

PATENT SPECIFICATION

(11) 1 492 352

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- (21) Application No. 7654/76 (22) Filed 26 Feb. 1976
 (31) Convention Application No. 554372
 (32) Filed 3 March 1975
 (31) Convention Application No. 641420
 (32) Filed 17 Dec. 1975 in
 (33) United States of America (US)
 (44) Complete Specification published 16 Nov. 1977
 (51) INT CL² C07D 233/54 A61K 31/44 31/415 C07D 401/04
 405/04 409/04 (C07D 401/04 213/00 233/00)
 (C07D 405/04 307/00) (C07D 409/04 333/00)



- (52) Index at acceptance
 C2C 1173 1300 1410 1470 1510 1530 215 21X 220 222 225 226
 227 22Y 246 247 248 250 251 252 253 254 257 25Y 280
 28X 29X 29Y 305 30Y 311 313 31Y 322 323 326 32Y 337
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 790 79Y KH LF LG LS LY LZ TA TB TCUK WA WK

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(54) IMIDAZOLES

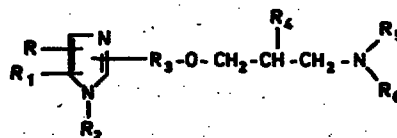
(71) We, MERCK & CO. INC., a corporation duly organized and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

Various chemical agents are available for treating hypertension in man and animals. Certain trifluoromethyl imidazoles are known to have substantial antihypertensive activity. These imidazoles are disclosed in U.S. 3,786,061.

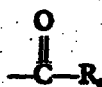
Another class of agents known as β -adrenergic blocking agents, are also available. These β -blocking agents affect cardiac, vascular and pulmonary functions and can be mild antihypertensives. Specifically, these agents have the capability of reducing heart rate, counteracting vasodepression and suppressing bronchodilatation. β -adrenergic blocking agents, their chemical structure and activity, are disclosed in "Clinical Pharmacology and Therapeutics" 10, 292—306 (1969). Various β -adrenergic blocking agents are also described in the following patents: U.S. 3,048,387; U.S. 3,337,628; U.S. 3,655,663; U.S. 3,794,650; U.S. 3,832,470; U.S. 3,836,666; U.S. 3,850,945; U.S. 3,850,946; U.S. 3,850,947; U.S. 3,852,291 and British 1,194,548.

Where an antihypertensive agent acts principally via vasodilation, it may cause undesirable side effects such as substantially increased heart rate (tachycardia).

The present invention provides novel imidazoles having the formula:

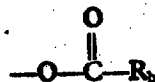


in which each of R and R₁, which are similar or dissimilar, is hydrogen, C₁₋₁₀ alkyl, substituted C₁₋₁₀ alkyl having 1—3 substituents, cycloalkyl, aryl, substituted aryl having 1—5 substituents, a heterocyclic group having 5—6 ring atoms, halogen, cyano, carboxy, carboxy derivatives, or



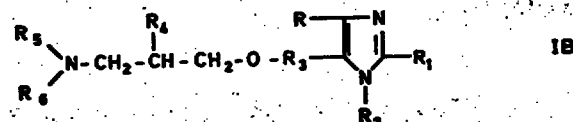
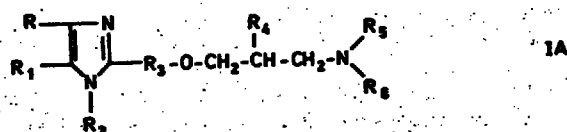
where R₄ is H or C₁₋₄ alkyl; R₂ is hydrogen, C₁₋₁₀ alkyl, hydroxy C₁₋₁₀ alkyl or

C_{3-6} alkenyl; R_3 is a bivalent aromatic group having 6 ring atoms of which 0—2 are other than carbon, a substituted bivalent aromatic group having 1—4 substituents, fused-ring bivalent aromatic group having 9—10 ring atoms of which 0—2 are other than carbon, or substituted fused-ring bivalent aromatic group having 1—4 substituents; R_4 is hydroxy or



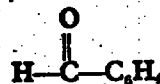
where R_6 is C_{1-6} alkyl, and each of R_3 and R_5 , which are similar or dissimilar, is hydrogen, C_{1-6} alkyl, cycloalkyl or substituted C_{1-6} alkyl or R_3 and R_5 are joined to form a 5—6 membered N-alicyclic ring; and pharmacologically acceptable salts thereof. Compounds of this present invention have unexpected antihypertensive activity and β -adrenergic-blocking activity. The salts may be acid-addition or quaternary ammonium salts.

Compounds of particular interest have the formulae:



Useful R and R_1 alkyl groups include unsubstituted as well as substituted alkyl, cycloalkyl as well as branched and linear alkyl groups. These alkyl groups may contain up to 10 alkyl carbons, preferably up to 8 alkyl carbon atoms and particularly from 1 to 6 alkyl carbons. Examples of suitable R and R_1 unsubstituted alkyl groups are methyl, isopropyl, cyclopropyl, cyclopentyl, 2-methyl-*n*-butyl, decyl and 2-ethyl-*n*-hexyl; suitable R and R_1 substituted alkyl groups have 1—3 substituents such as halo (Cl, Br, I, F), hydroxy, phenyl, C_{1-4} alkoxy, exemplified by $-CCl_3$, bromohexyl, $CH_3-O-CH_2-CH_2-$, hydroxypropyl, diiodethyl, trifluoromethyl, benzyl and chlorodecyl.

Useful R and R_1 aryl groups include aryl groups having up to 10 ring carbon atoms. These aryl groups include single-ring and fused-ring aryls, either unsubstituted having from 1 to 5 substituents. These substituents include alkyl, preferably C_{1-6} alkyl, especially methyl, alkoxy, preferably C_{1-6} alkoxy, cyano, halo, (Cl, I, Br and F), $-CO.NYZ$ where each of Y and Z is hydrogen or C_{1-6} alkyl, nitro, amino, carboxy, hydroxy, carbonyl, $-SH$, sulfamoyl, thioalkyl and phenyl. Examples of suitable aryl R and R_1 groups are phenyl, chlorophenyl, dibromophenyl, fluorophenyl, toluyl, xylyl, hexylphenyl, dodecylphenyl, *tert*-butylphenyl, methoxyphenyl, $C_6H_{13}-O$ -phenyl, $HO-C_6H_4-$, carboxyphenyl,



sulfamoylphenyl, *N,N*-dimethylsulfamoylphenyl, naphthyl, indanyl, chloronaphthyl, trichlorophenyl, $HO-CH_2-C_6H_4-$, pentafluorophenyl, the tetralin group (tetrahydronaphthyl), cyanophenyl, chlorohydroxyphenyl, $(C_{1-6} \text{ alkyl})-S-C_6H_4-$, and



Useful R and R_1 heterocyclic groups are those having 5—6 ring atoms of which 1—3 and preferably 1—2 are hetero atoms, and the quinoyl group. Substituted as well as unsubstituted heterocyclic groups are included. The hetero atoms are O, S and N. Examples of suitable R and R_1 heterocyclic groups are pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, substituted pyridyl such as dimethylpyridyl, methylpyridyl,

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—2 are other
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and 2-ethyl-
ents such as
Cl₃, bromo-
thyl, benzyl

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ring carbon
unsubstituted
eferably C₁₋₆
l, I, Br and
nitro, amino,
nples of suit-
fluorophenyl,
thoxyphenyl,

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naphthyl, tri-
(tetrahydro-
and

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oms of which
substituted as
ms are O, S
yl, pyrazinyl,
nethylpyridyl,

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chloropyridyl, dichloropyridyl, diethylpyridyl, trimethylpyridyl, methylethylpyridyl, ethylpyridyl, bromopyridyl, and analogous substituted pyrazinyl, pyrimidinyl and pyridazinyl groups; pyridyl-N-oxide, methylpyridyl-N-oxide, furyl and thienyl.

Other useful R and R₁ groups are cyano, carboxy, carboxy derivatives such as (C₁₋₆ alkoxy) carbonyl, carbamoyl, N-mono-(C₁₋₆ alkyl) carbamoyl and N,N-di-(C₁₋₆ alkyl) carbamoyl; halogen, preferably Br, Cl and F; and —CO—R₂ where R₂ is hydrogen or C₁₋₆ alkyl.

It is preferred that at least one of R and R₁ be hydrogen.

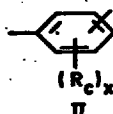
Useful R₂ alkyl groups have up to 10 carbons, are unsubstituted or mono-hydroxysubstituted and include cycloalkyl as well as branched and straight-chain alkyl. R₂ alkyl groups having 1—6 carbons and especially 1—4 carbon atoms are preferred. Examples of suitable R₂ alkyl groups are methyl, ethyl, decyl, *tert*-butyl, isopropyl, 2,2,4-trimethyl-*n*-butyl, cyclohexyl, 2-hydroxyethyl, 3-hydroxypropyl and 2-hydroxybutyl. Useful R₂ alkenyl groups have 3—6 carbon atoms and are exemplified by allyl and —CH₂—CH₂—CH₂—CH=CH₂.

Preferred compounds are those where R₂ is H.

R₃ is a bivalent aromatic group. It may be single-ring (6 ring atoms) or fused-ring, (9—10 ring atoms); it has 0, 1 or 2 nitrogen ring atoms, and it may be substituted or unsubstituted. Examples of useful heterocyclic groups are pyridinediyls, (1,2-pyridinediyl, 1,3-pyridinediyl and 1,4-pyridinediyl), halopyridinediyl, alkylpyridinediyls, especially C₁—C₃ alkylpyridinediyls, pyridinediyl-N-oxides, cyanopyridinediyl, pyrazinediyl, pyridazinediyl, pyrimidinediyl and quinolinediyl, preferably pyridinediyl and substituted pyridinediyl, e.g. chloropyridinediyl, methylethylpyridinediyl, methylpyridinediyl, 2-chloro-4-methylpyridinediyl, bromopyridinediyl, 2,4,6-trimethylpyridinediyl, dimethylpyridinediyl, and the N-oxides, e.g. pyridinediyl-N-oxide and methylpyridinediyl-N-oxide.

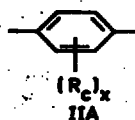
Useful R₃ carbocyclic aromatic groups include phenylene groups and fused ring groups such as naphthalenediyl, hydrogenated naphthalenediyls such as tetrahydronaphthalenediyl, and indanediyl.

Preferred R₃ carbocyclic aromatic groups are those having the formula



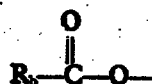
where *x* is 0, 1, 2, 3 or 4 and R_c is an alkyl group, linear or branched, and preferably containing from one to four carbon atoms, a C₃₋₆ cycloalkyl group, halogen such as Cl, I, Br or F, alkoxy, preferably C₁₋₄ alkoxy, hydroxy, nitro, cyano, phenyl, carbamoyl, N-(C₁₋₆ alkyl) carbamoyl and N,N-di-(C₁₋₆ alkyl)carbamoyl. Examples of suitable preferred carbocyclic aromatic groups of Formula II are phenylene, tetrahydronaphthalenediyl, fluorophenylene, dibromophenylene, trichlorophenylene, iodo-phenylene, hydroxyphenylene, methylphenylene, methyl-hydroxy-phenylene, nitro-phenylene, carboxyphenylene, methoxyphenylene, cyclohexylphenylene, amino-phenylene, dimethylchlorophenylene, butoxyphenylene, dichlorophenylene, cyano-phenylene, tetramethylphenylene, dimethylphenylene, carbamoylphenylene and N,N-dimethylcarbamoylphenylene.

An especially preferred R₃ group is the carbocyclic group having the formula



particularly when *x* is 0, 1 or 2 and especially 0.

R₄ includes the hydroxy group and the ester group



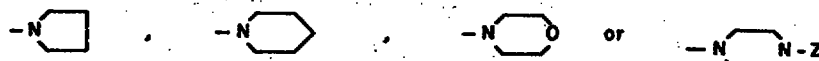
where R₅ is C₁—C₆ alkyl such as methyl, isopropyl, *tert*-butyl, hexyl or ethyl. Compounds where R₄ is OH are preferred.

The R₅ and R₆ groups are hydrogen or alkyl groups. The alkyl groups preferably have from 1—6 alkyl carbon atoms and may be branched, linear, or cyclic;

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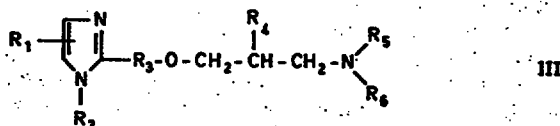
substituted or unsubstituted. Examples of suitable alkyl and substituted alkyl groups are methyl, *n*-hexyl, isopropyl, 2,2,4-trimethyl-*n*-butyl, cyclopropyl, cyclohexyl, chlorobutyl, *tert*-butyl, benzyl, 3,4-dimethoxyphenethyl and 6-phenylhexyl.

The R_5 and R_6 groups may also be joined to form a 5-6 membered N-alicyclic ring such as

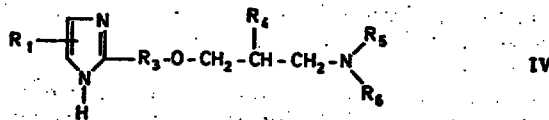


where Z is H or C_1-C_{10} alkyl.

It is preferred that one of R_5 and R_6 be hydrogen while the other is C_1-C_6 alkyl, preferably C_3-C_4 branched alkyl and particularly *t*-butyl. Compounds of formula I which are preferred are those in which R is hydrogen, which are represented by the formula



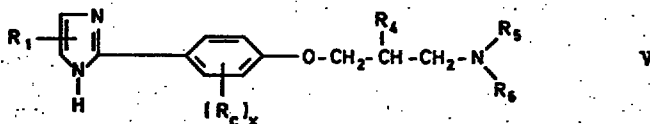
Another series of preferred compounds is that in which R and R_2 are both hydrogen. These compounds have the formula



When R_2 is hydrogen, the 4 and 5 positions in the imidazole are substantially equivalent.

In the compounds of Formula IV, it is preferred that R_1 be hydrogen, trihaloalkyl (preferably $-CF_3$), cyano, $-CH_3$, phenyl, substituted phenyl having 1-5 substituents (preferably Cl, Br or F), or a heterocyclic group such as thienyl, furyl, methylpyridyl, pyridyl or pyridyl-N-oxide.

