15.8 g (0.15 mol) aminoacetaldehyde dimethyl acetal is added and the reaction is warmed at 80°C for 24 hrs. The reaction is poured into water and extracted with ethyl acetate providing a dark residue on evaporation. This material is dissolved in 200 ml ethanol, 20 ml water and 20 ml concentrated hydrochloric acid. The mixture is refluxed for 5 hrs., cooled and poured onto 1 l ice. After purification, crystalline product is obtained as a tan solid.

EXAMPLE 9

1,3-Dihydro-1-(2-thienyl)-2H-imidazole-2-thione

A mixture of 2-isothiocyanatothiophene (16.9 g, 0.12 mol), aminoacetaldehyde dimethyl acetal (12.6 g, 0.12 mol) in 200 ml toluene is refluxed for 2 hrs. After removal of the toluene, the residue is dissolved in 200 ml ethanol and 45 ml conc. HCl added. After the reaction is refluxed for 5 hrs., it is poured onto ice. The product is collected and purified by recrystallization.

In a similar manner, by following the generic teachings related to Reaction Schemes A to C and by substantially following the procedures of the foregoing examples, there may be prepared the following 1,3-dihydro-2H-imidazole-2-thiones:

5-chloro-1-(2-thienylmethyl)-1,3-dihydro-2H-imidazole-2-thiones,
5-bromo-1-(2-thienylmethyl)-1,3-dihydro-2H-imidazole-2-thiones,
5-methyl-1-(2-thienylmethyl)-1,3-dihydro-2H-imidazole-2-thiones,
4-phenyl-1-(2-thienylmethyl)-1,3-dihydro-2H-imidazole-2-thiones,
5-benzyl-1-(2-thienylmethyl)-1,3-dihydro-2H-imidazole-2-thiones,
5-cyano-1-(2-thienylmethyl)-1,3-dihydro-2H-imidazole-2-thiones,
5-fluoro-1-(2-thienylmethyl)-1,3-dihydro-2H-imidazole-2-thiones,

and their 1-(2-thienylethyl)-, 1-(2-thienylpropyl)-, 1-(2-thienylbutyl) and 1-(2-thienyl) homlogs.

Similarly, the corresponding analogs of the foregoing may be prepared for the corresponding 1-position pyrazolyl, furyl, pyrimidinyl, pyrrolyl and imidazolyl substituted 1,3-dihydro-2H-imidazole-2-thiones.

EXAMPLE 10

1-(2-Thienyl)imidazole

Under nitrogen, solid imidazole (34 g, 0.5 mol) is added cautiously to a slurry of 20.9 g (0.55 mol) 50% NaH dispersion in 500 ml dry DMF. After hydrogen evolution ceases, 115 g (0.55 mol) 2-iodothiophene in 100 ml DMF is added. The reaction is heated at 150°C for 18 hrs. After cooling, the reaction is diluted with 2 l water and the product extracted into EtOAc (3 X 400 ml). After drying, (Na_2SO_4) the solvent is removed to give crude 1-(2-thienyl)imidazole. The product is purified by vacuum distillation.

EXAMPLE 11

1-(3-Thienylmethyl)imidazole

Procedure: In a 3 neck, round-bottomed flask reflux a mixture of 11.6 g (0.17 mol) imidazole, 30 g (0.17 mol) 3-bromomethylthiophene, 46 g (0.33 mol) K_2CO_3 and 400 ml dry acetone. After refluxing for 4 hrs. filter the reaction mixture and wash the inorganic solids with acetone. Remove the acetone under vacuum and partition the residue between H_2O/EtOAc. Wash the EtOAc layer several times with H_2O, dry (Na_2SO_4) and concentrate the washed material to obtain a pale yellow oil.

EXAMPLE 12

2-Cyano-1-(3-thienylmethyl)imidazole

In a 250 ml, 4-neck flask equipped with a nitrogen bubbler, gas inlet tube, thermometer and septum, add 100 ml acetonitrile and bubble cyanogen chloride (15 g, 0.24 mol) into the acetonitrile. Cool the solution in an ice bath and add 8.2 (0.05 mol) 1-(3-methylthienyl)-2H-imidazole. After the colorless solution turns yellow-orange and about 1 hr. after an orange precipitate forms, cool the slurry orange precipitates to -20°C, slowly add 42 ml (0.3 mol) of triethylamine, holding the temperature below 0°C. After 1 hr. at room temperature, pour the reaction onto 600 ml saturated $NaHCO_3$ and extract with ether (3 X 150 ml). Dry and combine organic layers to obtain tan oil. The oil is purified via Kugelrohr distillation to obtain a colorless oil.

