

PATENT SPECIFICATION

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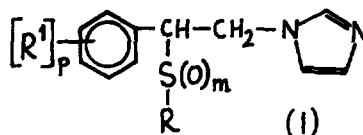


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(54) 1-[β-(R-THIO)PHENETHYL]IMIDAZOLES AND DERIVATIVES THEREOF

(71) We, SYNTEX (U.S.A.) INC., a Corporation organised under the laws of the State of Delaware, United States of America, of 3401 Hillview Avenue, Palo Alto, California 94304, 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:—

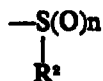
The present invention relates to novel imidazole derivatives. More particularly it provides 1-[β-(R-thio)phenethyl]imidazoles, 1-[β-(R-sulfinyl)phenethyl]imidazoles and 1-[β-(R-sulfonyl)phenethyl]imidazoles having the formula



and the addition salts thereof, wherein:

R is alkyl, alkenyl, aralkenyl, substituted aralkenyl, alkynyl, cycloalkyl, cycloalkyl alkyl, aralkyl, substituted aralkyl, aryl or substituted aryl, said substituted aralkenyl and substituted aralkyl containing at least one substituent on the aryl moiety selected from halo, lower alkyl, lower alkoxy, trifluoromethyl, nitro and cyano and said substituted aryl containing at least one substituent selected from halo, lower alkyl, lower alkoxy, trifluoromethyl, nitro, amino, acylamino and cyano;

R¹ is hydrogen, halo, lower alkyl, lower alkoxy, trifluoromethyl, nitro, cyano, thiocyanato or the group

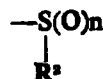


in which R² is alkyl, cycloalkyl, aralkyl, substituted aralkyl, aryl or substituted aryl, said substituted aralkyl and said substituted aryl containing at least one substituent on the aryl moiety selected from halo, lower alkyl, lower alkoxy, trifluoromethyl, nitro and cyano;

m, n and p are independently selected from the integers zero, 1 and 2;

provided that:

the value of m cannot be greater than the value of n except when R¹ is the group



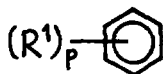
and R² is aryl or substituted aryl.

The term "alkyl" as used in the specification and appended claims refers to a saturated, unbranched or branched acyclic hydrocarbon group containing 1 to 20 carbon atoms inclusive, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, i-butyl, t-butyl, n-pentyl, n-heptyl, n-octyl, n-nonyl, n-dodecyl; n-octadecyl and the like. The term "lower alkyl" refers to an alkyl group as previously defined containing 1 to 6 carbon atoms, inclusive. The term "lower alkoxy" refers to groups of the formula

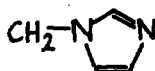


wherein the lower alkyl substituent is as previously defined. The term "cycloalkyl" as used herein refers to a saturated, monocyclic hydrocarbon group having 5 to 8 ring carbon atoms, such as cyclopentyl, cyclohexyl, cycloheptyl and the like. The term "cycloalkyl alkyl" refers to a cycloalkyl group as previously defined attached to an unbranched acyclic hydrocarbon group containing 1 to 3 carbon atoms, such as cyclopentylpropyl, cyclohexylmethyl, cyclohexylethyl, cycloheptylmethyl and the like. The term "alkenyl" refers to an unbranched or branched acyclic hydrocarbon group having carbon-carbon double bond unsaturation and containing 2 to 12 carbon atoms such as allyl, 2-hexenyl, 3-octenyl, 2-octenyl, 2-decenyl and the like. The term "aralkenyl" refers to a hydrocarbon moiety in which the alkenyl portion containing 2 to 4 carbon atoms is attached to a hydrocarbon group consisting of one or more aromatic rings and containing 6 to 10 carbon atoms such as 3-phenyl-2-propenyl, 4-phenyl-3-butenyl, styryl, 3-naphthyl-2-propenyl and the like. The term "alkynyl" refers to an unbranched or branched acyclic hydrocarbon group having carbon-carbon triple bond unsaturation and containing 2 to 12 carbon atoms, such as 2-propynyl, 2-hexynyl, 2-octynyl and the like. The term "aryl" refers to a hydrocarbon group consisting of one or more aromatic rings and containing 6 to 10 ring carbon atoms, such as phenyl and naphthyl. The term "aralkyl" refers to a hydrocarbon moiety in which the alkyl portion contains 1 to 4 carbon atoms and the aryl portion is defined as above. Representative examples of aralkyl groups include benzyl, 3-phenylpropyl and the like. The term acylamino, i.e., R-C(O)-NH- , refers to substituents containing up to 12 carbon atoms, wherein R in such substituents is alkyl (as defined above), e.g. methyl, ethyl, i-propyl, n-butyl, pentyl, octyl and the like. The term "halo" as used herein refers to chloro, fluoro and bromo. The term "acid addition salts" refers to salts of the subject compounds formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid and the like, or organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

All compounds of Formula (I) possess at least one chiral center, i.e., the carbon atom to which are attached the



RS(O)_m , H and



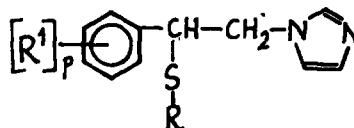
moieties. Accordingly, the compounds of the present invention may be prepared in either optically active form, or as a racemic mixture. Unless otherwise specified, the compounds described herein are all in the racemic form. However, the scope of the subject invention herein is not to be considered limited to the racemic form, but to encompass the individual optical isomers of the subject compounds.

If desired, racemic intermediates or final products prepared herein may be resolved into their optical antipodes by conventional resolution means known *per se*, for example, as described in U.S. Patents 3,717,655 and 3,839,574 or by the separation (e.g., fractional crystallization) of the diastereomeric salts formed by reaction of, e.g. racemic compounds of Formula (I) with an optically active acid, or the diastereomeric esters formed by reaction of the racemic alcohol precursors of compounds of Formula (II) with an optically active acid. Exemplary of such optically active acids are the optically active forms of camphor-10-sulfonic acid, α -bromo-camphor- π -sulfonic acid, camphoric acid, menthoxy-acetic acid, tartaric acid, malic acid, diacetyltartaric acid, pyrrolidone-5-carboxylic acid, and the like. The separated pure diastereomeric salts or

(14)

esters may then be cleaved by standard means to afford the respective optical isomers of the compounds of Formula (I) or the precursor alcohols.

A preferred subclass of compounds within the class defined by Formula (I) are those compounds having the formula



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and the acid addition salts thereof, wherein R , R' and p are as defined above.

A preferred group of compounds within the above defined subclass are those wherein R' is halo and R is alkyl, alkenyl, aralkenyl, halo substituted aralkenyl, aralkyl, halo substituted aralkyl, aryl or halo substituted aryl.

Particularly preferred compounds within the group described in the previous paragraph are those wherein $[R']_p$ is mono halo or dihalo and R is alkyl containing 1 to 12 carbon atoms, 2-alkenyl, phenyl-2-alkenyl, chloro substituted phenyl-2-alkenyl, benzyl, chloro or fluoro substituted benzyl, phenyl or chloro substituted phenyl. Most particularly preferred compounds are those wherein $[R']_p$ represents 2,4-dichloro, 2,4-dibromo or 2,4-difluoro.

The subject compounds of Formula (I) exhibit anti-fungal and anti-bacterial activity. For example, compounds of the present invention exhibit anti-fungal activity against human and animal pathogens such as

Microsporium audouini,
Microsporium gypseum,
Microsporium gypseum—canis,
Epidermophyton floccosum,
Trichophyton mentagrophytes,
Trichophyton rubrum,
Trichophyton tonsurans,
Candida albicans, and
Cryptococcus neoformans.

The compounds of the present invention also exhibit anti-fungal activity against fungi of primarily agricultural importance such as

Aspergillus flavus,
Cladosporium herbarum,
Fusarium graminearum,
Penicillium notatum,
Aspergillus niger,
Penicillium oxalicum,
Penicillium spinulosum, and
Pithomyces chartarum.

In addition, the compounds of the present invention exhibit anti-bacterial activity against human and animal pathogens, such as

Staphylococcus aureus,
Streptococcus faecalis,
Corynebacterium acnes,
Erysipelothrix insidiosa,
Escherichia coli,
Proteus vulgaris,
Salmonella choleraesuis,
Pasteurella multocida, and
Pseudomonas aeruginosa.