Another preferred series of compounds is that having the formula



where R_1 is $-CH_3$, H, phenyl, pentafluorophenyl, *p*-chlorophenyl, *p*-fluorophenyl, *p*-methoxyphenyl, 2-thienyl, $-CF_3$ or pyridyl; x is 0, 1, 2 or 3 and R_6 is halo (preferably chloro), C_1-3 alkyl (preferably $-CH_3$), or cyano.

Another series of preferred compounds are those having the formula V where R_4 is $-OH$.

In a particularly preferred series of compounds having formula V, R_1 is OH and only one of R_5 and R_6 is C_1-6 alkyl, preferably cyclic, cyclic-substituted or branched C_3-4 alkyl such as *tert*-butyl, cyclopropyl, 1-methyl-3-phenylpropyl or 1-methyl-2-phenylethyl.

An especially preferred series of compounds is one having formula V where R_1 is $-CF_3$, R_4 is OH and one of R_5 and R_6 is hydrogen while the other is C_1-6 alkyl, preferably C_3-4 cyclic or branched hydrocarbon alkyl, especially *tert*-butyl.

The compounds of the present invention include all the optical isomer forms. In other words, the compounds may be mixtures containing the optical isomers such as racemic mixtures, as well as the individual optical isomers.

The compounds of the present invention also include the non-toxic pharmacologically acceptable acid addition and quaternary ammonium salts of the present imidazoles. The acid addition salts are prepared by treating the imidazole with an appropriate amount of a suitable organic or inorganic acid. Examples of useful organic acids are carboxylic acids such as maleic acid, tartaric acid, acetic acid, pamoic acid, oxalic acid, propionic acid, salicylic acid, succinic acid, citric acid, malic acid and isethionic acid; useful inorganic acids are hydrohalo acids such as HCl, HBr and HI, sulfuric acid and H_3PO_4 .

alkyl groups
hexyl, chloro-
ed N-alicyclic



er is $\text{C}_1\text{--}\text{C}_6$
mpounds of
e represented

II

R_2 are both

V

substantially

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having 1-5
thienyl, furyl,

A

V

fluorophenyl,
 R_6 is halo

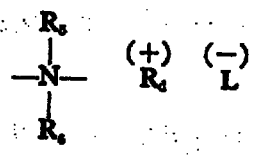
V where

is OH and
or branched
1-methyl-2-

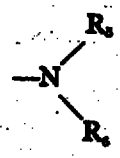
V where
other is C_{1-6}
tert-butyl.
forms.
isomers

pharmaco-
the present
with an
organic
pamoic acid,
acid and
HBr and

The quaternary salts are characterized by the group

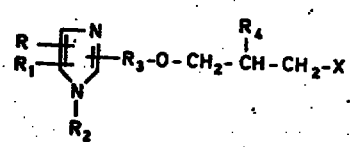


where R_3 and R_5 are C_{1-6} alkyl, R_4 is C_{1-6} alkyl and L is the anion of a non-toxic acid, preferably a halide such as the iodide. These salts are prepared by any suitable method—for example, by reacting any imidazole of the present invention having the



with an alkyl halide, preferably the iodide such as ethyl iodide or methyl iodide, in a suitable solvent such as methanol, ethanol or dimethylformamide (DMF). The reaction is generally carried out at room temperature. The quaternary salt is obtained directly on removing the solvent.

Compounds of the present invention may be prepared by any convenient method. One method (Method A) of preparing the present compounds is by amination of a compound having the formula

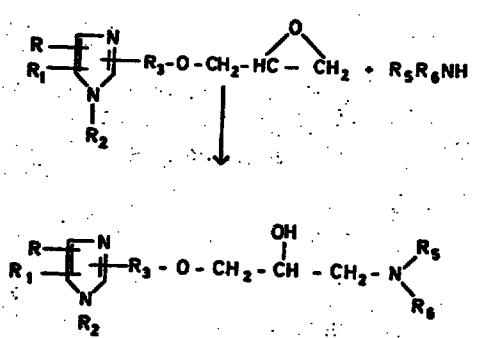


VI

where X is a halogen, preferably Br, I or Cl. When NH_3 is the aminating agent, X is replaced by ---NH_2 while when a primary or secondary, acyclic or alicyclic amine is used, X is replaced by the corresponding $\text{---NR}_5\text{R}_6$ group. Typically, the amination can be carried out by heating a mixture of the halo compound VI and the amine, e.g. *t*-butylamine, for a sufficient period of time and then isolating the aminated product

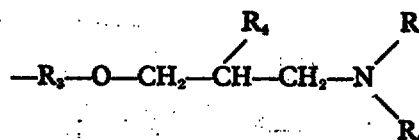
U.S. 3,337,628 discloses such procedures. An especially useful method of preparing imidazoles of the present invention where R_4 is ---OH is by reaction of ammonia or a suitable amine reactant with an epoxy compound as illustrated by the following general reaction equation:

Method B



The reaction is generally carried out in solution with excess amine reactant serving as the solvent. However, other solvents may be used such as triethylamine, pyridine and tetrahydrofuran. The reaction is conveniently conducted at reflux temperature. However, the reaction temperature can be varied from room temperature to temperatures above reflux. The reaction may be carried out at atmospheric pressure but it can be carried out at pressures above atmospheric, if desired.

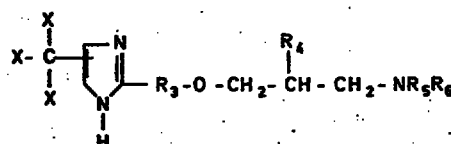
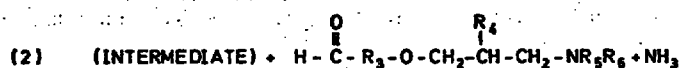
A method of preparing compounds of formula I where R and R_2 are H, R_1 is trihaloalkyl and



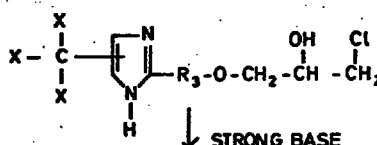
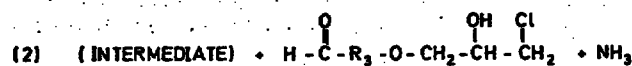
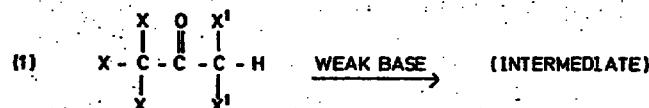
is in the 2 position in the imidazole ring involves the reaction of 1,1,1 trihalo-3,3-dihaloacetone, aryl aldehyde and NH_3 . Depending on the type of arylaldehyde used, different sequences of reactions are utilized, and these are illustrated by the following sets of equations. In these equations X and X^1 are F, Br or Cl—and it is preferred that X is F and X^1 is Br.

Method C

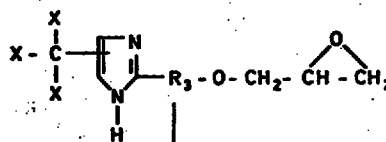
Sequence 1



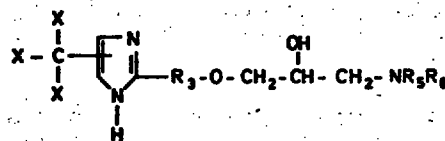
Sequence 2



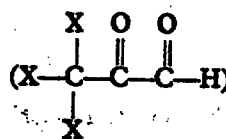
STRONG BASE



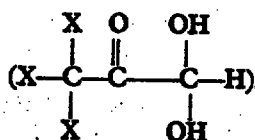
HNR_5R_6



The intermediate in the above equations is believed to be a glyoxal



or a hydrated glyoxal

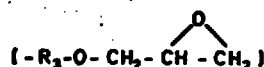


This intermediate is generally prepared as an aqueous mixture by treating the halogenated acetone with an aqueous solution of a weak base such as sodium acetate trihydrate. This solution is heated for a period of time and at a temperature sufficient to form the intermediate. On cooling, the intermediate-containing solution is added to a solution of the appropriate arylaldehyde and aqueous ammonia. Any suitable water-miscible solvent may be used. Methanol is conveniently used. The reaction to yield the substituted imidazole is generally conducted at room temperature, although elevated temperatures may be used. The solvent is then stripped and the product imidazole is recovered.

Where the imidazole intermediate has the

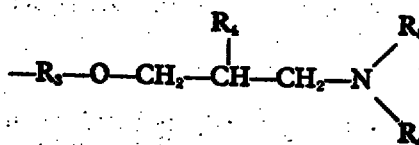


substituent, this intermediate is treated with a suitable strong base such as KOH, potassium butoxide or NaOH in a solvent such as methanol, to effect conversion to the epoxy



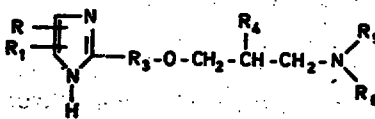
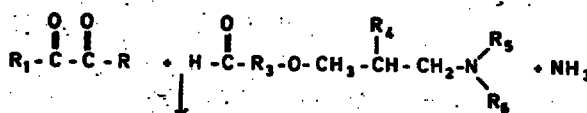
group. This epoxy derivative is then converted to the desired amine final product as illustrated above.

Still another method for preparing compounds of formula I where R₂ is H and



is in the 2 position in the imidazole is by the reaction of aryl aldehyde with a glyoxal or acetal thereof and NH₃. When the acetal is used, it must first be hydrolysed e.g. by treatment with a strong acid solution such as aqueous H₂SO₄. This reaction scheme is illustrated by the following equations:

Method D



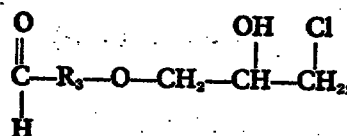
trihalo- β -di-
aldehyde used,
the following
it is preferred

TE)

NH₃

24

If, in Method D, the aryl aldehyde used has the formula



the imidazole product would require dehydrochlorination and treatment with amine, as shown in Method C sequence 2, steps (3) and (4), to afford the imidazole of the present invention.

The process of Method D is generally carried out in solution and at temperatures ranging from about room temperature to about 100°C. Pressure is not required. Solvents used will vary depending on the type of reactants used. Generally, this reaction is carried out in an aqueous solution e.g. H₂O or H₂O/miscible alkanol.

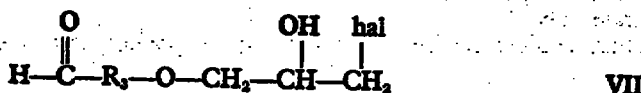
Another method for preparing Formula I compounds where R₂ is other than H is by treating the corresponding compound where R₂ is H with a suitable reagent using a recognized technique.

Where the R₂ group is to be an alkyl group, the corresponding Formula I compound where R₂ is H is alkylated using a suitable reagent such as diazomethane, an alkyl halide e.g. C₂H₅-Br, C₆H₁₃-I or *n*-butylchloride, or a dialkylsulfate.

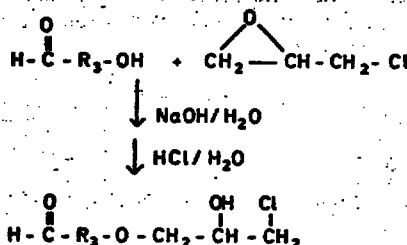
Where the R₂ group is to be an alkenyl group, recognized alkenylating reagents and techniques are used. Illustrative of these techniques is the reaction of the imidazole in which R₂ is hydrogen with NaH followed by treatment with an alkenyl halide e.g. allylbromide to produce the corresponding imidazole in which R₂ is alkenyl.

Where the R₂ group is to be hydroxyalkyl, the imidazole in which R₂ is H is reacted with an epoxy compound e.g. 1,2-epoxyethane, 1,2-epoxypropane, or 1,2-epoxyhexane to produce the corresponding imidazole where R₂ is monohydroxyalkyl. Conditions (temperature, catalysts, solvents etc.) for this type of reaction are disclosed in U.S. 3,786,061.

The aryl aldehyde intermediates having the formula



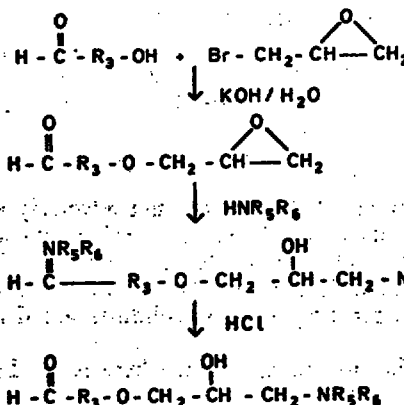
where hal is Cl or Br, are conveniently prepared by reacting the corresponding hydroxyaryl aldehyde with epihalohydrin as illustrated by the following reaction equation:



The aryl aldehyde intermediates having formula

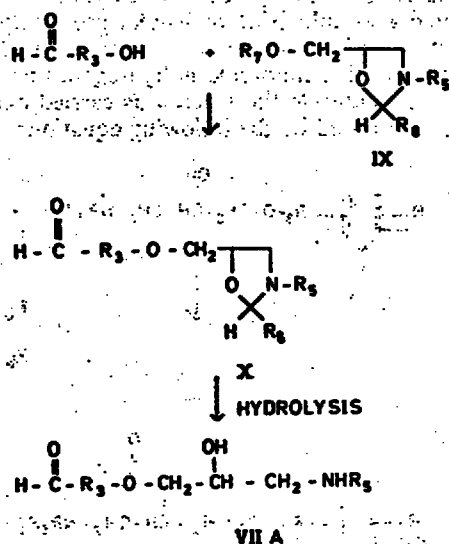


are conveniently prepared by reacting the corresponding hydroxyarylaldehyde with an epihalohydrin as the following equations illustrate:



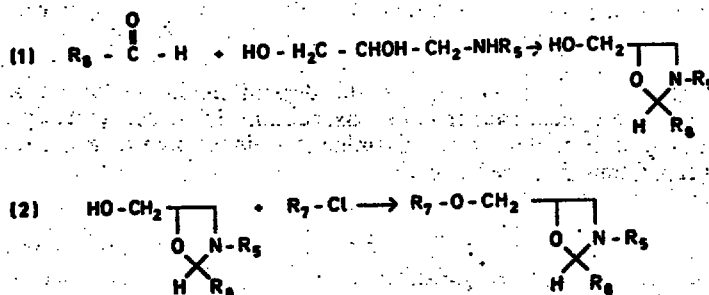
Reaction conditions are similar to those used to prepare the VII compound.