In a similar manner, by treating the 1-substituted-4X (or 5X)-1,3-dihydro-imidazoles of Example 13 according to the procedures of this example, there may be prepared the corresponding 2-cyano derivatives.

EXAMPLE 13

1-(4-Pyridyl)imidazole

An ethanolic solution of 5.9 g (0.028 mol) 1,3-dihydro-1-(4-pyridyl-2H-imidazole-2-thione prepared in Example 8 is charged with 23.0 g Raney nickel and 10 ml concentrated ammonium hydroxide. The black slurry is refluxed for 2 hrs., then filtered to remove the nickel catalyst. The ethanol is removed under vacuum and the product is extracted into CH_2Cl_2 (2 X 100 ml). Drying ($NaSO_4$) and concentration gives the 1-(4-pyridyl)imidazole.

In a similar manner, the 2-thiones preparable by the procedures of Examples 1-9 may be converted to their corresponding reduced product by following the procedure of this example.

EXAMPLE 14

Methyl-2-[(1-2-thienylmethyl)-imidazoll oxalate

A solution of 1-(2-thienylmethyl)imidazole (4 g, 0.024 mol) in 100 ml CH_3CN was charged with 3.0 g methyl oxalyl chloride. The solution was stirred for 1 hr and then 4.1 ml (0.03 mols) Et_3N was added. The color changed and a white precipitate was formed. (TLC (60% EtOAc/hex) showed mainly one spot.) The mixture was diluted with H_2O and the product extracted into EtoAc (2 X 150 ml). After drying (Na_2SO_4) and concentration , 6.7 g of a brown oil was obtained. Flash chromatography (60% ethylacetate/hexane) gives 6.2 of the desired product as an orange-yellow oil.

In a similar manner, by treating the 1-substituted-4X (or 5X)-1,3-dihydro-imidazole prepared according to the procedures of Example 13, the analogous alpha keto esters may be prepared, which compounds may also be converted to the analogous alpha keto acids by standard procedures.

EXAMPLE 15

1-(2-Thienylmethyl)-2-(dimethylaminoethylthio)-imidazole

Stir a mixture of 8 g (0.041 mol) 1,3-dihydro-1-(2-thienylmethyl)-2H-imidazole -2-thione, 5.9 g (0.041 mol) 2-dimethylaminoethyl chloride hydrochloride, 200 ml ethanol and 17 ml 5N NaOH at ambient temperatures for 18 hrs. Remove the ethanol under vacuum and extract the product into Et_2O. Prepare the hydrochloride salt by adding etheral HCl. Collect and dry hygroscopic white solid.

In a similar manner, by substituting the reactant with the appropriate 2-thiones and by substantially following the procedure of this example there may be produced:

1-(2-thienylpropyl)-2-(dimethylaminoethylthio)-imidazole,
1-(3-thienylmethyl)-2-(dimethylaminoethylthio)-imidazole,
1-(4-pyrazolylmethyl)-2-(dimethylaminoethylthio)-imidazole,
1-(1-methylpyrrol-2-ylmethyl)-2-(dimethylaminoethylthio)-imidazole,
1-(2-thiazolylmethyl)-2-(dimethylaminoethylthio)-imidazole,
1-(4-pyrimidinylmethyl)-2-(dimethylaminoethylthio)-imidazole,
1-(5-methylimidazol-2-ylmethyl)-2-(dimethylaminoethylthio)-imidazole,
1-(2-furanylmethyl)-2-(dimethylaminoethylthio)-imidazole,
1-(4-pyrazolylmethyl)-2-(dimethylaminoethylthio)-imidazole,
1-(2-thienyl)-2-(dimethylaminoethylthio)-imidazole,
1-(3-thienyl)-2-(dimethylaminoethylthio)-imidazole,
1-(4-pyrazolyl)-2-(dimethylaminoethylthio)-imidazole,
1-(1-methyl-2-pyrrolyl)-2-(dimethylaminoethylthio)-imidazole,
1-(4-pyrimidinyl)-2-(dimethylaminoethylthio)-imidazole,
1-(2-furanyl)-2-(dimethylaminoethylthio)-imidazole,
1-(4-pyrazolyl(-2-(dimethylaminoethylthio)-imidazole,

as well as the des-alkylated aminoethylthio analogs of the foregoing.