In view of the aforementioned activities, the subject compounds are found to be useful antimicrobials, having not only pharmaceutical but also agricultural and industrial application.

Accordingly, a further aspect of the present invention relates to compositions for pharmaceutical, agricultural, and industrial use, which compositions comprise the subject compounds of Formula (I) in combination with a suitable carrier. A still further aspect of the present invention relates to methods of inhibiting the growth of fungi and bacteria by applying to a host object containing, or subject to attack by, fungi or bacteria, a fungicidally or bacteriocidally effective amount of a compound of the present invention or a suitable composition containing same.

In pharmaceutical applications, compositions may be solid, semi-solid or liquid

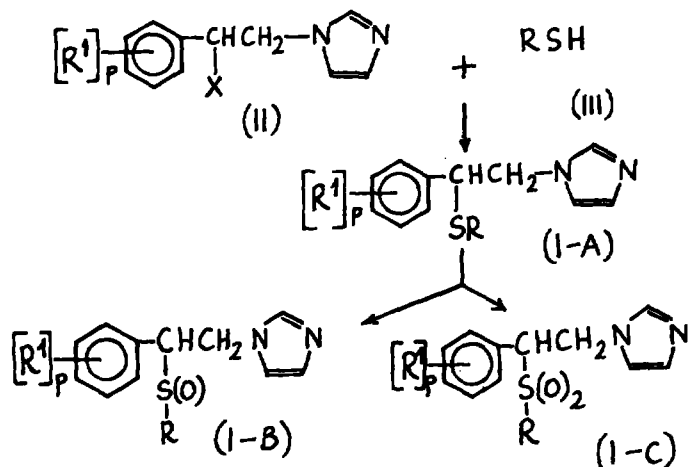
in form such as tablets, capsules, powders, suppositories, liquid solutions, suspensions, creams, lotions, ointments and the like. Pharmaceutically acceptable non-toxic carriers, or excipients normally employed for solid formulations include tricalcium phosphate, calcium carbonate, kaolin, bentonite, talcum, gelatin, lactose, starch and the like; for semi-solid formulations there may be mentioned, for example, polyalkylene glycols, Vaseline (Trade Mark) and other cream bases; for liquid formulations there may be mentioned, for example, water, oils of vegetable origin and low boiling solvents such as isopropanol, hydrogenated naphthalenes and the like. The pharmaceutical compositions containing the compounds of the present invention may be subjected to conventional pharmaceutical expedients such as sterilization and can contain conventional pharmaceutical excipients such as preservatives, stabilizing agents, emulsifying agents, salts for the adjustment of osmotic pressure and buffers. The compositions may also contain other therapeutically active materials. In pharmaceutical applications, the subject compounds and compositions may be administered to humans and animals by conventional methods, e.g., topically, orally, parenterally and the like. When given orally the compounds, alone or in admixture with a suitable carrier, may be administered at a dosage of from about 12.5 mg. to about 1000 mg. per dose (assuming a 70 kg. host subject), one or more times daily, extending over a period of several days to many weeks. Suppositories may contain from about 1 mg. to 500 mg. of active compounds.

Topical application is preferred. For such treatment, an area having an existing fungal or bacterial growth, or to be protected against attack by fungi or bacteria, may be treated with the subject compounds or compositions by, for example, dusting, sprinkling, spraying, rinsing, brushing, dipping, smearing, coating, impregnating and the like. Pharmaceutical compositions containing the compounds of the present invention exhibit anti-fungal and anti-bacterial activity over a wide range of concentration, for example, from about 0.1 to 10.0% by weight of the composition. In any event, the composition to be administered will contain a quantity of the subject compound in an amount effective for relief or prevention of the specific condition being treated. The exact regimen for pharmaceutical administration of the compounds and compositions disclosed herein will necessarily be dependent upon the needs of the individual subject being treated, the type of treatment e.g., whether preventative or curative, the type of organism involved and, of course, the judgment of the attending practitioner.

In agricultural applications, the subject compounds may be applied directly to plants (e.g., seeds, foliage) or to soil. For example, compounds of the present invention may be applied to seeds alone or in admixture with a powdered solid carrier. Typical powdered carriers are the various mineral silicates, e.g. mica, talc, pyrophyllite, and clays. The subject compounds may also be applied to the seeds in admixture with a conventional surface-active wetting agent with or without additional solid carrier. Surface-active wetting agents that can be used are any of the conventional anionic, non-anionic or cationic types. As a soil treatment for fungi and the like, the subject compounds can be applied as a dust in admixture with sand, soil or a powdered solid carrier such as a mineral silicate with or without additional surface-active agent, or the subject compounds can be applied as an aqueous spray optionally containing a surface-active dispersing agent and a powdered solid carrier. As a foliage treatment, the subject compounds may be applied to growing plants as an aqueous spray which contains a surface-active dispersing agent with or without a powdered solid carrier and hydrocarbon solvents.

In industrial applications, the subject compounds may be used to control bacteria and fungi by contacting the pathogens with the compounds in any known matter. Materials capable of supporting bacteria and fungi may be protected by contacting, mixing or impregnating these materials with the subject compounds. In order to increase their effect, the subject compounds may be combined with other pesticidal control agents such as fungicides, bactericides, insecticides, miticides and the like. A particularly important industrial/agricultural use for the subject compounds of the present invention is as a food preservative against bacteria and fungi which cause deterioration and spoilage of foods.

The present invention, in a still further aspect, is directed to methods for the preparation of the subject compounds of Formula (I) according to the following reaction sequence:



wherein R, R' and p are as previously described and X represents a conventional leaving group such as chloro, bromo or a reactive ester group such as $\text{CH}_2\text{-S(O)}_2\text{-O-}$ or $p\text{-CH}_2\text{-C}_6\text{H}_4\text{-S(O)}_2\text{-O-}$.

The 1-[(β-(R-thio)phenethyl)]imidazoles of Formula I—A are prepared by condensing a compound of Formula II with a thiol of Formula III.

In said condensation, the starting materials and reagents may be contacted in any convenient manner and maintained at a temperature and for a period of time sufficient to complete the reaction. Furthermore, the reaction products may be isolated and recovered from the reaction using, as in the case of the reaction conditions themselves, procedures conventional or known in the art for conducting such reactions or analogous reactions. The nature of the leaving group (X) is not critical, its selection being predicated on relative reactivity rates known for reactions of this type. Chloro, bromo, and the two ester groups noted above are given by way of typical examples only.

Generally, the reaction of compounds of Formula II with compounds of Formula III wherein R in Formula III is alkyl, alkenyl, aralkenyl, substituted aralkenyl, alkynyl, cycloalkyl, cycloalkyl alkyl, aralkyl and substituted aralkyl is carried out in the presence of an inert organic solvent, e.g. tetrahydrofuran, ether, methanol and the like in the presence of sodium hydride or other suitable base at a temperature of 20 to 66°C for a period of 30 minutes to 24 hours.

Generally the reaction of compounds of Formula II with compounds of Formula III wherein R in Formula III is aryl or substituted aryl is carried out in the presence of an inert organic solvent, e.g. acetone, methanol, and the like and in the presence of potassium carbonate or other suitable base under reflux conditions for a period of 30 minutes to 12 hours.

The thus obtained 1-[(β-(R-thio)phenethyl)]imidazole compounds of Formula I—A are then optionally oxidized to obtain the 1-[(β-(R-sulfinyl)phenethyl)]- and the 1-[(β-(R-sulfonyl)phenethyl)]imidazole compounds of Formulas I—B and I—C, respectively. Oxidation is conducted by methods well-known in the art using hydrogen peroxide, an organic peracid such as peracetic acid, p-nitroperbenzoic acid and m-chloroperbenzoic or an inorganic peracid such as periodic acid. The oxidation reaction is preferably conducted using m-chloroperbenzoic in a liquid reaction medium, such as a chlorinated hydrocarbon.

In said oxidation, the starting materials and reagents may be contacted in any convenient manner and maintained at a temperature and for a period of time sufficient to complete the reaction. Furthermore, the reaction products may be isolated and recovered from the reaction using, as in the case of the reaction conditions themselves, procedures conventional or known in the art for conducting such reactions or analogous reactions.