The aryl aldehydes VIII can also be prepared by reacting an aryl aldehyde with an oxazolidine as illustrated by the following equations:



R_3 is the residue of an aldehyde as will be described below. R_7 is an alkyl or aryl sulfonyl group e.g. benzene sulfonyl, toluene sulfonyl or methane sulfonyl. This coupling reaction of the oxazolidine IX and the aryl aldehyde is generally carried out in suitable solvent such as dimethylformamide (DMF), dimethylsulfoxide (DMSO), hexamethylenephosphoramide (HMPP) or alkanols such as methanol or ethanol. While the reaction can be carried out at temperatures ranging from 0°C. to 200°C., it is conveniently carried out at the reflux temperature of the solution. Conventional techniques and reagents e.g. HCl, H_2SO_4 , are used to effect the hydrolysis.

The oxazolidine IX is obtained from the reaction of an aldehyde with a 1-amino-2,3-dihydroxypropane followed by treatment with an appropriate alkyl or aryl sulfonyl halide. This reaction is illustrated by the following equations:



ent with amine,
imidazole of the

at temperatures
t required. Sol-
ly, this reaction
ol.
is other than H
suitable reagent

Formula I com-
lazomethane, an
sulfate.

ylating reagents
on of the imid-
n alkenyl halide
is alkenyl.

hich R_3 is H is
ropane, or 1,2-
mohydroxyalkyl.
on are disclosed

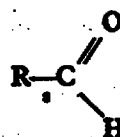
VII

corresponding
reaction equa-

(VIII)

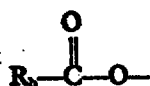
dehyde with an

Any

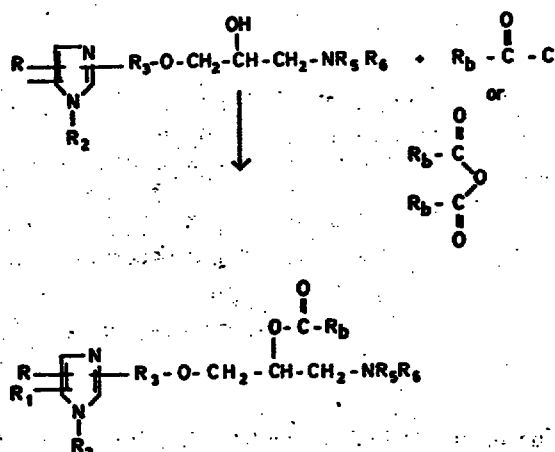


aldehyde may be used provided that it does not adversely affect the oxazolidine preparation. Examples of suitable aldehydes are aryl aldehydes such as benzaldehyde, substituted benzaldehydes and naphthaldehyde, and alkanals such as acetaldehyde, formaldehyde and butyraldehyde. Commercially available aldehydes are most conveniently used. Processes for preparing oxazolidines are disclosed in U.S. 3,718,647 and U.S. 3,657,237.

The imidazoles of the present invention where R_4 is the ester group



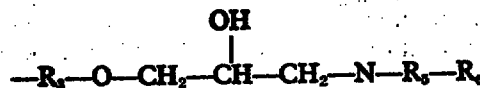
are conveniently prepared by treating the corresponding imidazole where R_4 is OH with the desired organic acid anhydride or halide, preferably the chloride. This reaction can be carried out at ambient temperature or an elevated temperature up to about 100°C. When R_2 in the starting imidazole is hydrogen, then in order to avoid acylating the 1-nitrogen in the imidazole the reaction is carried out under acidic conditions. The general reaction is illustrated by the following equation:



The present imidazoles encompass all optical isomer forms, that is, mixtures of isomers, e.g. racemates, as well as the individual optical isomers. These individual isomers are commonly designated, according to the optical rotation they effect, by (-) and (+), (L) and (D) or a combination of these signs and letters. These optical isomers may also be designated according to their absolute spatial configuration, by the symbols (S) for sinister and (R) for rectus.

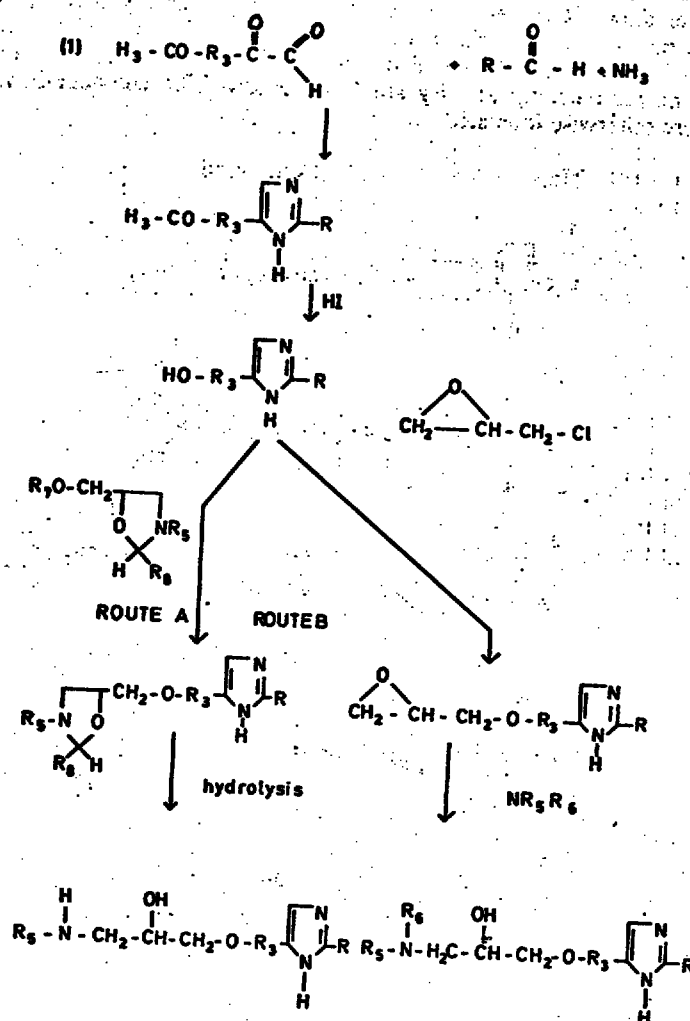
Ordinarily, the imidazoles of the present invention are obtained as racemates. These racemates can be separated into the individual optical isomers using techniques available in the art. These methods are normally tedious, time-consuming and rarely effect a complete separation of isomers. This separation of isomers can be circumvented and one or the other optical isomer of the present imidazoles can be directly prepared by utilizing a single enantiomer of the oxazolidine IX to prepare a single optical isomer of the arylaldehyde intermediate VIII. By using this single isomer intermediate, a single optical isomer form of the desired imidazole final product can be obtained. The single optical isomer of the oxazolidine IX is conveniently obtained by using a single optical isomer of the 1-amino-2,3-dihydroxy-propane reactant in the oxazolidine preparation disclosed above.

Compounds of formula I in which the



is in the 4-position in the imidazole ring can be prepared according to the method illustrated by the following equations:

Method E



Method E, as the equation illustrates, involves the reaction of alkoxyarylacetal with an aldehyde in the presence of ammonia. This ammonia may be liquid ammonia, in which the reaction temperature would range from about -33°C up to about 70°C , the reaction being carried out under pressure where the temperature requires. The ammonia may also be provided as aqueous solution i.e. ammonium hydroxide, in which case reaction temperatures of from about the freezing point of the reaction mixture to about 100°C can be used. With the aqueous ammonia system, room temperature is conveniently used. Other water-miscible aqueous solvents such as a C_{1-6} alkanol e.g. CH_3OH , or DMF may also be used as necessary. The ether cleavage, step (2), may be accomplished using any suitable reagents and procedure such as aqueous HI or aqueous HBr ; or AlCl_3 in a hydrocarbon solvent (hexane, benzene etc.). The Method E route A of course permits preparation of a single optical isomer while the route B results in a racemate.

Compounds of the present invention have been found to be active (1) as anti-hypertensives, i.e. they have an immediate blood pressure lowering effect in hypertensive animals and (2) as β -adrenergic blocking agents. Many of the present imidazoles also are active vasodilators.

The antihypertensive effect was determined by administering (orally or intraperitoneally) the present compounds to spontaneously hypertensive (SH) rats and measuring the effect on the blood pressure. Representative imidazoles, generally administered as salts e.g. the hydrochloride, were found to lower the SH rat's blood pressure.

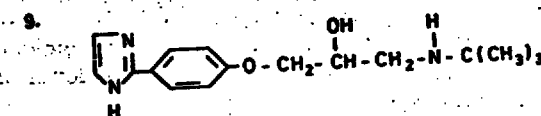
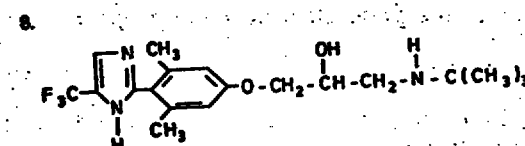
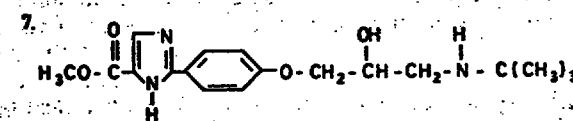
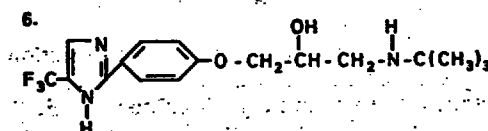
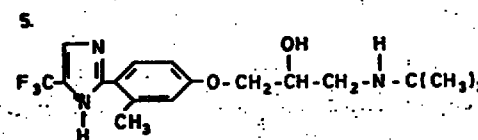
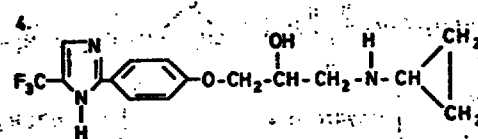
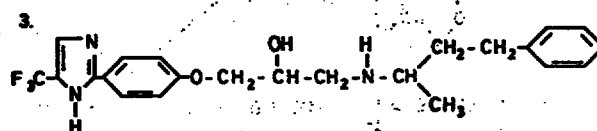
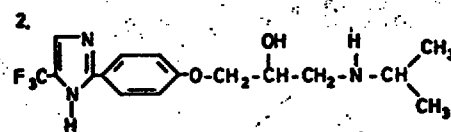
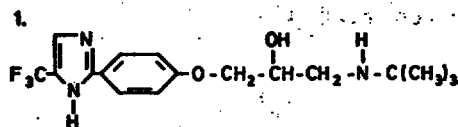
The β -adrenergic blocking activity (β -blockade) of the present compounds was determined by measuring the ability of representative compounds to block isoproterenol induced tachycardia, vasodepression and bronchodilatation in animals. Intravenous administration of the imidazole, (generally as an acid-addition salt) was used for this evaluation. Representative imidazoles showed ability to effect β -blockade in addition to having the aforesaid antihypertensive effect of immediate onset.

Representative compounds which were tested and found to have antihypertensive and β -adrenergic blocking activity are listed below. The compounds were racemates except where otherwise indicated.

10

No.

Compound

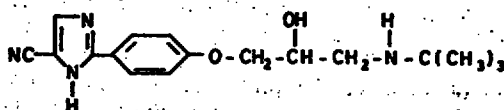


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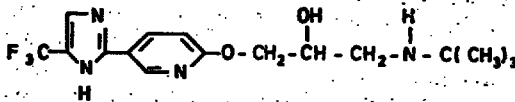
No.

Compound

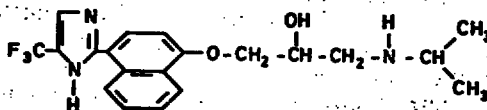
10.



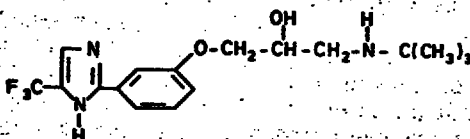
11.



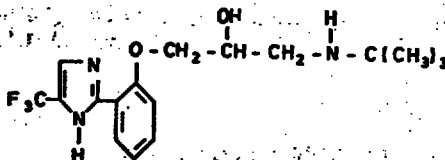
12.



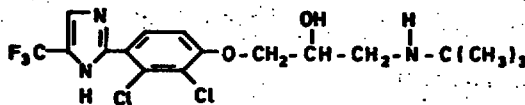
13.



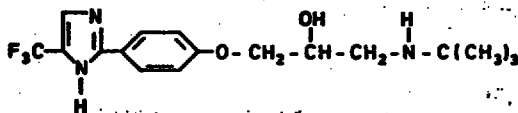
14.



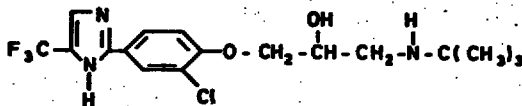
15.



16.



17.



18. 2-[4-(3-tert-butyl-2-hydroxypropoxy)phenyl]-4-(3-pyridyl)imidazole

19. 1-methyl-2-[4-(3-tert-butyl-2-hydroxypropoxy)phenyl]-4-(and 5)-trifluoromethylimidazole.

In evaluating the β -blocking effectiveness of the present compounds, it was noted that many of the compounds exhibit some cardioselectivity, that is, the compound is more effective in reducing the heart rate effects of isoproterenol than it is in blocking the isoproterenol effects on the bronchi. Expressed in different terms, a smaller amount of the compound is required to block isoproterenol-induced elevation in heart rate than is required to block the isoproterenol-induced relaxation of the bronchi. This cardioselectivity factor can be expressed as the ratio of ED_{50} for pulmonary effect (β_2): ED_{50} for cardiac effect (β_1). Where the β_2 : β_1 ratio is over 1, then the compound would be considered to have cardioselective activity. The tested compounds numbered 1-11 above are examples of compounds having β_2 : β_1 ratios greater than 1.