EXAMPLE 16

2-Aminomethyl-1-(3-furylmethyl)imidazole

Place 4.0 g (0.021 mol) 2-cyano-1(3-furanylmethyl)-2H-imidazole, 20 ml ethanolic HCl, 20 ml ethanol and 1 g 10% Pd/C in a Parr hydrogenator with an initial pressure of 52 psi. After 18 hrs. remove the reaction mixture from the Parr hydrogenator, add 20 ml H_2O, remove the catalyst by filtration, concentrate the filtrate to obtain an off-white solid which is recrystallized from ethanol containing a little concentrated HCl to give the desired product as a white solid.

In a similar manner, the 2-cyano derivatives prepared according to procedures of Example 12 may be converted to their 2-aminomethyl derivatives by following the procedure of this example.

EXAMPLE 17

Ethyl-2-([1-(3-furylmethyl)imidazole]methaneimidate)

Under a blanket of nitrogen, mechanically stir a solution of 2-cyano-1-(3-thienylmethyl)imidazole (10 g, 0.052 mol), absolute ethanol (2.4 g, 0.052 mol) and 500 ml chloroform is cooled to -10°C. Anhydrous HCl is sparged into the reaction for 1 hr. as the temperature is held below 0°C. Stir the reaction for 1 hr. at 0°C under dry nitrogen. The excess hydrogen chloride is removed by bubbling dry nitrogen through the reaction. Shake the chloroform solution with cold saturated sodium bicarbonate. After drying ($NaSO_4$) and concentration, the imidate is obtained as a colorless oil that rapidly crystallized.

In a similar manner, the 2-cyano derivatives prepared according to the procedures of Example 12 may be converted to their analogous imino esters by following the procedure of this example.

EXAMPLE 18

1-(3-Thienylmethyl)-2-thioamidoimidazole

Hydrogen sulfide is sparged into a solution of 3.0 g (0.015 mol) of the amidine of Example 21 in 20 ml pyridine for 5 minutes. The reaction is warmed at 50°C for 8 hrs. After cooling, the majority of the pyridine is removed under vacuum. The residue is mixed with 200 ml cold water. The yellow solid is collected and dried.

EXAMPLE 19

1-(3-Thienylmethyl)-2-amidoimidazole

A mixture of 5.0 g (0.026 mol) of the nitrile of Example 12 and 120 ml concentrated hydrochloric acid is placed in a 500 ml round bottomed flask. A small amount of ethanol is added to aid in solubility of the nitrile. The reaction is refluxed for 8 hrs. and then the ethanol is distilled away. The white crystals are collected and dried.

In a similar manner, the 2-cyano derivatives preparable according to the procedures of Example 12 may be converted to their analogous 2-amido derivatives by following the procedures of this example.

EXAMPLE 20

1,3-Dihydro-1-(2-thiazolylmethyl)-2H-imidazole-2-thione

In a 500 ml round bottom flask is placed 6 g (0.053 mol) 2-thiazolecarboxaldehyde, 7.0 g (0.053 mol) amino-acetaldehyde, diethylacetal, 0.1 g TsOH and 150 ml ethanol. The reaction is refluxed 2 hrs., cooled and concentrated. The residue is redissolved in 200 ml

is redissolved in 200 ml ethanol and 2.3 g (0.06 mol) $NaBH_4$ added. The reaction is refluxed 4 hrs. then poured onto 500 ml water. The amino derivative is extracted into CH_2Cl_2 (2 X 100 ml) dried (Na_2SO_4) and concentrated to give an orange oil. The entire product is dissolved in 200 ml ethanol and 5.1 g (0.053 mol) KSCN, 30 ml water and 8 ml concentrated HCl added. The reaction is refluxed for 6 hrs., cooled and then poured onto 1 l ice water. The tan solid is collected and dried.