In general, when the compounds of Formula I—A are contacted with about one up to about two equivalents of oxidizing agent, such as m-chloroperbenzoic acid, at a temperature of from about -30°C to about 30°C, preferably in an organic medium, such as chloroform, and for a period of about 30 minutes to about 6 hours, the corresponding sulfinyl products of Formula I—B are obtained. Similarly, when the compounds of Formula I—A are contacted with about two or more equivalents of oxidizing agent, such as m-chloroperbenzoic acid, at a temperature of from about 0°C to about 60°C, preferably in an organic medium, such as chloroform, and for a

period of about 1 to about 24 hours, the corresponding sulfonyl products of Formula I—C are obtained.

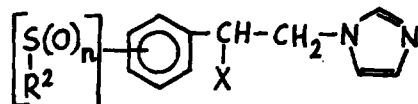
The subject compounds of the instant invention can be isolated as free bases. However, since many of the compounds in base form are oils or gums, it is more convenient to isolate and characterize the compounds as acid addition salts. These salts are prepared in the usual manner, i.e., by reaction of the base compound with suitable inorganic or organic acid. If desired, the salts can be readily converted to the compounds in base form by treatment with alkali, such as potassium carbonate, sodium carbonate or sodium or potassium hydroxide.

The starting compounds of Formula II, wherein R¹ is hydrogen, methyl, methoxy, halo, nitro or lower alkyl sulfonyl are disclosed together with a method for their preparation in U.S. Patent 3,679,697. Compounds of Formula II wherein R¹ is other than those groups disclosed in the above-identified patent, with the exception of R²S(O)—, can be analogously prepared, i.e., by bromination of the appropriate acetophenone, reaction of the resultant 2-bromo acetophenone compound with imidazole, reduction of the resultant 2-(1-imidazolyl)acetophenone compound with sodium tetrahydroborate, and finally, reaction of the resultant 1-imidazoleethanol compound with a thionyl halide to yield the 1-(β-halophenethyl)imidazole compounds of Formula II. Compounds of Formula II wherein R¹ is the group R²S(O)— are prepared by oxidation of corresponding compounds of Formula II where R¹ is the group R²S— using conventional methods known in the art as described earlier in this invention.

When acetophenones containing the group



wherein R² is as previously defined, are required as reactants for the preparation of starting compounds of Formula II, i.e.,



wherein R² and X are as previously defined, these acetophenones may be prepared by prepared by the following processes:

(A) Friedel-Crafts Acylation of a known alkyl-, cycloalkyl-, aralkyl- or aryl phenyl sulfide with acetyl chloride or with acetic anhydride in the presence of AlCl₃ to yield the corresponding alkylthio-, cycloalkylthio-, aralkylthio or arylthioacetophenone which can be converted to the corresponding sulfonyl derivatives by oxidation with hydrogen peroxide in acetic acid. These methods are described in the Journal of American Chemical Society 74, 5475—81, (1952) and U.S. 2,763,692.

(B) Coupling a diazotized aminoacetophenone with an aryl thiol or a substituted aryl thiol, said substituted thiol containing at least one substituent selected from the group consisting of halo, lower alkyl, lower alkoxy, trifluoromethyl, nitro and cyano, to obtain the substituted arylthio acetophenone. Alternatively, a diazotized aryl amino compound, substituted with at least one of the above substituents can be coupled with a mercaptoacetophenone to obtain the substituted arylthioacetophenone. These procedures are described in Boll. sci. fac. chim. ind. Bologna 17, 33—43 (1959).

(C) Alkylation of an o-, m- or p-mercaptoacetophenone with a known alkyl, cycloalkyl, aralkyl or substituted aralkyl halide, said substituted aralkyl halide substituted on the aryl moiety with at least one substituent selected from the group consisting of halo, lower alkyl, lower alkoxy, trifluoromethyl, nitro and cyano to obtain the corresponding alkylcycloalkyl-, aralkyl- or substituted aralkylthioacetophenone. This procedure is described in the Journal of American Chemical Society 78, 4792—7 (1956).

Oxidation of the products of processes (B) and (C) in the manner described in process (A) produced the corresponding R_s-sulfonylacetophenones wherein R_s is as previously defined.

The following specific description is given to enable those skilled in the art to more clearly understand and practice the present invention. It should not be considered

as a limitation upon the scope of the invention but merely as being illustrative and representative thereof.

Preparation A

A mixture of 1.52 g. of 4-mercaptoacetophenone, 1.72 g. of 4-methoxybenzyl chloride and 1.5 g. of anhydrous potassium carbonate in 50 ml. of acetone is stirred and refluxed under nitrogen. After 4 hours the solvent and excess 4-methoxybenzyl chloride are evaporated under vacuum and water is added to the residue. The resultant aqueous mixture is extracted with ether and the ether extract washed with water, dried over magnesium sulfate and evaporated to dryness. The resulting residue is recrystallized from cyclohexane to yield 4-(4'-methoxybenzyl-thio)-acetophenone.

Similarly, replacing 4-methoxy benzyl chloride with other aralkyl halides or substituted aralkyl halides containing at least one substituent on the aryl moiety selected from the group consisting of halo, lower alkyl, lower alkoxy, trifluoromethyl, nitro and cyano is productive of the corresponding substituted aralkylthioacetophenones.

The starting compounds of Formula II are prepared from the above substituted aralkylthioacetophenones according to the procedure in U.S. 3,679,697.

Preparation B

A mixture of 2 g. of 4-methylthioacetophenone, 5 g. of acetic acid, and approximately 3.8 g. of 30% hydrogen peroxide is heated at 85°—95°C. until an exothermic reaction is initiated. When the reaction subsides, .002 g. of palladium-on-carbon is introduced and the reaction mixture is filtered through diatomaceous earth. The filtrate is chilled to precipitate the product which is isolated by filtration and air dried to yield 4-methylsulfonyl acetophenone.

Similarly, replacing 4-methylthioacetophenone with other thioacetophenones, for example,

4-t-butylthioacetophenone,
4-benzylthioacetophenone,
4-(4'-chlorobenzylthio)acetophenone,
4-(4'-methoxybenzylthio)acetophenone,
4-phenylthioacetophenone, and
4-(4'-chlorophenylthio)acetophenone

is productive of the following sulfonyl substituted acetophenones:

4-t-butylsulfonylacetophenone,
4-benzylsulfonylacetophenone,
4-(4'-chlorobenzylsulfonyl)acetophenone,
4-(4'-methoxybenzylsulfonyl)acetophenone,
4-phenylsulfonylacetophenone, and
4-(4'-chlorophenylsulfonyl)acetophenone.

The starting compounds of Formula II are prepared from the above sulfonyl substituted acetophenones according to the procedure in U.S. 3,679,697.

EXAMPLE 1

A) A mixture of 1 g. of 1-(2,4,β-trichlorophenethyl)imidazole, 1.8 g. of 3,4-dichlorothiophenol and 1.5 g. of potassium carbonate in 50 ml. of acetone is stirred and refluxed for 4 hours. The solvent is evaporated under vacuum and 20 ml. of water is added to the residue. The resultant aqueous mixture is extracted with ether and the ether extract washed with 50 ml. of a saturated sodium chloride solution. The organic phase is dried over magnesium sulfate and evaporated to yield 1-[2,4-dichloro-β-(3',4'-dichlorophenylthio)phenethyl]imidazole.

The oxalate salt of the free base is prepared by the dropwise addition of ethereal oxalic acid to the free base in ether until precipitation is complete. The product is collected by filtration and recrystallized from a mixture of acetone and ethyl acetate to yield 1-[2,4-dichloro-β-(3',4'-dichlorophenylthio)phenethyl]imidazole oxalate, m.p. 161.5—163.5°C.