The ability of the compounds of the present invention to reduce blood pressure in the SH rat indicates that the compounds and their salts may be useful to treat essential hypertension in humans.

The β -adrenergic blocking effectiveness of the compounds of the present invention indicates that they are also useful to treat humans suffering from undesirable conditions such as angina pectoris or certain arrhythmias which are known to be amenable to treatment with β -adrenergic blocking agents. Furthermore, the cardio-selective nature of some of the present compounds offers the advantage of limiting blockade to only the β_1 receptors, i.e. those which control heart rate.

For use as antihypertensives and/or β -adrenergic blocking agents, the present compounds can be administered orally or parenterally i.e. intravenously, intraperitoneally, etc. and in any suitable dosage form. The compounds may be offered in a form (a) for oral administration e.g. as tablets in combination with other compounding ingredients customarily used such as talc, vegetable oils, polyols, benzyl alcohols, gums, gelatine, starches and other carriers; dissolved or dispersed or emulsified in a suitable liquid carrier; in capsules or encapsulated in a suitable encapsulating material or (b) for parenteral administration e.g. dissolved or dispersed in a suitable liquid carrier or emulsified or (c) as an aerosol. The ratio of active compound to compounding ingredients i.e. carrier, diluent etc. will vary as the dosage form requires. Whatever dosage form is used, the amount of compound of the present invention administered should be sufficient to effect (a) a reduction in blood pressure of the patient suffering from hypertension and/or (b) desirable level of β -blockade in the patient. Generally, doses of the present compounds of from about 0.01 to about 50 mg/kg and preferably from about 0.1 to about 10 mg/kg of body weight per day may be used. Dosage may be single or multiple depending on the daily total required and the unit dosage.

Following are examples illustrating representative pharmaceutical formulations containing imidazoles of the present invention. Conventional techniques are used to prepare these formulations.

Tablet Formulation I

Ingredient	Amount (Mg.)
(S)-2-[4-(3- <i>tert</i> -butylamino-2-hydroxypropoxy)-phenyl]-4-methylimidazole	5.0
calcium phosphate	120.0
lactose	50.0
starch	23.5
magnesium stearate	1.5

Tablet Formulation II

Ingredient	Amount (Mg.)
2-[4-(3-cyclopropylamino-2-hydroxypropoxy)-phenyl]-4-trifluoromethylimidazole	500.0
Starch paste—12-1/2%, 100 cc allon.	12.5
	512.5
Starch, U.S.P. corn	25.0
Magnesium stearate	5.5

Capsule Formulation III

Ingredient	Amount (Mg.)
(S)-2[4-(3- <i>tert</i> -butylamino-2-hydroxypropoxy)-phenyl]-4- <i>p</i> -methoxyphenylimidazole dihydrochloride dihydrate	250
lactose, U.S.P.	93
talc	7

Formulation IV Injectable Solution

Ingredient	Amount (Mg.)
2-[4-(3-isopropylamino-2-hydroxypropoxy)-phenyl]-4-cyanoimidazole hydrochloride	1
sodium chloride	9
distilled water, q.s. 1.0 ml.	

Formulation V
Liquid Suspension

Ingredient	Amount (g/l)
(S)-2-[4-(3-methylamino-2-hydroxypropoxy)-phenyl]-4-(4-pyridyl)imidazole	5.0
Veegum H.V.	3.0
methyl paraben	1.0
kaolin	10.0
glycerin	250.0
water, q.s.→1 liter (‘Veegum’ is a trade mark)	

The following examples illustrate preparation of representative imidazoles of the present invention. All parts and percentages are by weight unless otherwise indicated.

EXAMPLE 1

A. Preparation of 3-(3-Chloro-2-hydroxypropoxy)-Benzaldehyde

A mixture of m-hydroxybenzaldehyde (24.4 g.), epichlorohydrin (55.2 g.), and pyridine (0.4 ml.) is heated for 5 hours at 100°C. and then concentrated under reduced pressure (20 mm. Hg.) over steam. The residual oil is taken up in chloroform (200 ml.), concentrated hydrochloric acid (50 ml.) is added, and the mixture is stirred for 0.5 hours at room temperature. The chloroform layer is separated and washed with water, and the chloroform removed under reduced pressure (20 mm. Hg.) over steam. Distillation of the residual oil yields 28.9 g. of 3-(3-chloro-2-hydroxypropoxy)-benzaldehyde as a yellow-brown oil, b.p. 166°C./0.25 mm. Hg.

B. Preparation of 2-[3-(3-Chloro-2-hydroxypropoxy)-phenyl]-4-trifluoromethylimidazole

To a solution of sodium acetate trihydrate (11.6 g.) in water (40 ml.) is added trifluorodibromoacetone (11.6 g.) and the resulting solution is heated for 0.5 hours at 100°C. After cooling to room temperature, it is added in one portion to a solution of 3-(3-chloro-2-hydroxypropoxy)benzaldehyde (9.45 g.) in methanol (100 ml.) and aqueous ammonia (50 ml.). The resulting cloudy solution is allowed to stand for 5 hours at room temperature and the methanol is removed under reduced pressure (20 mm Hg.) over steam. An oil separates and crystallizes. The supernatant liquid is decanted and the residue is triturated with benzene and isolated by filtration to yield 6.97 g. of solid. After recrystallization from toluene, the solid is suspended in warm water and acetonitrile added to cause solution. Upon cooling, 2-[3-(3-chloro-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole is obtained as a white solid, m.p. 181—183°C.

C. Preparation of 2-[3-(2,3-Epoxypropoxy)phenyl]-4-trifluoromethylimidazole

To a solution of 2-[3-(3-chloro-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole (3.8 g.) in methanol (150 ml.) is added powdered potassium hydroxide (3 g.) and the mixture is stirred for 4 hours at room temperature. Glacial acetic acid (2.75 ml.) is added and the mixture concentrated under reduced pressure (20 mm. Hg.) over steam. The resulting residue is stirred with water, filtered and recrystallized from xylene to yield 2.5 g. of 2-[3-(2,3-epoxypropoxy)phenyl]-4-trifluoromethylimidazole, m.p. 145—146.5°C.

D. Preparation of 2-[3-(3-Isopropylamino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole

A solution of 2-[3-(2,3-epoxypropoxy)phenyl]-4-trifluoromethylimidazole (0.9 g.) in isopropylamine (10 ml.) is heated for 6 hours at reflux. The excess of isopropylamine is removed by distillation at atmospheric pressure over steam. The residue is triturated with nitromethane (5 ml.) and the resulting solid removed by filtration. After recrystallization from nitromethane, 0.65 g. of 2-[3-(3-isopropyl-amino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole is obtained, m.p. 162.5—163.5°C.

EXAMPLE 2

Preparation of 2-[4-(3-isopropylamino-2-hydroxypropoxy)-phenyl]-4-trifluoromethylimidazole

A solution of 2-[4-(2,3-epoxypropoxy)phenyl]-4-trifluoromethylimidazole (1 g) in isopropylamine (10 ml.) is heated for 7 hours at reflux and then allowed to stand for 16 hours at room temperature. The excess of isopropylamine is removed by distillation

at atmospheric pressure and the residue is triturated with nitromethane to yield a solid. After filtration and recrystallization from acetonitrile, 0.6 g. of 2-[4-(3-isopropylamino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole is obtained, m.p. 173°—173.5°C.

EXAMPLE 3

A. Preparation of 2-methyl-4-(2,3-epoxypropoxy)-benzaldehyde

To epichlorohydrin (20 g., 0.216 mole) heated at 55°C. is added dropwise a solution of 2-methyl-4-hydroxybenzaldehyde (9.0 g., 0.066 mole) in 2.5 N sodium hydroxide solution (40 ml.). After the addition, the solution is stirred for an additional 3 hours at 55°C. and then at room temperature overnight. The oil is distilled to give 8.3 g. of 2-methyl-4-(2,3-epoxypropyl)benzaldehyde, m.p. 160—170°C. at 1 mm. Hg.

B. Preparation of 2-methyl-4-(3-*tert*-butylamino-2-hydroxypropoxy)benzaldehyde

To 2-methyl-4-(2,3-epoxypropoxy)benzaldehyde (8.3 g., 0.043 mole) is added *tert*-butylamine (10 g., 0.137 mole) and the resulting solution is refluxed for 2 hours and allowed to stand overnight at room temperature. The excess of *tert* butylamine is removed under reduced pressure (20 mm. Hg.), the residue is heated on a steam bath with 6 N hydrochloric acid (50 ml.) for 5 hours, and then basified while hot with solid sodium hydroxide. The mixture is cooled to room temperature, extracted with chloroform (3×50 ml.), dried over sodium sulfate, filtered and concentrated to dryness. The residual oil is crystallized from hexane to give 8.75 g. of 2-methyl-4-(3-*tert*-butylamino-2-hydroxypropoxy)benzaldehyde, m.p. 82—84°C.

C. Preparation of 2-[2-methyl-4-(3-*tert*-butylamino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole

To sodium acetate trihydrate (6.26 g., .046 mole) in water (26 ml.) is added dibromotrifluoroacetone (6.26 g., .023 mole). The solution is heated for 45 minutes on a steam bath, cooled, and added to a solution of 2-methyl-4-(3-*tert*-butylamino-2-hydroxypropoxy)-benzaldehyde (3.05 g., 0.0115 mole) in methanol (60 ml.) and concentrated aqueous ammonia (20 ml.). The solution is allowed to stand for 5 hours at room temperature. The methanol is removed under reduced pressure (20 mm. Hg.) over steam and the residue treated with chloroform (3×50 ml.) and saturated sodium carbonate (50 ml.). The organic layer is concentrated to dryness and the residue crystallized from acetonitrile to give 1.2 g. of 2-[2-methyl-4-(3-*tert*-butylamino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole, m.p. 162—164°C.

EXAMPLE 4

Preparation of 2-[4-(3-*tert*. butylamino-2-hydroxypropoxy)phenyl]-4-phenylimidazole

A solution of *p*-(3-*tert*. butylamino-2-hydroxypropoxy)benzaldehyde 5.0 g., 0.02 mole), phenylglyoxal monohydrate (6.04 g., 0.04 mole), concentrated aqueous ammonia (50 ml.), water (50 ml.) and methanol (200 ml.) is allowed to stand at room temperature for 5 hours. The solution is concentrated to a residual oil under reduced pressure (20 mm. Hg.) over steam and treated with saturated sodium carbonate (50 ml.) and chloroform (3×50 ml.). The organic layer is concentrated to dryness and chromatographed on neutral alumina (500 g.) using a gradient elution technique starting with chloroform. The product is eluted with 10% methanol—90% chloroform. Final purification is accomplished by passing through a column of silica gel (150 g.) and eluted with 20% methanol—80% chloroform. The solvent is removed under reduced pressure (20 mm. Hg.) over steam and the residue crystallized from acetonitrile to give 0.7 g. of 2-[4-(3-*tert*. butylamino-2-hydroxypropoxy)-phenyl]-4-phenylimidazole, m.p. 176—178°C.

EXAMPLE 5

A. Preparation of S-4-(3-*tert*. butylamino-2-hydroxypropoxy)benzaldehyde

To a solution of S-2-phenyl-3-*tert*. butyl-5-hydroxymethylloxazolidine (47 g., 0.2 mole) in pyridine (75 ml.) is added portionwise *p*-toluenesulfonyl chloride, keeping the internal temperature between 25 and 30°C. The mixture is stirred for 2 hours after addition is complete, keeping the temperature between 25 and 30°C. Ice water (150 ml.) and potassium carbonate (27.6 g.) are added and the mixture is extracted with chloroform (3×100 ml.). The organic extract is dried over sodium sulfate and concentrated first at 20 mm. Hg. and then at 1 mm. Hg. keeping the temperature below 50°C. The residual oil is dissolved in N,N-dimethylformamide (150 ml.) and added dropwise to a refluxing solution of the sodium salt of *p*-hydroxybenzaldehyde (0.2 mole) in N,N-dimethylformamide (200 ml.). After refluxing for 10 hours, the reaction

mixture is concentrated first at 20 mm. Hg. and then at 1 mm. Hg. over steam. The residue is treated with 5% sodium hydroxide solution and extracted with chloroform (3×100 ml.). The organic extract is dried over sodium sulfate and the residue chromatographed on alumina (500 g. activity grade II). The chromatographic fractions are concentrated and the residue distilled at 240°C. at 0.3 mm. Hg. The distillate (21 g.) is treated with 1 N hydrochloric acid (75 ml.), heated for 1/2 hour over steam, cooled and extracted with ether. The aqueous layer is made basic to pH 10 by the addition of 2% sodium hydroxide solution and extracted with chloroform (3×100 ml.). The organic extract is dried over sodium sulfate and concentrated to an oil which after crystallization from hexane yields 14.5 g. of S-4-(3-*tert.* butylamino-2-hydroxypropoxy)benzaldehyde, m.p. 60–62°C.

B. Preparation of S-2-[4-(3-*tert.* butylamino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole

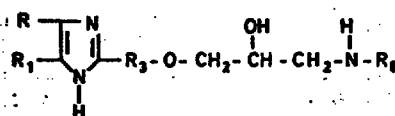
To sodium acetate trihydrate (20.2 g., 0.15 mole) in water (100 ml.) is added dibromotrifluoroacetone (20.2 g., 0.075 mole). The solution is heated for 45 minutes on a steam bath, cooled and added to a solution of S-*p*-(3-*tert.* butylamino-2-hydroxypropoxy)benzaldehyde (12.5 g., 0.05 mole) in methanol (200 ml.) and concentrated aqueous ammonio (75 ml.). The solution is allowed to stand for 5 hours at room temperature. The methanol is removed by distillation under reduced pressure (20 mm. Hg.) over steam. The mixture is made basic with saturated aqueous sodium carbonate solution and extracted with ethyl acetate (3×100 ml.). The organic extract is dried over sodium sulfate and concentrated at 20 mm. Hg. over steam. The resulting residue is recrystallized from acetonitrile to yield 7.6 g. of S-2-[4-(3-*tert.* butylamino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole, m.p. 181–182°C.