EXAMPLE 21

1-(3-Thienylmethyl)imidazolemethanimidamide Hydrochloride

An ethanolic solution of 12 g (0.051 mol) imino ester of Example 17 is treated with 4.0 g (0.074 mol) NH_4Cl in 20 ml ethanol. The solution was stirred at room temperature for 7 hrs., then concentrated to give a white solid. Recrystallization (ethanol) gives the amidine hydrochloride salt as colorless crystals.

In a similar manner, the 2-imino esters prepared by the procedures of Example 17 (or their N-alkyl derivatives) may be converted to the analogous amidine derivatives by following the procedure of this example.

EXAMPLE 22

1-(2-thienylmethyl)-2-imidazolemethanimidhydroxyamide Hydrochloride

A mixture of 2 g (0.0085 mol) of the imidate ester of Example 17 and 0.63 g (0.009 mol) hydroxylamine hydrochloride is stirred in 100 ml ethanol for 24 hrs. The reaction is diluted with water and the desired product as a white crystalline product, is collected and dried.

In a similar manner, the imidate esters preparable by the procedure of Example 17 may be converted to their corrresponding hydroxylamidines by following the procedure of this example.

The compounds of this invention exert valuable *in vitro* and *in vivo* pharmacological effects in that they are dopamine beta-hydroxylase (DBH) inhibitors and thus are expected to be valuable therapeutic agents useful in the treatment of hypertension.

The DBH inhibitory properties of the compounds of this invention can readily be determined *in vitro* by standard and well known procedures for assaying conversion of tyramine to octopamine in the presence of dopamine beta-hydroxylase. Enzymatic oxygenation by DBH is determined in aqueous solution in the presence of molecular oxygen, an electron donor such as ascorbate, and the necessary cofactors for the enzyme at pH of 5 and a temperature of 20°-40°C, preferably 37°C. The test compound is added at the desired concentration, and the system is incubated. Activity is measured by measuring the oxygen uptake using a polarographic electrode and an oxygen monitor by the method of S. May et al., J. Biol. Chem. 256, 2258 (1981). Inhibition is given in molar concentration of compound at which DBH activity was halved (IC_{50}) when the test compounds were tested according to the above described procedure. The IC_{50} (expressed in micromolar units) data of some of the compounds of this invention are expressed in Table I.

The compounds of this invention may also be tested for their *in vivo* DBH inhibiting property according to the procedure of Felice, Felice and Kessinger, J. Neurochem., 31, 1461-1465 (1978) wherein the effects on peripheral

dopamine and norepinephrine levels are determined. In this test spontaneously hypertensive rats are dosed (i.p.) at 50 mg per kilogram of body weight and sacrificed three hours later. Average results, expressed in micrograms of dopamine (DA) per gram of heart tissue are determined with the difference between the control and the treated rats being the *in vivo* (DBH) inhibitory effect of the test compound. Results on some of the compounds of this invention are shown in Table I.

The ability of the compounds of this invention to lower blood pressure can be determined *in vivo* using spontaneously hypertensive rats (SHR's) according to standard and well known procedures. The test compound is administered intraperitoneally (ip) to rats and the blood pressure monitored continuously. Since DBH is a major enzyme in the synthetic pathway of the catecholamines, it would be expected that the presence of an inhibitor would act to decrease the amount of catecholamines produced, and thereby have an antihypertensive effect. The results of the testing for this antihypertensive effect are shown in Table I.

TABLE I

Inhibition of DBH In Vitro and In Vivo at
50 mg/kg, IP, 3 Hours Post Dose in SHR's*

Compound	IC_{50} (μM)	Heart DA (μg/g)	Max Change MBP (mmHg)
1	5.4	Control .024±.003 Treated .066±.005***	-30±21[a] (18%)
2	1.6	Control .024±.003 Treated .066±.012***	-21±27 (12%)
3	1.0	Control .024±.003 Treated .079±.004***	--
4	8.1	Control .021±.002 Treated .046±.009***	-22±5 (13%)
5	6.0	Control .021±.002 Treated .048±.004***	-37±19 (10%)
6	2.9	Control .025±.007 Treated .045±.005***	-42±17 (25%)