B) Similarly, substituting other starting materials of Formula II for 1-(2,4,β-trichlorophenethyl)imidazole, for example,

1-(β-chlorophenethyl)imidazole;
1-(β-chloro-4-ethylphenethyl)imidazole;
1-(β-chloro-4-t-butylphenethyl)imidazole;
1-(β-chloro-4-ethoxyphenethyl)imidazole;
1-(β-chloro-4-n-butoxyphenethyl)imidazole;
1-(β-chloro-4-t-butoxyphenethyl)imidazole;
1-(4,β-dichlorophenethyl)imidazole;
1-(3,4,β-trichlorophenethyl)imidazole;

- 1-(4-bromo- β -chlorophenethyl)imidazole;
 1-(2,4-dibromo- β -chlorophenethyl)imidazole;
 1-(β -chloro-4-fluorophenethyl)imidazole;
 1-(β -chloro-2,4-difluorophenethyl)imidazole;
 5 1-(β -chloro-2-trifluoromethylphenethyl)imidazole;
 1-(β -chloro-4-trifluoromethylphenethyl)imidazole;
 1-(β -chloro-4-cyanophenethyl)imidazole,
 1-(β -chloro-4-nitrophenethyl)imidazole, and
 1-(β -chloro-2-thiocyanatophenethyl)imidazole
 10 is productive of the following 1- $[\beta$ -(3',4'-dichlorophenylthio)phenethyl]imidazoles
 which, where indicated, are further characterized as the acid addition salts by treatment
 in the conventional manner with the appropriate acid:
 1- $[\beta$ -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-ethyl- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 15 1-(4-*t*-butyl- β -(3',4'-dichlorophenylthio)phenethyl]imidazole, nitrate salt, decomp.
 142.5—146.5°C.
 1-[4-ethoxy- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-*n*-butoxy- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-*t*-butoxy- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 20 1-[4-chloro- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[3,4-dichloro- β -(3',4'-dichlorophenylthio)phenethyl]imidazole, nitrate salt,
 decomp. 133—137°C.;
 1-[4-bromo- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[2,4-dibromo- β -(3',4'-dichlorophenylthio)phenethyl]imidazole, nitrate salt,
 25 decomp. 132.5—134.5°C.;
 1-[4-fluoro- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[2,4-difluoro- β -(3',4'-dichlorophenylthio)phenethyl]imidazole, oxalate salt,
 decomp. 172.5—175°C.;
 1-[2-trifluoromethyl- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-trifluoromethyl- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 30 1-[4-cyano- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-nitro- β -(3',4'-dichlorophenylthio)phenethyl]imidazole, and
 1-[2-thiocyanato- β -(3',4'-dichlorophenylthio)phenethyl]imidazole.
 C) In like manner, substituting other starting materials of Formula III for 3,4-
 35 dichlorothiophenol, for example, 4-chlorothiophenol and 2,4-dichlorothiophenol and
 using the above recited starting compounds of Formula II is productive of the follow-
 ing 1- $[\beta$ -(*R*-thio)phenethyl]imidazoles which, where indicated, are further charac-
 terized as the acid addition salts by treatment in the conventional manner with the
 appropriate acid:
 40 1- $[\beta$ -(4'-chlorophenylthio)phenethyl]imidazole, oxalate salt, decomp. 147.5—
 149°C.;
 1- $[\beta$ -(2',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-ethyl- β -(4'-chlorophenylthio)phenethyl]imidazole;
 1-[4-ethyl- β -(2',4'-dichlorophenylthio)phenethyl]imidazole;
 45 1-[4-*t*-butyl- β -(4'-chlorophenylthio)phenethyl]imidazole;
 1-[4-butyl- β -(2',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-ethoxy- β -(4'-chlorophenylthio)phenethyl]imidazole;
 1-[4-ethoxy- β -(2',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-*n*-butoxy- β -(4'-chlorophenylthio)phenethyl]imidazole;
 50 1-[4-*n*-butoxy- β -(2',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-*t*-butoxy- β -(4'-chlorophenylthio)phenethyl]imidazole;
 1-[4-*t*-butoxy- β -(2',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-chloro- β -(4'-chlorophenylthio)phenethyl]imidazole, oxalate salt, decomp.
 190—191°C.;
 55 1-[4-chloro- β -(2',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[2,4-dichloro- β -(4'-chlorophenylthio)phenethyl]imidazole, nitrate salt, M.P.
 169.5—170°C.;
 1-[2,4-dichloro- β -(2',4'-dichlorophenylthio)phenethyl]imidazole, nitrate salt, M.P.
 150—151°C.;
 60 1-[3,4-dichloro- β -(4'-chlorophenylthio)phenethyl]imidazole, nitrate salt, decomp.
 123—125.5°C.;
 1-[3,4-dichloro- β -(2',4'-dichlorophenylthio)phenethyl]imidazole, oxalate salt,
 decomp. 169—171.5°C.;
 1-[4-bromo- β -(4'-chlorophenylthio)phenethyl]imidazole;
 65 1-[4-bromo- β -(2',4'-dichlorophenylthio)phenethyl]imidazole;

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- 1-[2,4-dibromo- β -(4'-chlorophenylthio)phenethyl]imidazole;
1-[2,4-dibromo- β -(2',4'-dichlorophenylthio)phenethyl]imidazole;
1-[4-fluoro- β -(4'-chlorophenylthio)phenethyl]imidazole;
1-[4-fluoro- β -(2',4'-dichlorophenylthio)phenethyl]imidazole;
5 1-[2,4-difluoro- β -(4'-chlorophenylthio)phenethyl]imidazole;
1-[2,4-difluoro- β -(2',4'-dichlorophenylthio)phenethyl]imidazole;
1-[2-trifluoromethyl- β -(4'-chlorophenylthio)phenethyl]imidazole;
1-[2-trifluoromethyl- β -(2',4'-dichlorophenylthio)phenethyl]imidazole;
1-[4-trifluoromethyl- β -(4'-chlorophenylthio)phenethyl]imidazole;
10 1-[4-trifluoromethyl- β -(2',4'-dichlorophenylthio)phenethyl]imidazole;
1-[4-cyano- β -(4'-chlorophenylthio)phenethyl]imidazole;
1-[4-cyano- β -(2',4'-dichlorophenylthio)phenethyl]imidazole;
1-[4-nitro- β -(4'-chlorophenylthio)phenethyl]imidazole; and
1-[4-nitro- β -(2',4'-dichlorophenylthio)phenethyl]imidazole.

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EXAMPLE 2

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(A) A solution of 1 g. of 1-(2,4,6-trichlorophenethyl)imidazole in 10 ml. of tetrahydrofuran is added to a mixture of 1 g. of 2,4-dichlorobenzylmercaptan and 220 mg. of 56% sodium hydride dispersion in 40 ml. of tetrahydrofuran. After stirring for 12 hours at room temperature, the solvent is evaporated under vacuum and 10 ml. of water is added to the residue. The resultant aqueous mixture is extracted with ether and the ether extract washed with 50 ml. of a saturated sodium chloride solution. The organic phase is dried over magnesium sulfate and evaporated to yield 1-[2,4-dichloro- β -(2',4'-dichlorobenzylthio)phenethyl]imidazole.

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The nitrate salt of the free base is prepared by the dropwise addition of nitric acid to the free base in ether until precipitation is complete. The product is collected by filtration and recrystallized from ethyl acetate to yield 1-[2,4-dichloro- β -(2',4'-dichlorobenzylthio)phenethyl]imidazole nitrate, decomp. 133.5—134.5°C.

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(B) Similarly, substituting other starting materials of Formula II, i.e., those recited in paragraph B of Example 1, is productive of the following 1-[β -(2',4'-dichlorobenzylthio)phenethyl]imidazoles which, where indicated, are further characterized as the acid addition salts by treatment in the conventional manner with the appropriate acid:

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- 1-[β -(2',4'-dichlorobenzylthio)phenethyl]imidazole;
1-[4-ethyl- β -(2',4'-dichlorobenzylthio)phenethyl]imidazole;
35 1-[4-*t*-butyl- β -(2',4'-dichlorobenzylthio)phenethyl]imidazole;
1-[4-ethoxy- β -(2',4'-dichlorobenzylthio)phenethyl]imidazole;
1-[4-*n*-butoxy- β -(2',4'-dichlorobenzylthio)phenethyl]imidazole;
1-[4-*t*-butoxy- β -(2',4'-dichlorobenzylthio)phenethyl]imidazole;
1-[4-chloro- β -(2',4'-dichlorobenzylthio)phenethyl]imidazole;
40 1-[3,4-dichloro- β -(2',4'-dichlorobenzylthio)phenethyl]imidazole, nitrate salt, decomp. 107—110°C.;
1-[4-bromo- β -(2',4'-dichlorobenzylthio)phenethyl]imidazole;
1-[2,4-dibromo- β -(2',4'-dichlorobenzylthio)phenethyl]imidazole;
1-[4-fluoro- β -(2',4'-dichlorobenzylthio)phenethyl]imidazole;
45 1-[2,4-difluoro- β -(2',4'-dichlorobenzylthio)phenethyl]imidazole;
1-[2-trifluoromethyl- β -(2',4'-dichlorobenzylthio)phenethyl]imidazole;
1-[4-trifluoromethyl- β -(2',4'-dichlorobenzylthio)phenethyl]imidazole;
1-[4-cyano- β -(2',4'-dichlorobenzylthio)phenethyl]imidazole;
1-[4-nitro- β -(2',4'-dichlorobenzylthio)phenethyl]imidazole; and
50 1-[2-thiocyanato- β -(2',4'-dichlorobenzylthio)phenethyl]imidazole.