Other Formula I imidazoles prepared using the procedures substantially as described in Examples 1–5 are listed in the following table. It is to be understood that analogous reactants are used to obtain the particular imidazole products.

TABLE I
Prepared Imidazoles of Formula

Example No	Using Procedure of Example	Imidazole Substituents				M.P. (°C.)
		R	R ₁	R ₃	R ₆	
6	1	H	-CF ₃		<i>t</i> -butyl	207°–210°
7	2	H	-CF ₃		<i>t</i> -butyl	139°–141°
8	2	H	-CF ₃			158°–170°
10	2	H	-CF ₃		<i>n</i> -propyl	153°–155°
9	2	H	-CF ₃			120°–133°
11	2	H	-CF ₃		cyclo-propyl	163.5°–165°
12	3	H	-CF ₃		<i>t</i> -butyl	187°–190°

TABLE 1 (Contd.)
Prepared Imidazoles of Formula



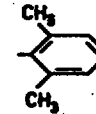
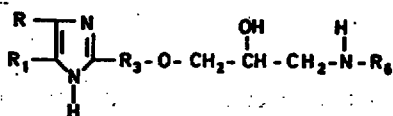
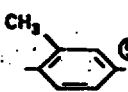
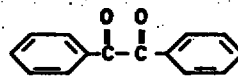
Using Example No	Procedure of Example	Imidazole Substituents				M.P. (°C)
		R	R ₁	R ₃	R ₆	
5	13	3	H	-CF ₃	 t-butyl	183°-185°
	13a	3	H	-CF ₃	 t-butyl	159°-162°
	14	3	H	-CF ₃	 isopropyl	210°-213°
	15	3	H	-CF ₃	 t-butyl	181°-182°
	16	3	H	-CF ₃	 t-butyl	167°-171°
10	17	3	H	-CF ₃	 t-butyl	207°-210°
	18	3	H	-CF ₃	 t-butyl	174°-177°
	19 ^①	4			t-butyl	180°-181°
	20	4	H	H	 t-butyl	162°-164°
	21	4	H	H	 t-butyl	193.5°-196° ^②
15	22	4	H	Cl 	 t-butyl	186°-188°
	23	4	H	F 	 t-butyl	167°-169°
	24	4	H	CHO 	 t-butyl	179°-181°
	25	4	H	Cl 	 t-butyl	189°-190°
	26	4	H		 t-butyl	101°-105°

TABLE 1 (Contd.)
Prepared Imidazoles of Formula



		Imidazole Substituents				M.P. (°C)
Using Example No	Procedure of Example	R	R ₁	R ₂	R ₃	
27	4	H	H		t-butyl	158°-162° ^③
28	4	H			t-butyl	172°-173°
29	4	H			t-butyl	178°-180°
30	4	H			t-butyl	168°-170°
31	5	H	-CF ₃		t-butyl	178°-179.5° ^④
32	5	H	-CF ₃		t-butyl	141°-143° ^⑤
33	5	H	-CF ₃		t-butyl	110°-120° ^⑥

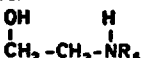


① The glyoxal reagent used

② HCl Salt

③ S-isomer

④ R-isomer

⑤  attached at this position

⑥ Monohydrate; S-isomer

Additional Examples illustrating preparation of other imidazoles of the present invention follow. All parts and percentages are by weight unless otherwise indicated.

EXAMPLE 34

A. Preparation of 2-[4-(3-Chloro-2-hydroxypropoxy)-phenyl]-4-trifluoromethylimidazole

To sodium acetate trihydrate (5.8 g.) in water (20 ml.) is added trifluorodibromoacetone (5.8 g.); the resulting mixture is heated for 0.5 hour on a steam bath. After cooling, the solution is added to p-(3-chloro-2-hydroxypropoxy)benzaldehyde (4.2 g.) in methanol (100 ml.) and concentrated aqueous ammonia (25 ml.). After standing for 4.5 hours at room temperature, the methanol is removed by distillation at 20 mm. Hg. over steam; a solid separates and is filtered. After recrystallization from nitromethane, 1.65 g. of 2-[4-(3-chloro-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole is obtained, m.p. 181-183°C.

B. Preparation of 2-[4-(2,3-Epoxypropoxy)phenyl]-4-trifluoromethylimidazole

To a solution of 2-[*p*-(3-chloro-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole (1.92 g.) in methanol (100 ml.) is added crushed potassium hydroxide (1.5 g.). The mixture is stirred for 3 hours at room temperature, neutralized with acetic acid and concentrated under reduced pressure (20 mm. Hg.) over steam. The residue is triturated with water (25 ml.), filtered and recrystallized by dissolving in benzene and adding hexane until turbid.

A yield of 1.2 g. of 2-[4-(2,3-epoxypropoxy)phenyl]-4-trifluoromethylimidazole is obtained, m.p. 152—153.5°C.

C. Preparation of 2-[4-(3-*tert.* Butylamino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole

A solution of 2-[4-(2,3-epoxypropoxy)phenyl]-trifluoromethylimidazole (2.5 g.) in *tert.* butylamine (20 ml.) is heated 6 hours at reflux. The excess of *tert.* butylamine is removed by distillation at atmospheric pressure over steam. The residue is triturated with nitromethane (5 ml.) and the resulting solid removed by filtration. After recrystallization from acetonitrile, (1.2 g.) of 2-[4-(3-*tert.* butylamino-2-hydroxypropoxy)-phenyl]-4-trifluoromethylimidazole is obtained, m.p. 185.5—186.5°C.

EXAMPLE 35

A. Preparation of 4-(3-*tert.* Butylamino-2-hydroxypropoxy)benzaldehyde

To 4-(2,3-epoxypropoxy)benzaldehyde (20 g.) is added *tert.* butylamine (50 ml.) and the resulting solution is refluxed for 17 hours. The excess of *tert.* butylamine is removed by heating at atmospheric pressure to yield a solid residue. To this residue is added 6 *N* hydrochloric acid (200 ml.) and the resulting mixture is heated for 5 hours on a steam bath. The solution is cooled and concentrated to 100 ml. on a steam bath under reduced pressure (20 mm. Hg.). The concentrated solution is made basic to pH 10 with saturated aqueous sodium carbonate and extracted with chloroform. The chloroform extract is concentrated to a solid which, after recrystallization from acetonitrile, yields 18 g. of 4-(3-*tert.* butylamino-2-hydroxypropoxy)benzaldehyde, m.p. 123—125.5°C.

B. Preparation of 2-[4-(3-*tert.* Butylamino-2-hydroxypropoxy)-phenyl]-4-trifluoromethylimidazole

To sodium acetate trihydrate (11.8 g., 0.088 moles) in water (40 ml.) is added dibromotrifluoroacetone (11.8 g., 0.044 moles). The solution is heated for 45 minutes on a steam bath, cooled and added to a solution of 4-(3-*tert.* butylamino-2-hydroxypropoxy)benzaldehyde (5 g., 0.02 mole) in methanol (200 ml.) and concentrated aqueous ammonia (25 ml.). The solution is allowed to stand for 5 hours at room temperature. The methanol is removed under reduced pressure (20 mm. Hg.) over steam and chloroform (50 ml.) and saturated aqueous sodium carbonate (25 ml.) are added to the residue. After stirring a solid separates and is filtered and washed with water. After recrystallization from acetonitrile, 3 g. of 2-[4-(3-*tert.* butylamino-2-hydroxypropoxy)-phenyl]-4-trifluoromethylimidazole is obtained, m.p. 189—191°C.

EXAMPLE 36

A. Preparation of Salicylaldehyde Diethyl acetal

A mixture of salicylaldehyde (80 g., 0.0655 mole), triethylorthoformate (110 g., 0.765 mole), absolute ethanol (40 ml.) and concentrated sulfuric acid (3 drops) is heated to reflux overnight. The volatiles are removed under reduced pressure (20 mm. Hg.) over steam to give diethyl acetal of salicylaldehyde which is used without further purification.

B. Preparation of 2-(2,3-Epoxypropoxy)benzaldehyde Diethyl acetal

To epichlorohydrin (37 g., 0.4 mole) heated at 50°C. is added dropwise a solution of salicylaldehyde diethyl acetal (25 g., 0.13 mole) in 2 *N* sodium hydroxide solution extracted with chloroform (3×100 ml.), dried over potassium carbonate, and concentrated to dryness to give 34.3 g. of 2-(2,3-epoxypropoxy)benzaldehyde diethyl acetal.

C. Preparation of 2-(3-*tert.* butylamino-2-hydroxypropoxy)benzaldehyde

A solution of 2-(2,3-epoxypropoxy)benzaldehyde diethyl acetal (53 g., 2.1 mole) and *tert.* butylamine (100 ml.) is heated to reflux for 2 hours and allowed to stand at room temperature overnight. The excess of *tert.* butylamine is removed under reduced pressure (20 mm. Hg.) and the residue heated on a steam bath with 6 *N* hydrochloric acid (300 ml.). After cooling, the solution is neutralized with solid sodium bicarbonate,

extracted with chloroform (3×100 ml.), dried over sodium sulfate, filtered and concentrated to dryness. The residue is chromatographed on silica gel (500 ml.) using gradient elution techniques starting with chloroform, and the product is obtained with 10% methanol—90% chloroform. After removal of the solvent under reduced pressure (20 mm. Hg.), the residue is crystallized from acetonitrile to give 13.8 g. of 2-(3-*tert.* butylamino-2-hydroxypropoxy)benzaldehyde, m.p. 156—160°C.

D. Preparation of 2-[2-(3-*tert.* butylamino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole

To sodium acetate trihydrate (5.4 g., 0.0396 mole) in water (20 ml.) is added dibromotrifluoroacetone (5.4 g., 0.02 mole). The solution is heated for 45 minutes on a steam bath, cooled and added to a solution of 2-(3-*tert.* butylamino-2-hydroxypropoxy)benzaldehyde (3.6 g., 0.0143 mole) in methanol (100 ml.) and concentrated aqueous ammonia (25 ml.). The solution is allowed to stand overnight at room temperature. The methanol is removed by distillation under reduced pressure (20 mm. Hg.) and the residue treated with saturated sodium carbonate (50 ml.), extracted with chloroform (3×50 ml.) and separated. The organic layer is dried over sodium sulfate, filtered and concentrated to dryness. The residue is chromatographed on silica gel (400 ml.) and the product eluted with 20% methanol—80% chloroform. Recrystallization of the product from nitromethane gives 700 mg. of 2-[2-(3-*tert.* butylamino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole, m.p. 105—107°C.

EXAMPLE 37

2-[4-(3-*tert.* butylamino-2-hydroxypropoxy)phenyl]-4-methylimidazole

To a mixture of cupric acetate (5.0 g., 0.025 mole), acetoxyacetone (1.5 g., .013 mole), concentrated aqueous ammonia (25 ml.) is added a solution of *p*-(3-*tert.* butylamino-2-hydroxypropoxy)benzaldehyde (3.2 g., 0.0127 mole) in methanol (25 ml.). After the addition, the mixture is heated at reflux overnight. The methanol is removed by distillation under reduced pressure (20 mm. Hg.) over steam, and water (200 ml.) is added to the residue. The resulting solution is treated with hydrogen sulfide, filtered through a filter aid, treated with solid potassium carbonate until basic and extracted with chloroform (3×50 ml.). The chloroform is concentrated to dryness and the residue chromatographed on neutral alumina (170 g.) using a gradient elution technique starting with chloroform. The material is eluted off the column using 5% methanol—95% chloroform. The organic solvent is removed by distillation under reduced pressure (20 mm. Hg.) and the residue crystallized from acetonitrile to give 0.79 g. of 2-[4-(3-*tert.* butylamino-2-hydroxypropoxy)phenyl]-4-methylimidazole, m.p. 202—203°C.

EXAMPLE 38

A. β -Pyridylglyoxal-dimethylacetal

To a solution of butyl lithium (129 ml., 193N, 0.25 m.) in ether (300 ml.) cooled below -50°C. is added 3-bromopyridine (33.02, 0.209 m.) in ether (60 ml.). The yellow suspension which results is stirred for an additional 1/2 hour at -50°C, an dimethoxyacetic acid piperidine (33.6 g., 0.179 m.) in ether (90 ml.) is added over 1 hour at -50°C. After complete addition, the reaction mixture is allowed to warm to room temperature and heated to reflux for 1/2 hour. After cooling, a solution of ammonium chloride (500 ml.) is added and separated and the aqueous layer extracted with 2×100 ml. ether. The ethereal layer is washed with 3N H₂SO₄ till acid; the aqueous layer is neutralized with KOH, extracted with 3×100 ml. CH₂Cl₂, dried over Na₂SO₄, filtered and concentrated to dryness. The remainder is distilled at 95—100/0.4 mm. to give 13.8 g. of β -pyridylglyoxaldimethylacetal.

B. 4-(3-Pyridyl)-2-[4-(3-*tert.*butylamino-2-hydroxypropoxy)phenyl]-imidazole

To concentrated sulfuric acid (15 g.) cooled to 0—4° is added β -pyridylglyoxal-dimethylacetal (5.4 g., 0.03 m) and the solution allowed to stand at room temperature. After 3 days, the mixture is cooled and neutralized with NaHCO₃ (26 g., 0.30 m).

To this solution is added water (25 ml.), 37% aqueous ammonia (75 ml.), methanol (25 ml.) and a solution of *p*-(3-*tert.*butylamino-2-hydroxypropoxy)benzaldehyde (5.1 g., 0.02 m) in methanol (200 ml.). After standing at room temperature for 3 days, the methanol is removed under reduced pressure (20 mm) over steam and the residue is covered with saturated Na₂CO₃ (100 ml.), extracted with CHCl₃ (3×150 ml.), dried over Na₂SO₄, filtered and concentrated to dryness. The residue is chromatographed on silica gel (600 ml.) and the product eluted with 50% CHCl₃/MeOH. The crude product is further purified by chromatography on No. 2 neutral alumina (90 g.) and eluted with 2% MeOH/CHCl₃. Recrystallization from aceto-

nitrile/chloroform gave 125 mg. of 4-(3-pyridyl)-[4-(3-*tert*-butylamino-2-hydroxypropoxy)phenyl]-imidazole.