Compound 1 - 1,3-Dihydro-1-(2-thienylmethyl)-2H-imidazole-2-thione

Compound 2 - 1,3-Dihydro-1-(3-thienylmethyl)-2H-imidazole-2-thione

Compound 3 - 1-(2-Furanylmethyl)-1,3-dihydro-2H-imidazole-2-thione

Compound 4 - 1-[(5-Chloro-2-thienyl)methyl]-1,3-dihydro-2H-imidazole-2-thione

Compound 5 - 1,3-Dihydro-1-[(5-methyl-2-thienyl)methyl]-2H-imidazole-2-thione

Compound 6 - 1-[(Fluoro-2-thienyl)methyl]-1,3-dihydro-2H-imidazole-2-thione

* Spontaneously Hypertensive Rats. *** $p<.001$.

a Mean Difference ± Standard Deviation.

Based on the foregoing test results, as well as by comparison with similar test results for compounds known to be useful, the compounds of this invention exert their DBH inhibiting effects (i.e., their IC_{50} effects) at from 1 to 100 micromolar concentrations and are expected to exhibit end-use antihypertensive activity at doses of about 10 mg to 100 mg per kilogram of body weight.

As is true in most large classes of compounds suitable for use as chemotherapeutic applications, certain subgeneric groups and certain specific compounds will exhibit properties which render them more preferably than the entire class. In this instance it is expected that those compounds of formula I wherein X is hydrogen or lower alkyl, particularly methyl and ethyl are preferred, compounds wherein Y is SH or $-SCH_2CH_2NH_2$, $-CH_2NH_2$ or amidine are also preferred, compounds wherein n is 1 or 3 are preferred and compounds wherein the heterocycle is 2- or 3- thiophene or furan are preferred particularly when these heterocycles bear a halogen or lower alkyl function in the ring. Specifically preferred compounds are

2-[1-(2-thienylmethyl)-imidazoyl] oxylate;
2-aminomethyl-1-(3-thienylmethyl)imidazole;
1-(3-thienylmethyl)imidazolemethanimidamide hydrochloride;
1,3-dihydro-1-(2-thiazolylmethyl)-2H-imidazole-2-thione;
1,3-dihydro-1-(2-thienylmethyl)-2H-imidazole-2-thione;
1,3-dihydro-1-(2-furanylmethyl)-2H-imidazole-2-thione;
1-(2-thienylmethyl)-2-imidazolemethanimidhydroxyamide hydrochloride;
1,3-dihydro-1-(3-thienylmethyl)-2H-imidazole-2-thione; and
1,3-dihydro-1-(4-pyrazolylmethyl)-2H-imidazole-2-thione.

As stated above, the compounds of this invention are useful in the treatment of hypertension. In the management of hypertension, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like. The compounds of this invention can be administered to patients (animals and human) in need of such treatment in dosages that will provide optimal pharmceutical efficacy. Although the dose will vary from patient to patient depending upon the nature and severity of disease, the patient's weight, special diets then being followed by a patient, concurrent medication, and other factors which those skilled in the art will recognize, the dosage range will generally be about 10 to 100 mg per kilogram of patient body weight per day, which can be administered in single or multiple doses. Naturally these dose ranges can be adjusted on a unit basis as necessary to permit divided daily dosage and, as noted above, the dose will vary depending on the nature and severity of the disease, weight of patient, special diets and other factors.

Typically, these combinations can be formulated into pharmaceutical compositions according to standard procedures generally known in the art.

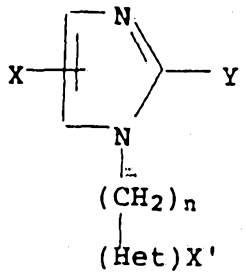
About 1 to 100 mg of a compound or mixture of compounds of Formula I or a physiologically acceptable salt is compounded with a physiologically acceptable vehicle carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in thses compositions or preparations is such that a suitable dosage in the range indicated is obtained.

Illustrative of the adjuvants which may be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent such as corn starch, pregelatinized starch, algenic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or a synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, antioxidants and the like can be incorporated as required.