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(C) In like manner, substituting other starting materials of Formula III for 2,4-dichlorobenzylmercaptan, for example, 4-chlorobenzylmercaptan, 3,4-dichlorobenzylmercaptan or heptylmercaptan and using the starting materials of Formula II recited in paragraph B of Example 1 is productive of the following 1-[β -(R-thio)phenethyl]imidazoles which, where indicated, are further characterized as the acid addition salts by treatment in the conventional manner with the appropriate acid:

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- 1-[β -(4'-chlorobenzylthio)phenethyl]imidazole;
1-[β -(3',4'-dichlorobenzylthio)phenethyl]imidazole;
1-[β -(*n*-heptylthio)phenethyl]imidazole;
60 1-[4-ethyl- β -(4'-chlorobenzylthio)phenethyl]imidazole;
1-[4-ethyl- β -(3',4'-dichlorobenzylthio)phenethyl]imidazole;
1-[4-ethyl- β -(*n*-heptylthio)phenethyl]imidazole;
1-[4-*i*-butyl- β -(4'-chlorobenzylthio)phenethyl]imidazole, oxalate salt, decomp. 156—158.5°C.;

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60

- 1-[4-t-butyl- β -(3',4'-dichlorobenzylthio)phenethyl]imidazole;
 1-[4-t-butyl- β -(n-heptylthio)phenethyl]imidazole;
 1-[4-ethoxy- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-ethoxy- β -(3',4'-dichlorobenzylthio)phenethyl]imidazole;
 1-[4-ethoxy- β -(n-heptylthio)phenethyl]imidazole;
 1-[4-n-butoxy- β -(4'-chlorobenzylthio)phenethyl]imidazole, nitrate salt, decomp. 113—114°C.;
 1-[4-n-butoxy- β -(3',4'-dichlorobenzylthio)phenethyl]imidazole;
 1-[4-n-butoxy- β -(n-heptylthio)phenethyl]imidazole, oxalate salt, decomp. 124.5—130°C.;
 1-[4-t-butoxy- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-t-butoxy- β -(3',4'-dichlorobenzylthio)phenethyl]imidazole;
 1-[4-t-butoxy- β -(n-heptylthio)phenethyl]imidazole;
 1-[4-chloro- β -(4'-chlorobenzylthio)phenethyl]imidazole, oxalate salt, decomp. 148—149.5°C., nitrate salt, m.p. 103.5—105.5°C.;
 1-[4-chloro- β -(3',4'-dichlorobenzylthio)phenethyl]imidazole;
 1-[4-chloro- β -(n-heptylthio)phenethyl]imidazole;
 1-[2,4-dichloro- β -(4'-chlorobenzylthio)phenethyl]imidazole, nitrate salt, M.P. 130.5—132°C.;
 1-[2,4-dichloro- β -(3',4'-dichlorobenzylthio)phenethyl]imidazole, nitrate salt, decomp. 95—96.5°C.;
 1-[2,4-dichloro- β -(n-heptylthio)phenethyl]imidazole, oxalate salt, M.P. 106—109°C.;
 1-[3,4-dichloro- β -(4'-chlorobenzylthio)phenethyl]imidazole, oxalate salt, decomp. 174—175°C.;
 1-[3,4-dichloro- β -(3',4'-dichlorobenzylthio)phenethyl]imidazole, oxalate salt, decomp. 176—177.5°C.;
 1-[3,4-dichloro- β -(n-heptylthio)phenethyl]imidazole;
 1-[4-bromo- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-bromo- β -(3',4'-dichlorobenzylthio)phenethyl]imidazole;
 1-[4-bromo- β -(n-heptylthio)phenethyl]imidazole;
 1-[2,4-dibromo- β -(4'-chlorobenzylthio)phenethyl]imidazole, nitrate salt, decomp. 126.5—128°C.;
 1-[2,4-dibromo- β -(3',4'-dichlorobenzylthio)phenethyl]imidazole;
 1-[2,4-dibromo- β -(n-heptylthio)phenethyl]imidazole;
 1-[4-fluoro- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-fluoro- β -(3',4'-dichlorobenzylthio)phenethyl]imidazole;
 1-[4-fluoro- β -(n-heptylthio)phenethyl]imidazole;
 1-[2,4-difluoro- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[2,4-difluoro- β -(3',4'-dichlorobenzylthio)phenethyl]imidazole, oxalate salt, decomp. 89.5—93.5°C.;
 1-[2,4-difluoro- β -(n-heptylthio)phenethyl]imidazole;
 1-[2-trifluoromethyl- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[2-trifluoromethyl- β -(3',4'-dichlorobenzylthio)phenethyl]imidazole, nitrate salt, decomp. 134.5—137°C.;
 1-[2-trifluoromethyl- β -(n-heptylthio)phenethyl]imidazole;
 1-[4-trifluoromethyl- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-trifluoromethyl- β -(3',4'-dichlorobenzylthio)phenethyl]imidazole;
 1-[4-trifluoromethyl- β -(n-heptylthio)phenethyl]imidazole;
 1-[4-cyano- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-cyano- β -(3',4'-dichlorobenzylthio)phenethyl]imidazole;
 1-[4-cyano- β -(n-heptylthio)phenethyl]imidazole;
 1-[4-nitro- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-nitro- β -(3',4'-dichlorobenzylthio)phenethyl]imidazole;
 1-[4-nitro- β -(n-heptylthio)phenethyl]imidazole;
 1-[2-thiocyanato- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[2-thiocyano- β -(3',4'-dichlorobenzylthio)phenethyl]imidazole; and
 1-[2-thiocyanato- β -(n-heptylthio)phenethyl]imidazole.

EXAMPLE 3

Repeating the procedure recited in paragraph A of Example 1 using 1-(2,4,6-trichlorophenethyl)imidazole and 1-(3,4,6-trichlorophenethyl)imidazole as starting materials of Formula II and using 4-trifluoromethylthiophenol, 4-chloro-3-trifluoromethylthiophenol, 3,4,5-trichlorothiophenol and pentachlorothiophenol as starting materials of Formula III is productive of the following 1-[β (R-thio)phenethyl]imi-

dazoles which, where indicated, are further characterized as the acid addition salts by treatment in the conventional manner with the appropriate acid:

- 1-[2,4-dichloro- β -(4'-trifluoromethylphenylthio)phenethyl]imidazole, oxalate salt, decomp. 178—178.5°C.;
- 5 1 - [2,4 - dichloro - β - (4' - chloro - 3' - trifluoromethylphenylthio)phenethyl]-imidazole, oxalate salt, decomp. 186—187.5°C.;
- 1-[2,4-dichloro- β -(3',4',5'-trichlorophenylthio)phenethyl]imidazole, nitrate salt, decomp. 178—185.5°C.;
- 10 1-[2,4-dichloro- β -(pentachlorophenylthio)phenethyl]imidazole, nitrate salt, decomp. 201—202.5°C.;
- 1-[3,4-dichloro- β -(4'-trifluoromethylphenylthio)phenethyl]imidazole, oxalate salt, decomp. 170—171°C.;
- 1 - [3,4 - dichloro - β - (4' - chloro - 3' - trifluoromethylphenylthio)phenethyl] - imidazole, oxalate salt, decomp. 165—166°C.;
- 15 1-[3,4-dichloro- β -(3',4',5'-trichlorophenylthio)phenethyl]imidazole; and
- 1-[3,4-dichloro- β -(pentachlorophenylthio)phenethyl]imidazole.