EXAMPLE 39

(S) Methyl-2-[4-(3-*tert*-butylamino-2-hydroxypropoxy)-phenyl]imidazole-4-carboxylate

To 1N sodium hydroxide solution (20 ml.) is added (S)-2-[4-(3-*tert*-butylamino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole (1 g.) and the mixture is heated for 0.5 hour over steam. The resulting solution is neutralized to pH 7 with concentrated hydrochloric acid and concentrated on a steam bath over a stream of nitrogen. The resulting solid crude S-2-[4-(3-*tert*-butylamino-2-hydroxypropoxy)phenyl]-4-carboxy-imidazole is suspended in methanol (25 ml.) saturated with hydrogen chloride. The mixture is refluxed for three hours, with hydrogen chloride being added after the first and second hours. After being concentrated under reduced pressure (20 mm.) over steam, saturated aqueous sodium carbonate solution is added (25 ml.) and the mixture is extracted with ethyl acetate. The organic extract is concentrated to a gum which on trituration with aqueous sodium carbonate solidifies and is filtered. After recrystallization from acetonitrile 200 mg. of (S)-methyl 2-[4-(3-*tert*-butylamino-2-hydroxypropoxy)phenyl]imidazole-4-carboxylate melting at 159–161°C. is obtained.

EXAMPLE 40

A. S-2-Phenyl-3-Tert. butyl-5-(3-cyano-6-pyridyloxymethyl)oxazolidine

To a solution of S-2-phenyl-3-*tert*. butyl-5-hydroxymethyloxazolidine (12.35 g., 0.0526 mole) in dimethylformamide (65 ml.) is added sodium hydride (2.22 g., 0.0526 mole of 57%). After heating for 25 minutes on a steam bath, the mixture is stirred and cooled to room temperature in 30 minutes and added to a solution of 6-chloronicotinonitrile (7.28 g., 0.0526 mole) in dimethylformamide (35 ml.). The reaction mixture is stirred at room temperature for 4-1/2 hours and is then concentrated under reduced pressure. The fluid residue is taken up in ether and washed with water. The ethereal solution is dried and concentrated under reduced pressure to yield 18.5 g. of S-2-phenyl-3-*tert*. butyl-5-(3-cyano-6-pyridyl-oxymethyl)oxazolidine as an oil.

B. S-6-(3-Tert. butylamino-2-hydroxypropoxy)nicotinonitrile

A suspension of S-2-phenyl-3-*tert*. butyl-5-(3-cyano-6-pyridyloxymethyl)oxazolidine (18.5 g.) in 1N hydrochloric acid (60 ml.) is heated for 5 minutes on a steam bath and then stirred at room temperature for 1/2 hour. The mixture is extracted with chloroform and the aqueous layer is made basic with 40% sodium hydroxide solution. The basic solution is extracted with ethyl acetate and the extract is dried and concentrated under reduced pressure. The residual white solid is recrystallized from hexane-*n*-butyl chloride to yield 5.14 g. of S-6-(3-*tert*. butylamino-2-hydroxypropoxy)nicotinonitrile, m.p. 103–105°C.

C. S-6-(3-Tert. butylamino-2-hydroxypropoxy) nicotinaldehyde

A suspension of S-6-(3-*tert*. butylamino-2-hydroxypropoxy) nicotinonitrile (5.14 g. 0.0204 mole) in toluene (128 ml.) in a flamed flask is heated with stirring until a solution is obtained. The toluene is allowed to distil off until a total of 21 ml. is collected. Heating is discontinued and the reaction solution is cooled in a dry-ice-acetone bath causing the starting material to reprecipitate. To the cold reaction mixture is added diisobutyl aluminium hydride in toluene (62.6 ml. 0.075 mole of 0.17 g./ml.) dropwise under nitrogen with stirring. The yellow reaction mixture is stirred cold for 1 hour, and then the acetone bath is removed as methanol (22 drops) is added followed by the addition of water (22 drops). Chloroform is added to the mixture and then water (43 ml.), and after good stirring the mixture is filtered. The filtrate is shaken in a separatory funnel and the organic layer is separated, dried, and concentrated under reduced pressure. To the residual oil is added 1% hydrochloric acid (43 ml.) and the mixture is heated on a steam bath for 1/2 hour. At this point the pH is basic. Concentrated hydrochloric acid is added until the pH is acid and heating is continued for 15 minutes. The mixture is cooled and made basic with 40% sodium hydroxide solution and then extracted with chloroform. The extract is dried and concentrated under reduced pressure to yield 5.1 g. of S-6-(3-*tert*. butylamino-2-hydroxypropoxy) nicotinaldehyde as an oil which solidifies.

D. S-2-[2-[3-*tert*.-Butylamino-2-hydroxypropoxy)-5-pyridyl]-4-trifluoromethylimidazole

To sodium acetate trihydrate (2.16 g., 0.016 mole) in H₂O (15 ml.) is added dibromotrifluoroacetone (2.16 g., 0.008 moles) and the mixture is heated for 1/2 hour

on a steam bath. After cooling the solution is added to 6-(3-*tert*-butylamino-2-hydroxypropoxy) nicotinaldehyde (1 g.) in methanol (50 ml.) and concentrated aqueous ammonium hydroxide (15 ml.). After standing for 20 hours at room temperature, the methanol is removed under reduced pressure (20 mm.) over steam. Concentrated aqueous sodium carbonate (10 ml.) and ethyl acetate (50 ml.) are added to the concentrated solution. After extracting the organic layer is separated, dried over sodium sulfate and concentrated to a gum, which is chromatographed on activity grade II alumina with chloroform-methanol using a gradient elution technique. The fractions containing product are combined and concentrated to a gum, which is dissolved in ethyl acetate. The ethyl acetate solution is washed with saturated sodium carbonate solution, dried and concentrated to yield 2-[2-(3-*tert*-butylamino-2-hydroxypropoxy)-5-pyridyl]-4-trifluoromethylimidazole as a non-crystalline solid (650 mg).

This non-crystalline solid was covered with hexane and allowed to stand at about 0°C for 7 days. The hexane was then decanted and the residue triturated with ether to yield a solid. The ethereal filtrate also yielded solid on standing at room temperature. These solids were combined and dissolved in benzene. Hexane was added to the point of turbidity, which on cooling yielded a solid. The solid was dried at 66°—73°C. and 0.2 mm for about 48 hours. The dried solid was S-2-[2-(3-*tert*. butylamino-2-hydroxypropoxy)-5-pyridyl]-4-trifluoromethylimidazole monohydrate (NMR and Mass Spectroscopic analysis), melting at 110°—120°C.

EXAMPLE 41

A. 4-(*p*-methoxyphenyl)-2-(3-pyridyl)imidazole

A solution of sodium acetate trihydrate (5.8 g, 0.04 m), 3-pyridinecarboxaldehyde (2.3 g., 0.02 m), *p*-methoxyphenylglyoxal monohydrate (3.92 g., 0.02 m), water (20 ml.), concentrated aqueous ammonia (25 ml.), and methanol (75 ml.) is allowed to stand at room temperature overnight. The solution is concentrated to dryness under reduced pressure (20 mm) over steam, treated with saturated Na₂CO₃ (100 ml.) and extracted with chloroform (3×100 ml.). The organic layer is dried over Na₂SO₄, filtered and concentrated to dryness. The residue is chromatographed on silica gel (300 ml.) and the product eluted with 3—5% MeOH/CHCl₃. The material is crystallized from acetonitrile to give 2.3 g. of 4-(*p*-methoxyphenyl)-2-(3-pyridyl)imidazole of m.p. 184—186.

B. 2-(3-pyridyl)-4-(4-hydroxyphenyl)imidazole

A mixture of 4-(*p*-methoxyphenyl)-2-(3-pyridyl)-imidazole (2.0 g.) and 48% HBr (100 ml.) is heated to reflux for 20 hrs. After cooling, the precipitate is filtered off and crystallized from isopropanol-methanol to give 2.05 g. of 2-(3-pyridyl)-4-(4-hydroxyphenyl)-imidazole of m.p. 315—318°C.

C. 4-[4-(3-*tert*-butylamino-2-hydroxypropoxy)phenyl]-2-(3-pyridyl)imidazole

A solution of 2-phenyl-3-*tert*-butyl-5-hydroxy-methyloxazolidine (2.4 g., 0.01 m) in pyridine (3 ml.) is cooled to 0—4°C. and treated portionwise with *p*-toluenesulfonyl chloride (2.0 g., 0.01 m). The cooled solution is slowly warmed to room temperature while not allowing the temperature of the reaction mixture to exceed 30°C. After 2.5 hrs., the mixture is treated with a solution of K₂CO₃ (1.4 g.) in water (20 ml.) and extracted with chloroform (3×50 ml.). The organic layer is dried over Na₂SO₄, filtered, and concentrated to dryness under reduced pressure (20 mm) over steam and finally at 60°C. and 1 mm. The residual oil is dissolved in dry N,N-dimethylformamide (DMF) (20 ml.) and added dropwise to a mixture of 2-(3-pyridyl)-4-(4-hydroxyphenyl)imidazole:2HBr:H₂O (4.0 g., .0095 m) in DMF (20 ml.) and sodium hydride (57% oil suspension, 1.3 g., .031 m). After refluxing for 11 hours, the mixture is concentrated to dryness under reduced pressure (1—2 mm Hg.) over steam. The residue is treated with 1N HCl (100 ml.), heated for 1/2 hr. on a steam bath, cooled, and extracted with ether. The aqueous layer is neutralized with 10N NaOH (12 ml.), extracted with CHCl₃ (3×50 ml.), dried over Na₂SO₄, filtered and concentrated to dryness.

The residue is chromatographed on No. 2 neutral alumina (200 g.) and eluted with 4% MeOH/CHCl₃. The crude product is further purified by chromatography on silica gel (200 ml.) and eluted with 40—50% MeOH/CHCl₃. The material is crystallized from acetonitrile to give 0.425 g. of 4-[4-(3-*tert*-butylamino-2-hydroxypropoxy)phenyl]-2-(3-pyridyl)imidazole of m.p. 163—165°C.

EXAMPLE 42

Methyl 2-[4-(3-*tert*-butylamino-2-hydroxypropoxy)phenyl]-imidazole-4-carboxylate

A solution of 30 g. of crude 2-[4-(3-*tert*-butylamino-2-hydroxypropoxy)phenyl]-

(41)

4-carboxyimidazole, prepared from the corresponding 4-trifluoromethylimidazole by the product of Example 39, methanol (600 ml.) is heated to reflux, and then heating is discontinued as hydrogen chloride is bubbled rapidly through the solution with stirring for a half hour, followed by two and a half hours at reflux. Bubbling of hydrogen chloride is continued for another two hours followed by another hour at reflux and then the reaction mixture is stirred at room temperature overnight. The mixture is filtered and the filtrate is then concentrated to dryness under reduced pressure. The residue is dissolved in water (150 ml.) and the pH is adjusted to 8 with saturated sodium carbonate solution. The basic mixture is extracted with ethyl acetate and the extracts are dried, filtered, and concentrated under reduced pressure to yield a solid which is recrystallized from acetonitrile to yield the methyl 2-[4-(3-*tert.*butylamino-2-hydroxypropoxy)phenyl]-imidazole-4-carboxylate as a cream-colored solid, m.p. 168—172°C.

EXAMPLE 43

A. 2-[4-(3-*Tert.* butylamino-2-hydroxypropoxy)phenyl]-4-carbamoylimidazole

A solution of methyl 2-[4-(3-*tert.* butylamino-2-hydroxypropoxy)phenyl]imidazole-4-carboxylate (10 g.) in methanol (100 ml.) is reacted in a bomb with ammonia (44 g.) at 100°C. for 24 hours. The reaction mixture is concentrated under reduced pressure and the residue is chromatographed on silica gel. The product is eluted with chloroform that is washed with concentrated aqueous ammonia (90% and methanol (10%)) and is recrystallized from acetonitrile to yield the 2-[4-(3-*tert.* butylamino-2-hydroxypropoxy)phenyl]-4-carbamoylimidazole as a white solid, m.p. 149—154°C.

B. 2-[4-(3-*tert.*-butylamino-2-hydroxypropoxy)phenyl]-4-cyanoimidazole

To a solution of 2-[4-(3-*tert.*-butylamino-2-hydroxypropoxy)phenyl]-4-carbamoylimidazole (0.5 g.) in dry pyridine (10 ml.) is added trifluoroacetic anhydride (1.26 g.) portionwise with stirring. The reaction solution is refluxed with stirring for four hours and then concentrated under reduced pressure. The residual gum is taken up in ethanol and saturated sodium carbonate solution (15 ml.) and stirred at room temperature for 20 hours. The ethanol is removed under reduced pressure and the remaining aqueous mixture is extracted with ethyl acetate. The extract is dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residual glass is converted to its hydrochloride salt with ethanolic HCl and is recrystallized from ethanol-ether. The resulting tan solid is converted back to its free base by trituration with saturated sodium carbonate solution. The free base is extracted into ethyl acetate and the extract is dried over sodium sulfate, filtered and concentrated under reduced pressure. The residual gum is recrystallized from acetonitrile to yield 40 mg. of 2-[4-(3-*tert.*-butylamino-2-hydroxypropoxy)phenyl]-4-cyanoimidazole, m.p. 174 — 177°C.

EXAMPLE 44

A. 4-Hydroxy-5,6,7,8-tetrahydronaphthaldehyde

Step A:

Dry hydrogen chloride gas is bubbled into a suspension of 5.0 gms. of 5,6,7,8-tetrahydronaphthol and 6.0 gm. zinc cyanide in 60 ml. of dry ethyl ether for two hours. To the mixture is added cautiously 50 ml. of water and 10 ml. 95% ethanol, and the resulting mixture is refluxed for 1/2 hour. After cooling, the mixture is extracted with ethyl ether. The ethereal layer is washed with water and dried over anhydrous sodium sulfate. The ether is filtered and concentrated to an oil. The oil is dissolved in benzene, and 4-hydroxy-5,6,7,8-tetrahydronaphthaldehyde crystallizes and is filtered.