The claims defining the invention are as follows:

1. A compound of the formula



I

including the 2-thione tautomers thereof, and the non-toxic pharmaceutically acceptable salts thereof, wherein n is zero or 1-4, X is hydrogen, cyano, C_{1-6} lower alkyl, ~~halogeno~~ Cl, Br, phenyl, or benzyl, z-substituted phenyl and benzyl with Z being C_{1-6} lower alkyl or halogeno, Y is ~~hydrogen,~~ aminomethyl, amido, alpha keto acid and their C_{1-6} esters, thioamido, amidino, aminoethylthio, or sulfhydryl, with the proviso that when Y is sulfhydryl or aminoethylthio, then X is hydrogen, (Het)X' is a heterocycle of the group consisting of thienyl, furyl, ~~pyridyl,~~ pyrimidinyl, pyrazolyl, pyrrolyl, thiazolyl and imidazol-2-yl, optionally substituted with either a halogen or a C_{1-6} lower alkyl with the proviso that when Y is SH and Het is 2-thienyl, then n is other than one.

2. Compounds of claim 1 wherein n is one.

3. Compounds of claim 1 wherein X is hydrogen.

4. Compounds of claim 1 wherein X is lower alkyl.

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5. Compounds of claim 1 wherein Y is -SH or $-SCH_2CH_2NH_2$.

6. Compounds of claim 1 wherein Y is $-CH_2NH_2$.

7. Compounds of claim 1 wherein Het is 2- or 3-furyl.

8. Compounds of claim 7 wherein n is zero or one.

9. Compounds of claim 8 wherein Y is SH.

10. Compounds of claim 1 wherein Het is 2- or 3-thienyl.

11. Compounds of claim 10 wherein n is zero or one.

12. Compounds of claim 11 wherein Y is SH.

13. A compounds of claim 1, said compound being 2-(1-(2-thienylmethyl)-imidazoyl) formic acid.

14. A compound of claim 1, said compound being 2-aminomethyl-1-(3-thienylmethyl)imidazole.

15. A compound of claim 1, said compound being 1-(3-thienylmethyl)imidazolemethanimidamide hydrochloride.

16. A compound of claim 1, said compound being 1,3-dihydro-1-(2-thiazolylmethyl)-2H-imidazole-2-thione.

~~17. A compound of claim 1, said compound being 1,3-dihydro-1-(2-thienylmethyl)-2H-imidazole-2-thione.~~

~~18.~~ 17. A compound of claim 1, said compound being 1,3-dihydro-1-(2-furanylmethyl)-2H-imidazole-2-thione.

~~19.~~ 18. A compound of claim 1, said compound being 1-(2-thienylmethyl)-2-imidazolemethanimidhydroxyamide hydrochloride.

~~20.~~ 19. A compound according to claim 1 substantially as hereinbefore described with reference to any one of the examples.

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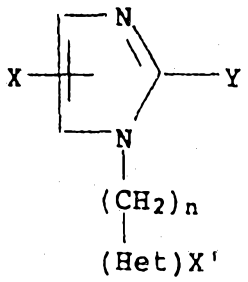
~~21.~~ 20. A method for treating hypertension which comprises administering to a patient in need of such treatment a pharmaceutically effective amount of a compound according to any one of claims 1 to ~~19~~ 19.

~~22.~~ 21. The processes for preparing compounds of the general formula



I

including the 2-thione tautomers thereof, and the non-toxic pharmaceutically acceptable salts thereof, wherein n is zero or 1-4, X is hydrogen, cyano, C_{1-6} lower alkyl, chloro, bromo, phenyl, or benzyl, Z-substituted phenyl and benzyl with Z being C_{1-6} lower alkyl or halogeno, Y is aminomethyl, amido, alpha-keto acid and their C_{1-6} esters, thioamido, amidino, aminoethylthio, or sulfhydryl, with the proviso that when Y is sulfhydryl or aminoethylthio, then X is hydrogen, (Het)X' is a heterocycle of the group consisting of thienyl, furyl, pyrazolyl, pyrimidinyl, pyrrolyl, thiazolyl and imidazol-2-yl, optionally substituted with either a halogen or a C_{1-6} lower alkyl, said processes being comprised of

a) the cyclization of a Schiff's base of the formula

$$X'\text{-(Het)-}(CH_2)_n NHCHX^2CH(O\text{-}C_{1-6}\text{ alkyl})_2$$

II

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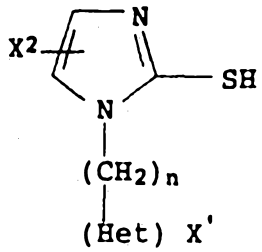
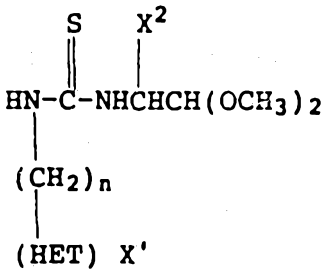
by the treatment with an aqueous acid in the presence of an alkali metal isothiocyanate to produce a compound of the formula