EXAMPLE 4

Repeating the procedure recited in paragraph A of Example 2 but substituting other starting materials of Formula III for 2,4-dichlorobenzyl mercaptan, for example

- 20 ethyl mercaptan,
- 20 pentyl mercaptan,
- 20 octyl mercaptan,
- 20 nonyl mercaptan,
- 25 dodecyl mercaptan,
- 25 octadecyl mercaptan,
- 25 3-phenylpropyl mercaptan,
- 25 3-cyclopentylpropyl mercaptan,
- 30 cyclohexyl mercaptan,
- 30 cyclohexylmethyl mercaptan,
- 30 2-cyclohexylethyl mercaptan,
- 30 cycloheptylmethyl mercaptan,
- 30 allyl mercaptan,
- 30 2-octenyl mercaptan,
- 35 3-phenyl-2-propenyl mercaptan,
- 35 3-(4-chlorophenyl)-2-propenyl mercaptan,
- 35 2-hexynyl mercaptan,
- 35 2-octynyl mercaptan,
- 40 benzyl mercaptan,
- 40 4-methylbenzyl mercaptan,
- 40 4-*t*-butylbenzyl mercaptan,
- 40 4-trifluoromethylbenzyl mercaptan,
- 40 4-methoxybenzyl mercaptan,
- 45 3,4,5-trimethoxybenzyl mercaptan,
- 45 4-*n*-butoxybenzyl mercaptan,
- 45 2,4,5-trichlorobenzyl mercaptan,
- 45 4-bromobenzyl mercaptan,
- 45 4-fluorobenzyl mercaptan,
- 45 4-nitrobenzyl mercaptan, and
- 45 4-cyanobenzyl mercaptan,
- 50 is productive of the following 1-[2,4-dichloro- β -(R-thio)phenethyl]imidazoles which, where indicated, are further characterized as the acid addition salts by treatment in the conventional manner with the appropriate acid:
- 1-[2,4-dichloro- β -(ethylthio)phenethyl]imidazole;
- 55 1-[2,4-dichloro- β -(*n*-pentylthio)phenethyl]imidazole, oxalate salt, coalesces 99°C.;
- 55 1-[2,4-dichloro- β -(*n*-octylthio)phenethyl]imidazole, oxalate salt, M.P. 101.5—103.5°C.;
- 1-[2,4-dichloro- β -(*n*-nonylthio)phenethyl]imidazole, oxalate salt, gels 82.5°C.;
- 1-[2,4-dichloro- β -(*n*-dodecylthio)phenethyl]imidazole, oxalate salt, M.P. 124.5°C.
- 60 1-[2,4-dichloro- β -(octadecylthio)phenethyl]imidazole, oxalate salt, gels 91.5—150°C.;
- 1-[2,4-dichloro- β -(3-phenylpropylthio)phenethyl]imidazole, oxalate salt, M.P. 87.5—90°C.;
- 1-[2,4-dichloro- β -(3-cyclopentylpropylthio)phenethyl]imidazole;

- 1-[2,4-dichloro- β -(cyclohexylthio)phenethyl]imidazole nitrate salt, M.P. 114.5—117.5°C.;
- 1-[2,4-dichloro- β -(cyclohexylmethylthio)phenethyl]imidazole, oxalate salt, decomp. 122.5—140°C.;
- 5 1-[2,4-dichloro- β -(2-cyclohexylethylthio)phenethyl]imidazole, oxalate salt, decomp. 104—108.5°C.;
- 1-[2,4-dichloro- β -(cycloheptylmethylthio)phenethyl]imidazole;
- 1-[2,4-dichloro- β -(allylthio)phenethyl]imidazole oxalate salt, M.P. 84.5—123°C.;
- 10 1-[2,4-dichloro- β -(2-octenylthio)phenethyl]imidazole, oxalate salt, M.P. 112.5—116.5°C.;
- 1-[2,4-dichloro- β -(3-phenyl-2-propenylthio)phenethyl]imidazole, oxalate salt, decomp. 151—160.5°C.;
- 15 1-[2,4-dichloro- β -(3-(4'-chlorophenyl)-2-propenylthio)phenethyl]imidazole, nitrate salt, decomp. 123—126°C.;
- 1-[2,4-dichloro- β -(3-hexynylthio)phenethyl]imidazole, oxalate salt, M.P. 90.5—95°C.;
- 1-[2,4-dichloro- β -(2-octynylthio)phenethyl]imidazole, oxalate salt, decomp. 118—119.5°C.;
- 20 1-[2,4-dichloro- β -(benzylthio)phenethyl]imidazole; nitrate salt, m.p. 110—112°C.;
- 1-[2,4-dichloro- β -(4'-methylbenzylthio)phenethyl]imidazole, nitrate salt, M.P. 110.5—112°C.;
- 25 1-[2,4-dichloro- β -(4'-t-butylbenzylthio)phenethyl]imidazole, nitrate salt, decomp. 162.5—163°C.;
- 1-[2,4-dichloro- β -(4'-trifluoromethylbenzylthio)phenethyl]imidazole, nitrate salt, decomp. 112—114°C.;
- 1-[2,4-dichloro- β -(4'-methoxybenzylthio)phenethyl]imidazole, nitrate salt, decomp. 118—119.5°C.;
- 30 1-[2,4-dichloro- β -(3',4',5'-trimethoxybenzylthio)phenethyl]imidazole, oxalate salt, gels 147°C.;
- 1-[2,4-dichloro- β -(4'-n-butoxybenzylthio)phenethyl]imidazole;
- 1-[2,4-dichloro- β -(2',4',5'-trichlorobenzylthio)phenethyl]imidazole, nitrate salt, decomp. 172.5—173.5°C.;
- 35 1-[2,4-dichloro- β -(4'-bromobenzylthio)phenethyl]imidazole, nitrate salt, decomp. 137—138°C.;
- 1-[2,4-dichloro- β -(4'-fluorobenzylthio)phenethyl]imidazole, nitrate salt, decomp. 104.5—107.5°C.;
- 1-[2,4-dichloro- β -(4'-nitrobenzylthio)phenethyl]imidazole, nitrate salt, decomp. 129.5—132°C.;
- 40 1-[2,4-dichloro- β -(4'-cyanobenzylthio)phenethyl]imidazole, nitrate salt, decomp. 119.5—123°C.;

EXAMPLE 5

- Repeating the procedure recited in paragraph A of Example 1 using 1-(4, β -dichlorophenylethyl)imidazole and 1-[2,4, β -trichlorophenethyl]imidazole as starting materials of Formula II and using other starting materials of Formula III for 3,4-dichlorothiophenol for example,
- thiophenol,
- β -thionaphthol,
- 4-methylthiophenol,
- 4-methoxythiophenol;
- 3-methoxythiophenol,
- 2-chlorothiophenol,
- 3-chlorothiophenol,
- 2,5-dichlorothiophenol,
- 4-bromothiophenol,
- 4-fluorothiophenol,
- 4-nitrothiophenol,
- 4-aminothiophenol,
- 4-acetamidothiophenol, and
- 4-cyanothiophenol,
- is productive of the following 1-[4-chloro- β -(R-thio)phenethyl]imidazoles and 1-[2,4-dichloro- β -(R-thio)phenethyl]imidazoles which, where indicated, are further characterized as the acid addition salts by treatment in the conventional manner with the appropriate acid:

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13	1,485,719	13
	1-[4-chloro- β -(phenylthio)phenethyl]imidazole, oxalate salt, decomp. 166—167°C.;	
	1-[4-chloro- β -(2-naphthylthio)phenethyl]imidazole, oxalate salt, M.P. 193.5—194°C.;	
5	1-[4-chloro- β -(4'-methylphenylthio)phenethyl]imidazole, oxalate salt, decomp. 199.5—200°C.;	5
	1-[4-chloro- β -(4'-methoxyphenylthio)phenethyl]imidazole, oxalate salt, decomp. 177—178°C.;	
10	1-[4-chloro- β -(3'-methoxyphenylthio)phenethyl]imidazole, oxalate salt, M.P. 164.5—165.5°C.;	10
	1-[4-chloro- β -(2'-chlorophenylthio)phenethyl]imidazole, oxalate salt, M.P. 177—178°C.;	
	1-[4-chloro- β -(3'-chlorophenylthio)phenethyl]imidazole, oxalate salt, M.P. 169.5—171.5°C.;	
15	1-[4-chloro- β -(2',5'-dichlorophenylthio)phenethyl]imidazole, oxalate salt, M.P. 181.5—183.5°C.;	15
	1-[4-chloro- β -(4'-bromophenylthio)phenethyl]imidazole, oxalate salt, decomp. 185—186.5°C.;	
20	1-[4-chloro- β -(4'-fluorophenylthio)phenethyl]imidazole, oxalate salt, M.P. 182.5—183°C.;	20
	1-[4-chloro- β -(4'-nitrophenylthio)phenethyl]imidazole, oxalate salt, M.P. 203—204.5°C.;	
	1-[4-chloro- β -(4'-aminophenylthio)phenethyl]imidazole;	
25	1-[4-chloro- β -(4'-acetamidophenylthio)phenethyl]imidazole, oxalate salt, M.P. 149.5—152°C.;	25
	1-[4-chloro- β -(4'-cyanophenylthio)phenethyl]imidazole;	
	1-[2,4-dichloro- β -(phenylthio)phenethyl]imidazole;	
	1-[2,4-dichloro- β -(2-naphthylthio)phenethyl]imidazole;	
30	1-[2,4-dichloro- β -(4'-methylphenylthio)phenethyl]imidazole;	30
	1-[2,4-dichloro- β -(4'-methoxyphenylthio)phenethyl]imidazole;	
	1-[2,4-dichloro- β -(3'-methoxyphenylthio)phenethyl]imidazole;	
	1-[2,4-dichloro- β -(2'-chlorophenylthio)phenethyl]imidazole;	
	1-[2,4-dichloro- β -(3'-chlorophenylthio)phenethyl]imidazole;	
35	1-[2,4-dichloro- β -(2',5'-dichlorophenylthio)phenethyl]imidazole;	35
	1-[2,4-dichloro- β -(4'-bromophenylthio)phenethyl]imidazole;	
	1-[2,4-dichloro- β -(4'-fluorophenylthio)phenethyl]imidazole;	
	1-[2,4-dichloro- β -(4'-nitrophenylthio)phenethyl]imidazole;	
	1-[2,4-dichloro- β -(4'-aminophenylthio)phenethyl]imidazole;	
40	1-[2,4-dichloro- β -(4'-acetamidophenylthio)phenethyl]imidazole; and	40
	1-[2,4-dichloro- β -(4'-cyanophenylthio)phenethyl]imidazole.	

EXAMPLE 6

To a solution of 400 mg. of 1-[4-chloro- β -(4'-aminophenylthio)phenethyl]-imidazole oxalate in 20 ml. of tetrahydrofuran containing 1 ml. of triethylamine is added 0.5 ml. of hexanoyl chloride. After stirring for 30 minutes at room temperature, the solvent is evaporated under vacuum and aqueous potassium carbonate is added to the residue. The resultant aqueous mixture is extracted with dichloromethane and the organic phase is acidified with oxalic acid. The product which precipitates is filtered off and recrystallized from a mixture of acetone and ethyl acetate to yield 1-[4-chloro- β -(4'-hexanoylamino)phenethyl]imidazole oxalate, M.P. 98.5—102°C.

Similarly, substituting other acid chlorides for hexanoyl chloride, for example propionyl chloride, n-valeryl chloride, decanoyl chloride and the like is productive of the corresponding.

- 1-[4-chloro- β -(4'-propionylaminophenylthio)phenethyl]imidazole oxalate;
- 1-[4-chloro- β -(4'-valerylaminophenylthio)phenethyl]imidazole oxalate;
- 1-[4-chloro- β -(4'-decanoylamino)phenethyl]imidazole oxalate, and so forth.

EXAMPLE 7

1-[4-chloro- β -(4'-chlorophenylthio)phenethyl]imidazole nitrate (1 g.) is treated with aqueous potassium carbonate until a pH of approximately 11 is obtained, whereupon the free base, i.e., 1-[4-chloro- β -(4'-chlorophenylthio)phenethyl]imidazole, which separates is extracted with dichloromethane. The extract is dried with magnesium sulfate and evaporated. To the resulting residue, in 50 ml. of chloroform at 0°C. is slowly added with stirring, a solution of 700 mg. of 85% m-chloroperbenzoic acid in 50 ml. of chloroform. When the addition is complete, stirring at 0°C. is continued for

approximately 3 hours. Thereafter, the reaction mixture is washed with aqueous potassium carbonate and aqueous sodium chloride, dried over magnesium sulfate and evaporated. The residue is crystallized from benzene to yield 1-[4-chloro- β -(4'-chlorophenylsulfinyl)phenethyl]imidazole, M.P. 139—140°C., which is further characterized as the oxalate salt, M.P. 167—167.5°C.

Similarly, repeating the above procedure on the 1-[β -(R-thio)phenethyl]imidazole salts obtained in Examples 1 thru 6 is productive of the corresponding 1-[β -(R-sulfinyl)phenethyl]imidazoles which can be further characterized by conversion in the usual manner to the indicated acid addition salts, e.g.,

1-[2,4-dichloro- β -(n-dodecylsulfinyl)phenethyl]imidazole, oxalate salt, decomp. 134—138°C.;

1-[4-chloro- β -(4'-chlorobenzylsulfinyl)phenethyl]imidazole, nitrate salt, decomp. 161.5—162°C.; and so forth.

EXAMPLE 8

1-[4-(chloro- β -(4'-chlorophenylthio)phenethyl]imidazole nitrate (1 g.) is treated with aqueous potassium carbonate until a pH of approximately 11 is obtained whereupon the free base, i.e. 1-[4-chloro- β -(4'-chlorophenylthio)phenethyl]imidazole, which separates is extracted with dichloromethane. The extract is dried with magnesium sulfate and evaporated. To the resulting residue in 50 ml. of chloroform at room temperature is slowly added with stirring a solution of 1.7 g. of 85% m-chloroperbenzoic acid in 50 ml. of chloroform. When the addition is complete, stirring at room temperature is continued for approximately 24 hours. Thereafter, the reaction mixture is washed with aqueous potassium carbonate and aqueous sodium chloride, dried over magnesium sulfate and evaporated. The residue is crystallized from benzene to yield 1-[4-chloro- β -(4'-chlorophenylsulfonyl)phenethyl]imidazole, M.P. 176—178.5°C.

Similarly, repeating the above procedure on the 1-[β -(R-thio)phenethyl]imidazoles or acid addition salts obtained in Examples 1 thru 6 is productive of the corresponding 1-[β -(R-sulfonyl)phenethyl]imidazoles which can be further characterized by conversion in the usual manner to the indicated acid addition salts, e.g.,

1-[2,4-dichloro- β -(dodecylsulfonyl)phenethyl]imidazole, oxalate salt, decomp. 105.5—110°C.;

1-[4-chloro- β -(4'-chlorobenzylsulfonyl)phenethyl]imidazole, nitrate salt, decomp. 181°C.; and so forth.

EXAMPLE 9

A solution of 85% m-chloroperbenzoic acid in chloroform (2 g/100 ml.) is added dropwise, over a period of one hour, to a stirred solution of 2.53 g. of 1-[β -chloro-4-methylthiophenethyl]imidazole in 150 ml. of chloroform at 0°C. After 6 hours, the resultant solution is washed with aqueous potassium carbonate and with water. The organic phase is separated and dried over magnesium sulfate. Evaporation of the solvent yields 1-[β -chloro-4-methylsulfinylphenethyl]imidazole.

Similarly, replacing 1-[β -chloro-4-methylthiophenethyl]imidazole with other 1-[β -chloro-thiophenethyl]imidazoles, for example,

1-[β -chloro-4-t-butylthiophenethyl]imidazole;

1-[β -chloro-4-benzylthiophenethyl]imidazole;

1-[β -chloro-4-(4'-chlorobenzylthio)phenethyl]imidazole;

1-[β -chloro-4-(4'-methoxybenzylthio)phenethyl]imidazole;

1-[β -chloro-4-phenylthiophenethyl]imidazole, and

1-[β -chloro-4-(4'-chlorophenylthio)phenethyl]imidazole, is productive of:

1-[β -chloro-4-t-butylsulfinylphenethyl]imidazole;

1-[β -chloro-4-benzylsulfinylphenethyl]imidazole;

1-[β -chloro-4-(4'-chlorobenzylsulfinyl)phenethyl]imidazole;

1-[β -chloro-4-(4'-methoxybenzylsulfinyl)phenethyl]imidazole;

1-[β -chloro-4-phenylsulfinylphenethyl]imidazole, and

1-[β -chloro-4-(4'-chlorophenylsulfinyl)phenethyl]imidazole.