B. 4-(2,3-Epoxypropoxy)-5,6,7,8-tetrahydronaphthaldehyde

Step B:

To a solution of 4-hydroxy-5,6,7,8-tetrahydronaphthaldehyde (20 gms., 0.012 m) in 1.5N sodium hydroxide (20 ml.) at 50°C. is added epichlorohydrin (3.3 gms., 0.036 m) dropwise. After 3 hours at 50°C., the solution is cooled and extracted with chloroform. The chloroform is dried over anhydrous sodium sulfate, filtered and concentrated to an oil. The oil is purified by column chromatography to give 2.4 gm. of 4-(2,3-epoxypropoxy)-5,6,7,8-tetrahydronaphthaldehyde.

C. 4-(3-*tert.*-Butylamino-2-hydroxypropoxy)-5,6,7,8-tetrahydronaphthaldehyde

Step C:

To 4-(2,3-epoxypropoxy)-5,6,7,8-tetrahydronaphthaldehyde (2.4 gms) is added *tert.*-butylamine (15 ml.). The resulting solution is heated at 45°C. for 15 hours. The

excess of *tert*.-butylamine is removed at reduced pressure (20 mm). To the residue is added 30 ml. 6*N* hydrochloric acid, and the resulting mixture is refluxed for three hours. The acidic mixture is poured into a saturated solution of sodium carbonate which is heated on a steam bath with nitrogen bubbling through it. The basic mixture is extracted with chloroform, which is dried over anhydrous sodium sulfate, filtered and concentrated to give 2.3 g of 4-(3-*tert*.-butylamino-2-hydroxypropoxy)-5,6,7,8-tetrahydronaphthaldehyde as an oil.

D. 2-[(3-*tert*.-Butylamino-2-hydroxypropoxy)-5,6,7,8-tetrahydronaphthyl]-4-trifluoromethylimidazole

Step D:

To sodium acetate trihydrate (2.07 gm., 0.015 m) in water (20 ml.) is added dibromotrifluoroacetone (2.07 g., 0.0075 m). The solution is heated for 40 minutes on a steam bath, cooled and added to a solution of 4-(3-*tert*.-butylamino-2-hydroxypropoxy)-5,6,7,8-tetrahydronaphthaldehyde (2.3 mgs., 0.0075 m) in methanol (100 ml.) with concentrated aqueous ammonium hydroxide (15 ml.). The solution is allowed to stand at room temperature for 17 hours. The methanol is removed under reduced pressure (20 mm) over steam, and ethyl acetate (100 ml.) and saturated aqueous sodium carbonate are added to the residue. The ethyl acetate is separated, dried over anhydrous sodium sulfate, filtered and concentrated. The oil is crystallized from acetonitrile to give 500 mg. of 2-[(3-*tert*.-butylamino-2-hydroxypropoxy)-5,6,7,8-tetrahydronaphthyl]-4-trifluoromethyl-imidazole. Melting point 203°—205°C.

EXAMPLE 45

A. 4-(3-*n*-Butylamino-2-hydroxypropoxy)benzaldehyde

Step A:

To 4-(2,3-epoxypropoxy)benzaldehyde (8.9 gms., 0.05 m) is added *n*-butylamine (30 ml.) and the resulting solution is refluxed for 17 hours. The excess of *n*-butylamine is removed under reduced pressure (20 mm). The oil is dissolved in 6*N* hydrochloric acid (30 ml.) and the solution is heated on a steam bath for 40 minutes. The hot acidic solution is poured into a hot saturated aqueous sodium carbonate solution with nitrogen bubbling through it. The basic solution is extracted with chloroform. The chloroform is dried over sodium sulfate and concentrated to yield 4-(3-*n*-butylamino-2-hydroxypropoxy)benzaldehyde, as an oil.

B. 2-[4-(3-*n*-Butylamino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole

Step B:

To a solution of sodium acetate trihydrate (5.0 g.) in water (20 ml.) is added dibromotrifluoroacetone (5.0 g.). The solution is heated on a steam bath for 30 minutes. After cooling to room temperature, this solution is added to the methanolic solution of 4-(3-*n*-butylamino-2-hydroxypropoxy)benzaldehyde and concentrated aqueous ammonium hydroxide (25 ml.). After standing at room temperature for 48 hours, the methanol is removed under reduced pressure (20 mm). The residue is dissolved in ethyl acetate and saturated aqueous sodium carbonate, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The oil is placed in acetonitrile to yield 800 mg. of 2-[4-(3-*n*-butylamino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole, melting at 151—154°C.

EXAMPLE 46

S-4-(4-methoxyphenyl)-2-[4-(3-*tert*-butylamino-2-hydroxypropoxy)-phenyl]-imidazole dihydrochloride dihydrate

A heterogeneous solution of *p*-methoxyphenylglyoxal monohydrate (3.19 g., 0.018 m) sodium acetate (2.90 g., 0.036 m), water (23 ml), 37 %aqueous ammonia (23 ml) and (S)-*p*-(3-*tert*-butylamino-2-hydroxypropoxy)-benzaldehyde (2.90 g., 0.012 m) in methanol (75 ml) is stirred at 25°C. for 72 hours. The reaction mixture is concentrated to dryness under reduced pressure (15 mm) at 80°C. The residual solid is treated with saturated aqueous Na₂CO₃ (75 ml), extracted with chloroform (4×75 ml), dried over anhydrous MgSO₄, filtered and concentrated to dryness. The residue is dissolved in chloroform (50 ml) and absorbed on an alumina pad (200 g). The pad is eluted with chloroform (2 l), 5% methanol/chloroform (1 liter), 10% methanol/chloroform (1), 20% methanol/chloroform (1), 40% methanol/chloroform (1 l) and methanol (1 liter). Concentration of the 20% methanol/chloroform, 40% methanol/chloroform and methanol solutions gives 1.5 g of crude (S)-4-(4-methoxyphenyl)-2-[4-(3-*tert*-butylamino-2-hydroxypropoxy)-phenyl]-imidazole. This treatment of this crude product with 8*N* ethanolic hydrogen chloride (1 ml) yields the

hydrochloride salt, which is purified by three precipitations from isopropyl alcohol/ethyl acetate to give 810 mg of (S)-4-(4-methoxyphenyl)-2-[4-(3-*tert*-butylamino-2-hydroxypropoxy)-phenyl]-imidazole dihydrochloride dihydrate; m.p. 132.0–135.0°C.

EXAMPLE 47

5 A. 2,6-Dichloro-4-hydroxybenzaldehyde 5

To a stirred suspension of calcium hydroxide (61 gm), sodium carbonate (69.7 gm), and 3,5-dichlorophenol (20.97 gm) in water (436 ml) at 74°C is added chloroform (45.3 gm) over 90 minutes. The solution is refluxed for 3-1/2 hours. After the slow addition of concentrated hydrochloric acid (170 ml), the acidic solution is steam-distilled, the aqueous residue is cooled and the solid which separates is filtered. Recrystallization from toluene gives 1.1 gm of 2,6-dichloro-4-hydroxybenzaldehyde. 10

15 B. 2,6-Dichloro-4-(2,3-epoxypropoxy)benzaldehyde 15

To a stirred solution of 2,6-dichloro-4-hydroxy benzaldehyde (3.0 gm 0.0167 m) in 1.5 N sodium hydroxide (25 m) at 50°C is added epichlorohydrin (4.4 gm, 0.048 m). After stirring at 50°C for 3 hours, the solution is cooled and extracted with chloroform. The chloroform is dried over anhydrous sodium sulfate, filtered and concentrated to 2,6-dichloro-4-(2,3-epoxypropoxy)-benzaldehyde (3 g) which is used without further purification.

20 C. 2,6-Dichloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)benzaldehyde 20

A mixture of 2,6-dichloro-4-(2,3-epoxypropoxy)benzaldehyde (3 gm) and *tert*-butylamine (20 ml) is heated at 45°C for 17 hours. The excess of *tert*-butylamine is removed under reduced pressure (20 mm). The oil is dissolved in 6 N hydrochloric acid (25 ml) and heated for 1 hour. The acid solution is added to boiling saturated aqueous sodium carbonate with nitrogen ebullition. The basic solution is extracted with chloroform. The chloroform is dried over anhydrous sodium sulfate, filtered and concentrated to 2,6-dichloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)benzaldehyde, which is used without further purification. 25

30 D. 2-[2,6-Dichloro-4-(*tert*-butylamino-2-hydroxypropoxy)-phenyl]-4-trifluoromethyl imidazole 30

A solution of sodium acetate trihydrate (2.7 gm 0.02 m) and dibromotrifluoroacetone (276 gm (0.01 m) in water (20 ml) is refluxed for 45 minutes. It is cooled and added to a solution of 2,6-dichloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)benzaldehyde (3.0 gm, 0.009 m) in methanol (200 ml) and saturated aqueous ammonia (30 ml). After standing at room temperature for 17 hours, the solution is concentrated to an oil. The oil is dissolved in ethyl acetate and washed with saturated aqueous sodium carbonate. The ethyl acetate is dried over anhydrous sodium sulfate, filtered and concentrated. The gum is purified by chromatograph on silica gel with chloroform and washed with ammonium hydroxide and methanol as solvents. After purification 90 mg of 2-[2,6-dichloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-phenyl]-4-trifluoromethyl imidazole is obtained. 35 40

EXAMPLE 48

1-Methyl-2-[4-(3-*tert*-butylamino-2-hydroxypropoxy)phenyl]-4 (and 5)-trifluoromethyl imidazole

An ethereal solution of diazomethane (1.5 gm) is added to a solution of 2-[4-(3-*tert*-butylamino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole (1.7 g.) in ether (100 ml) and methanol (50 ml). The solution is allowed to stand at room temperature until the yellow color has disappeared. The solvents are removed under reduced pressure. The resulting gum is chromatographed on silica gel with chloroform treated with aqueous ammonium hydroxide and methanol to yield 1-methyl-2-[4-(*tert*-butylamino-2-hydroxypropoxy)phenyl]-4-(and 5)-trifluoromethyl imidazole, which is a 50–50 mixture of the two N-methyl isomers. 45 50

Analysis:

NMR (d DMSO) N—CH₃ doublet. 3.72 3.74
(CH₃)—*tert*-butyl 1.04
Mass spec 371 m⁺ peak
356 m—15

EXAMPLE 49

2-[4-(3-dimethylamino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole

A solution of 2-[4-(2,3-epoxypropoxy)phenyl]-4-trifluoromethylimidazole in tri-

ethylamine (15 ml) is added 1.1 equivalents of a dimethylamine. This solution is refluxed until reaction is complete as indicated by TLC. The solvent is removed under reduced pressure and the residue recrystallized to yield 2-[4-(3-dimethylamino-2-hydroxypropoxy)phenyl]-4-trifluoromethylimidazole.

The methods illustrated in the examples 1—49 above are readily utilized to prepare other analogous imidazoles which are encompassed by the present invention.

EXAMPLE 50

S-2-[2-(3-tert. butylamino-2-hydroxypropoxy)-3-chloro-5-pyridyl]-4-trifluoromethylimidazole hydrogen maleate

A. A mixture of 57% sodium hydride in mineral oil (0.53 g., equivalent to 0.30 g., 0.0126 m, of active sodium hydride) is added over a period of ten minutes to a stirred solution of S-2-phenyl-3-tert. butyl-5-hydroxymethylloxazolidine (2.97 g, 0.0126 m) in 25 ml of anhydrous toluene under nitrogen. The reaction mixture is stirred at 25°C for 15 minutes, 100°C for 15 minutes and finally at 25°C for 30 minutes. The homogeneous solution obtained is added dropwise over a period of 60 minutes to a rapidly stirred solution of 2,3-dichloro-5-cyanopyridine (2.0 g, 0.0126 m) in 20 ml of anhydrous toluene at 0°C under nitrogen. The heterogeneous reaction mixture is stirred rapidly at 0—5°C for 60 minutes and at 25°C for 16 hours. This reaction mixture is then poured into 50 ml of water and the toluene layer separated. The aqueous phase is extracted with additional toluene (3×25 ml). The toluene extracts are combined, washed with saturated aqueous sodium chloride (50 ml), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure (25 mm). The residue is diluted with 60 ml of 1N aqueous hydrochloric acid and stirred on a steam bath for 5 minutes and at 25°C for 30 minutes. The acidic reaction mixture is extracted with diethylether (5×50 ml) and chilled in an ice bath. 10 M aqueous sodium hydroxide is added dropwise until the pH is approximately 12—14. The basic reaction mixture is extracted with chloroform (4×50 ml). The chloroform extracts are combined, dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure (25 mm). The remaining oil is dissolved in refluxing petroleum ether (400 ml), and on cooling to 25°C., 1.38 g of S-2-(tert. butylamino-2-hydroxypropoxy)-3-chloro-5-cyanopyridine is isolated melting at 62.0—63.0°C.

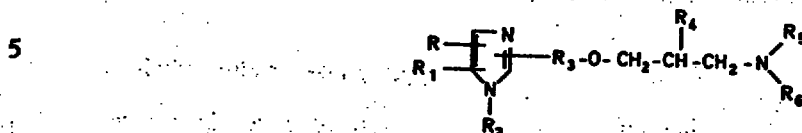
B. A solution of S-2-(3-tert. butylamino-2-hydroxypropoxy)-3-chloro-5-cyanopyridine (11.19 g, 0.0394 m) in anhydrous toluene (100 ml) is stirred rapidly at -73°C. under nitrogen. A solution of diisobutylaluminum hydride in toluene (66.3 ml, (0.0394 m) of a 9.37 M solution) is added dropwise over a ten minute period. The heterogeneous reaction mixture is stirred at -73°C for 6 hours and then allowed to stand at 0°C. for 16 hours. The reaction mixture is stirred at 0°C. and treated dropwise with methanol (50 ml) followed by water (200 ml). The turbid solution is extracted with chloroform (3×200 ml). Chloroform extracts are combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure (25 mm). The residual oil (11.4 g) is diluted with 60 ml of 6N aqueous hydrochloric acid and stirred at 100°C for 30 minutes. The homogeneous acid solution is cooled to 0—5°C. and treated with 10 M aqueous sodium hydroxide until the pH is approximately 12—14. The basic solution is saturated with sodium chloride and extracted with chloroform (3×150 ml). The chloroform extracts are combined, dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure (25 mm) to yield 11.66 g of S-2-(3-tert. butylamino-2-hydroxypropoxy)-3-chloronicotinaldehyde as a light brown oil.