III

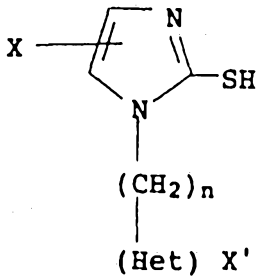
wherein n is other than zero, X^2 is hydrogen, cyano, C1-6 alkyl, phenyl or benzyl, the phenyl or benzyl each optionally bearing a C_{1-6} alkyl substituent,

b) the cyclization of a compound of the formula



IV

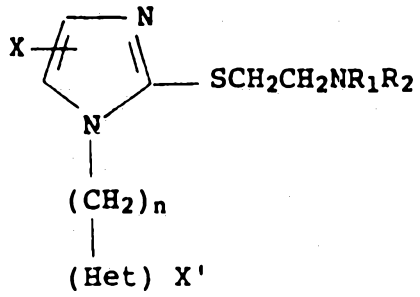
by treatment with an aqueous acid to produce a compound of the formula



V

c) the alkylation of a compound of formula V by contacting with an aminoethylhalide of the formula $R_1R_2NCH_2CH_2$ halide

at ambient temperatures, in the presence of a base, to produce a compound of formula VI



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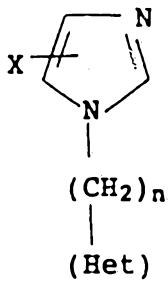
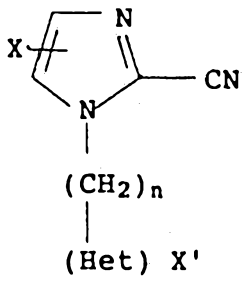
d) the cyanogenation of a compound of formula VII



VII

by treatment with a cyanogen halide, in an inert atmosphere, at room temperature followed by treatment, with a base, of the so-obtained in situ product, at temperatures below °C to prepare a compound of formula VIII



VIII

e) the conversion of the cyano moiety of a compound of formula VIII

(1) to its aminomethyl derivative by chemical reduction procedures, and optionally converting said amino

methyl substituent to its corresponding N-alkyl derivatives by reaction with an appropriate aldehyde under Borsch reduction conditions,

(2) to its imidate ester derivative (i.e., HN=C-OR) by reaction with an appropriate alcohol, followed by

(a) an optional conversion of the HN=C-OR moiety to its corresponding amidino derivatives (i.e., HN=C-NH_2 or HN=C-NR_1R_2) by reaction with the appropriate amine in an acidic medium, and optionally converting said amidino moieties to their corresponding thioamido derivatives (i.e., S=C-NH_2 or S=C-NR_1R_2)by reaction with H_2S in pyridine, or

(b) conversion of the HN=C-OR moiety to its hydroxy amidino (i.e., HON=C-NH_2) derivative which derivative optionally is converted to its alkylated derivative (i.e., HON=C-NR_1R_2) by treatment with an appropriate amine in the presence of 1 equivalent of acid,

(3) to its thioamide derivative (i.e., S-C-NH_2) by reaction with H_2S in pyridine, and

(4) to its amide (i.e., $CONH_2$) by acid catalysis.

22. A process according to claim 21 substantially as hereinbefore described with reference to any one of the examples.

~~22~~ 23. A compound when prepared by the process of claim ~~22~~ 21 or claim 22.

~~23~~ 24. A pharmaceutical composition suitable for use in the the treatment of hypertension which comprises the dopamine beta hydroxylase inhibitor 1-(2-thienylmethyl)-1H-imidazol-2-thione in admixture with a pharmaceutically acceptable carrier.

~~24~~ 25. A pharmaceutical composition suitable for use in the treatment of hypertension which comprises a compound according to any one of claims 1 to 19 or claim 23 in admixture with a pharmaceutically acceptable carrier.

DATED : 14th November, 1988
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