C. Sodium acetate (8.66 g., 0.0636 m) is treated with 60 ml of water and the homogeneous solution stirred rapidly at 25°C. Trifluorodibromoacetone (8.58 g, 0.0318 m) is added in one portion and the mixture heated at 100°C for 40 minutes and cooled to 25°C. This solution is immediately added to a homogeneous mixture of S-2-(3-tert. butylamino-2-hydroxypropoxy)-3-chloronicotinaldehyde (6.09 g, 0.0212 m), methanol (150 ml) and concentrated aqueous ammonium hydroxide (60 ml). The reaction mixture is allowed to stir at 25°C for 16 hrs., and concentrated at reduced pressure (25 mm) to remove the methanol. The aqueous solution is extracted with 3% methanol/chloroform (2×100 ml) and 5% methanol/chloroform (2×100 ml). All extracts are combined, dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure (25 mm) to yield 6.98 g. of glassy foam. This foam is dissolved in absolute ethanol and the solution filtered through a 150 g silica pad. The filtrate is concentrated to a small volume, treated with a 10% excess of maleic acid and chilled. Upon dilution with diethyl ether, 1.82 g of S-2-[2-(3-tert. butylamino-2-hydroxypropoxy)-3-chloro-5-pyridyl]-4-trifluoromethylimidazole hydrogen maleate was isolated melting at 80.0—85°C.

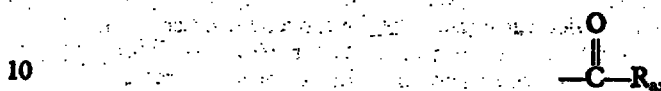
The free base may be obtained by conventional neutralization of the hydrogen maleate salt.

WHAT WE CLAIM IS:—

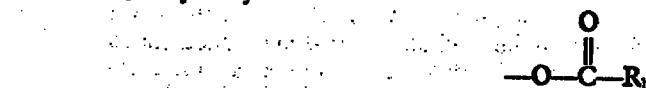
1. A compound having the formula:



in which each of R and R₁, which are similar or dissimilar, is hydrogen, C₁₋₁₀ alkyl, substituted C₁₋₁₀ alkyl having 1-3 substituents, cycloalkyl, aryl, substituted aryl having 1-5 substituents, a heterocyclic group having 5-6 ring atoms, halogen, cyano, carboxy, carboxy derivatives, or

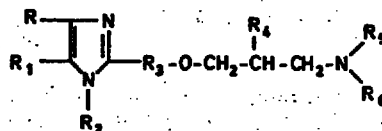


where R₁ is H or C₁₋₈ alkyl; R₂ is hydrogen, C₁₋₁₀ alkyl, hydroxy-C₁₋₁₀ alkyl or C₃₋₈ alkenyl; R₃ is a bivalent aromatic group having 6 ring atoms of which 0-2 are other than carbon, a substituted bivalent aromatic group having 1-4 substituents, fused-ring bivalent aromatic group having 9-10 ring atoms of which 0-2 are other than carbon, or substituted fused-ring bivalent aromatic group having 1-4 substituents; R₄ is hydroxy or



where R₅ is C₁₋₈ alkyl, and each of R₅ and R₆, which are similar or dissimilar, is hydrogen, C₁₋₈ alkyl, cycloalkyl or substituted C₁₋₈ alkyl or R₅ and R₆ are joined to form a 5-6 membered N-alicyclic ring; and pharmacologically acceptable salts thereof.

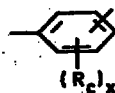
2. A compound of the formula:



in which R, R₁, R₂, R₃, R₄, R₅ and R₆ are as defined in claim 1.

3. A compound as claimed in claim 2 in which R₃ is a pyridinediyl, alkylpyridinediyl, halopyridinediyl, naphthalenediyl, or hydrogenated naphthalenediyl radical.

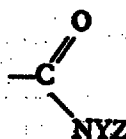
4. A compound as claimed in claim 2 in which R₃ is phenylene having the formula:



where x is 0, 1, 2, 3 or 4 and each R₉, which may be the same as or different from any other R₉, is halogen, C₁₋₄ alkoxy, hydroxy, cyano, phenyl or C₁₋₄ alkyl.

5. A compound as claimed in claim 4 where each R₉ is, independently of any other R₉, halogen or C₁₋₄ alkyl.

6. A compound as claimed in claim 3 in which R₁ is hydrogen, haloalkyl, C₁₋₈ alkyl, heterocyclic, phenyl, substituted phenyl having 1-5 substituents independently selected from halogen, C₁₋₄ alkyl, cyano,



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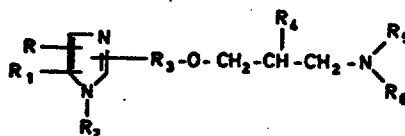
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The free base may be obtained by conventional neutralization of the hydrogen malcate salt.

WHAT WE CLAIM IS:—

1. A compound having the formula:

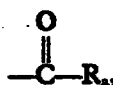
5



5

in which each of R and R₁, which are similar or dissimilar, is hydrogen, C₁₋₁₀ alkyl, substituted C₁₋₁₀ alkyl having 1—3 substituents, cycloalkyl, aryl, substituted aryl having 1—5 substituents, a heterocyclic group having 5—6 ring atoms, halogen, cyano, carboxy, carboxy derivatives, or

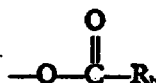
10



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where R₇ is H or C₁₋₆ alkyl; R₂ is hydrogen, C₁₋₁₀ alkyl, hydroxy-C₁₋₁₀ alkyl or C₃₋₆ alkenyl; R₃ is a bivalent aromatic group having 6 ring atoms of which 0—2 are other than carbon, a substituted bivalent aromatic group having 1—4 substituents, fused-ring bivalent aromatic group having 9—10 ring atoms of which 0—2 are other than carbon, or substituted fused-ring bivalent aromatic group having 1—4 substituents; R₄ is hydroxy or

15

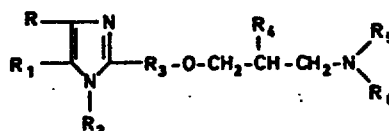


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where R₈ is C₁₋₆ alkyl, and each of R₅ and R₆, which are similar or dissimilar, is hydrogen, C₁₋₆ alkyl, cycloalkyl or substituted C₁₋₆ alkyl or R₅ and R₆ are joined to form a 5—6 membered N-alicyclic ring; and pharmacologically acceptable salts thereof.

20

2. A compound of the formula:



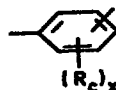
25

in which R, R₁, R₂, R₃, R₅ and R₆ are as defined in claim 1.

25

3. A compound as claimed in claim 2 in which R₃ is a pyridinediyl, alkylpyridinediyl, halopyridinediyl, naphthalenediyl, or hydrogenated naphthalenediyl radical.

4. A compound as claimed in claim 2 in which R₃ is phenylene having the formula:



30

where x is 0, 1, 2, 3 or 4 and each R₉, which may be the same as or different from any other R₉, is halogen, C₁₋₄ alkoxy, hydroxy, cyano, phenyl or C₁₋₄ alkyl.

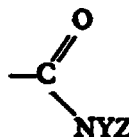
30

5. A compound as claimed in claim 4 where each R₉ is, independently of any other R₉, halogen or C₁₋₄ alkyl.

35

6. A compound as claimed in claim 3 in which R₁ is hydrogen, haloalkyl, C₁₋₆ alkyl, heterocyclic, phenyl, substituted phenyl having 1—5 substituents independently selected from halogen, C₁₋₆ alkyl, cyano,

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where each of Y and Z is hydrogen or C₁₋₆ alkyl; or a (C₁₋₆ alkoxy) carbonyl.

7. A compound as claimed in claim 3 in which R₁ is trifluoromethyl, phenyl, pyridyl, thienyl, furyl, C₁₋₆ alkyl, cyano, (C₁₋₆ alkoxy)phenyl, halophenyl or methylphenyl.

8. A compound as claimed in claim 7 in which R₆ is H and R₅ is C₁₋₆ alkyl.

9. A compound as claimed in claim 8 in which R₅ is C₃₋₄ branched alkyl.

10. A compound as claimed in claim 9 in which R₅ is *tert*-butyl.

11. A compound as claimed in claim 9 in which R₁ is trifluoromethyl.

12. A compound as claimed in claim 2 in which R is H, R₂ is H, R₃ is H, R₄ is C₁₋₆ alkyl and R₅ is hydroxy.

13. A compound as claimed in claim 12 in which R₁ is —CF₃.

14. A compound as claimed in claim 12 in which R₃ is as defined in claim 3.

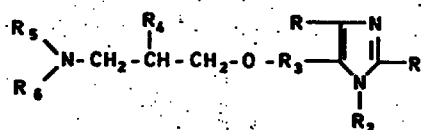
15. A compound as claimed in claim 12 in which R₃ is as defined in claim 4.

16. A compound as claimed in claim 15 in which R₆ in the formula of R₃ is as defined in claim 5.

17. A compound as claimed in claim 15 in which x is the formula of R₃ is 1.

18. A compound as claimed in claim 15 in which x is 0.

19. A compound of the formula:



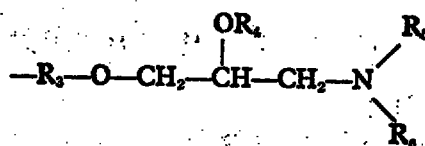
in which R, R₁, R₂, R₃, R₄, R₅ and R₆ are as defined in claim 1.

20. A compound as claimed in claim 19 in which R is hydrogen.

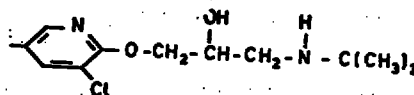
21. A compound as claimed in claim 1 in which R₃ is cyanopyridinediyl.

22. A compound as claimed in claim 20 in which R₃ is halopyridinediyl.

23. A compound as claimed in claim 22 in which the



group has the formula:



24. 2 - [4 - (3 - *tert* - butylamino - 2 - hydroxypropoxy) - phenyl] - 4 - trifluoromethylimidazole and pharmacologically acceptable salts thereof.

25. (S) - 2 - [4 - (3 - *tert* - butylamino - 2 - hydroxypropoxy) - phenyl] - 4 - trifluoromethylimidazole and pharmacologically acceptable salts thereof.

26. (S) 2 - [4 - (3 - *tert* - butylamino - 2 - hydroxypropoxy) - phenyl] - 4 - methylimidazole and pharmacologically acceptable salts thereof.

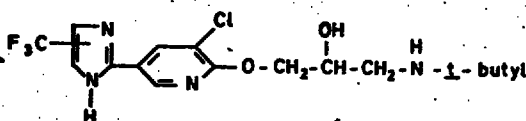
27. 2 - [4 - (3 - cyclopropylamino - 2 - hydroxypropoxy) - phenyl] - 4 - trifluoromethylimidazole and pharmacologically acceptable salts thereof.

28. (S) - 2 - [4 - (3 - *tert* - butylamino - 2 - hydroxypropoxy) - phenyl] - 4 - (4 - methoxyphenyl)imidazole and pharmacologically acceptable salts thereof.

29. 2 - [4 - (3 - *tert* - butylamino - 2 - hydroxypropoxy) - phenyl] - 4 - cyanoimidazole and pharmacologically acceptable salts thereof.

30. (S) - 2 - [4 - (3 - *tert* - butylamino - 2 - hydroxypropoxy) - phenyl] - 4 - (2 - thienyl)imidazole and pharmacologically acceptable salts thereof.

31. A compound having the formula



and pharmacologically acceptable salts thereof.

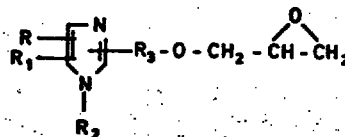
32. A compound as claimed in Claim 31 having the S-isomer configuration.



33. S - 2 - [2 - (3 - *tert.*butylamino - 2 - hydroxypropoxy) - 3 - chloro - 5-pyridyl] - 4 - trifluoromethylimidazole.

34. S - 2 - [2 - (3 - *tert.*butylamino - 2 - hydroxypropoxy) - 3 - chloro - 5-pyridyl] - 4 - trifluoromethylimidazole hydrogen maleate.

35. A method of preparing an imidazole as claimed in claim 1 in which R_4 is hydroxy, that comprises the reaction of an epoxide having the formula:

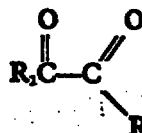


with an amine having the formula:

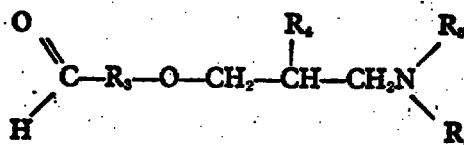


where R , R_1 , R_2 , R_3 , R_4 and R_5 are as defined in claim 1.

36. A method of preparing an imidazole as claimed in claim 1 in which R_2 is hydrogen, that comprises reacting a compound having the formula:



with a compound having the formula:



in the presence of ammonia, where R , R_1 , R_2 , R_3 , R_4 and R_5 are as defined in claim 1.

37. A method of preparing a compound as claimed in claim 1, substantially as hereinbefore described in any one of examples 1-50.

38. A compound as claimed in claim 1 when prepared by a method as claimed in any one of claims 35 to 37.

39. A pharmaceutical composition comprising a compound as claimed in claim 1 and a pharmacologically acceptable compounding agent.

40. A composition as claimed in claim 39, in the form of a tablet.

41. A composition as claimed in claim 39, in the form of a capsule.

42. A composition as claimed in claim 39, in the form of an injectable solution.

43. A composition as claimed in claim 39, in the form of a liquid suspension.

44. A composition as claimed in claim 39, in the form of a solution, dispersion, emulsion or aerosol.

45. A composition as claimed in any one of claims 39 to 44, in which the said compound is a compound as claimed in any one of claims 1 to 34 and 38.

46. A composition as claimed in claim 39 substantially as hereinbefore described in any one of Formulations I to V.

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