EXAMPLE 10

Repeating the procedure recited in paragraph A of Example 1 using 3,4-dichlorothiophenol as the starting material of Formula III and using other starting materials of Formula II for 1-(2,4,6-trichlorophenethyl)imidazole, for example,

1-(β -chloro-4-methylthiophenethyl)imidazole;

1-(β -chloro-4-t-butylthiophenethyl)imidazole;

1-(β -chloro-4-benzylthiophenethyl)imidazole;

1-[β -chloro-4-(4'-chlorobenzylthio)phenethyl]imidazole;

- 1-[β -chloro-4-(4'-methoxybenzylthio)phenethyl]imidazole;
 1-(β -chloro-4-phenylthiophenethyl)imidazole;
 1-[β -chloro-4-(4'-chlorophenylthio)phenethyl]imidazole;
 1-(β -chloro-4-methylsulfinylphenethyl)imidazole;
 5 1-(β -chloro-4-t-butylsulfinylphenethyl)imidazole;
 1-(β -chloro-4-benzylsulfinylphenethyl)imidazole;
 1-[β -chloro-4-(4'-chlorobenzylsulfinyl)phenethyl]imidazole;
 1-[β -chloro-4-(4'-methoxybenzylsulfinyl)phenethyl]imidazole;
 1-(β -chloro-4-phenylsulfinylphenethyl)imidazole;
 10 1-[β -chloro-4-(4'-chlorophenylsulfinyl)phenethyl]imidazole;
 1-(β -chloro-4-methylsulfonylphenethyl)imidazole;
 1-(β -chloro-4-t-butylsulfonylphenethyl)imidazole;
 1-(β -chloro-4-benzylsulfonylphenethyl)imidazole;
 1-[β -chloro-4-(4'-chlorobenzylsulfonyl)phenethyl]imidazole;
 15 1-[β -chloro-4-(4'-methoxybenzylsulfonyl)phenethyl]imidazole;
 1-(β -chloro-4-phenylsulfonylphenethyl)imidazole, and
 1-[β -chloro-4-(4'-chlorophenylsulfonyl)phenethyl]imidazole;
 is productive of the following 1-[β -(3',4'-dichlorophenylthio)phenethyl]imidazoles:
 1-[4-methylthio- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 20 1-[4-t-butylthio- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-benzylthio- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-(4-chlorobenzylthio)- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-(4-methoxybenzylthio)- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 25 1-[4-phenylthio- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-(4-chlorophenylthio)- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-methylsulfinyl- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-t-butylsulfinyl- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-benzylsulfinyl- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 30 1-[4-(4-chlorobenzylsulfinyl)- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-(4-methoxybenzylsulfinyl)- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-phenylsulfinyl- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-(4-chlorophenylsulfinyl)- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-methylsulfonyl- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 35 1-[4-t-butylsulfonyl- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-benzylsulfonyl- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-(4-chlorobenzylsulfonyl)- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-(4-methoxybenzylsulfonyl)- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;
 1-[4-phenylsulfonyl- β -(3',4'-dichlorophenylthio)phenethyl]imidazole; and
 1-[4-(4-chlorophenylsulfonyl)- β -(3',4'-dichlorophenylthio)phenethyl]imidazole.

EXAMPLE 11

- Repeating the procedure recited in paragraph A of Example 2 using 4-chlorobenzyl mercaptan as the starting material of Formula III and using other starting materials of Formula II for 1-(2,4,6-trichlorophenethyl)imidazole, i.e., those starting materials of Formula II recited in Example 10, is productive of the following 1-[β -(4'-chlorobenzylthio)phenethyl]imidazoles:
 1-[4-methylthio- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-t-butylthio- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-benzylthio- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-(4-chlorobenzylthio)- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 50 1-[4-(4-methoxybenzylthio)- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-phenylthio- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-(4-chlorophenylthio)- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-methylsulfinyl- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-t-butylsulfinyl- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 55 1-[4-benzylsulfinyl- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-(4-chlorobenzylsulfinyl)- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-(4-methoxybenzylsulfinyl)- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-phenylsulfinyl- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-(4-chlorophenylsulfinyl)- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 60 1-[4-methylsulfonyl- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-t-butylsulfonyl- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-benzylsulfonyl- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-(4-chlorobenzylsulfonyl)- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[4-(4-methoxybenzylsulfonyl)- β -(4'-chlorobenzylthio)phenethyl]imidazole;

1-[4-phenylsulfonyl- β -(4'-chlorobenzylthio)phenethyl]imidazole; and
 1-[4-(4-chlorophenylsulfonyl)- β -(4'-chlorobenzylthio)phenethyl]imidazole.

EXAMPLE 12

Repeating the procedure recited in Example 7 (using the appropriate quantity of m-chloroperbenzoic acid) on the products obtained in Examples 10 and 11 is productive of the following 1-[β -R-sulfinyl]phenethyl]imidazoles;

1-[4-phenylthio- β -(3',4'-dichlorophenylsulfinyl)phenethyl]imidazole;
 1-[4-(4-chlorophenylthio)- β -(3',4'-dichlorophenylsulfinyl)phenethyl]imidazole;
 1-[4-methylsulfinyl- β -(3',4'-dichlorophenylsulfinyl)phenethyl]imidazole;
 1-[4-t-butylsulfinyl- β -(3',4'-dichlorophenylsulfinyl)phenethyl]imidazole;
 1-[4-benzylsulfinyl- β -(3',4'-dichlorophenylsulfinyl)phenethyl]imidazole;
 1-[4-(4-chlorobenzylsulfinyl)- β -(3',4'-dichlorophenylsulfinyl)phenethyl]imidazole;
 1-[4-(4-methoxybenzylsulfinyl)- β -(3',4'-dichlorophenylsulfinyl)phenethyl]imidazole;
 1-[4-phenylsulfinyl- β -(3',4'-dichlorophenylsulfinyl)phenethyl]imidazole;
 1-[4-(4-chlorophenylsulfonyl)- β -(3',4'-dichlorophenylsulfinyl)phenethyl]imidazole;
 1-[4-methylsulfonyl- β -(3',4'-dichlorophenylsulfinyl)phenethyl]imidazole;
 1-[4-t-butylsulfonyl- β -(3',4'-dichlorophenylsulfinyl)phenethyl]imidazole;
 1-[4-benzylsulfonyl- β -(3',4'-dichlorophenylsulfinyl)phenethyl]imidazole;
 1-[4-(4-chlorobenzylsulfonyl)- β -(3',4'-dichlorophenylsulfinyl)phenethyl]imidazole;
 1-[4-(4-methoxybenzylsulfonyl)- β -(3',4'-dichlorophenylsulfinyl)phenethyl]imidazole;
 1-[4-phenylsulfonyl- β -(3',4'-dichlorophenylsulfinyl)phenethyl]imidazole;
 1-[4-(4-chlorophenylsulfonyl)- β -(3',4'-dichlorophenylsulfinyl)phenethyl]imidazole;
 1-[4-phenylthio- β -(4'-chlorobenzylsulfinyl)phenethyl]imidazole;
 1-[4-(4-chlorophenylthio)- β -(4'-chlorobenzylsulfinyl)phenethyl]imidazole;
 1-[4-methylsulfinyl- β -(4'-chlorobenzylsulfinyl)phenethyl]imidazole;
 1-[4-t-butylsulfinyl- β -(4'-chlorobenzylsulfinyl)phenethyl]imidazole;
 1-[4-benzylsulfinyl- β -(4'-chlorobenzylsulfinyl)phenethyl]imidazole;
 1-[4-(4-chlorobenzylsulfinyl)- β -(4'-chlorobenzylsulfinyl)phenethyl]imidazole;
 1-[4-(4-methoxybenzylsulfinyl)- β -(4'-chlorobenzylsulfinyl)phenethyl]imidazole;
 1-[4-phenylsulfinyl- β -(4'-chlorobenzylsulfinyl)phenethyl]imidazole;
 1-[4-(4-chlorophenylsulfonyl)- β -(4'-chlorobenzylsulfinyl)phenethyl]imidazole;
 1-[4-methylsulfonyl- β -(4'-chlorobenzylsulfinyl)phenethyl]imidazole;
 1-[4-t-butylsulfonyl- β -(4'-chlorobenzylsulfinyl)phenethyl]imidazole;
 1-[4-benzylsulfonyl- β -(4'-chlorobenzylsulfinyl)phenethyl]imidazole;
 1-[4-(4-chlorobenzylsulfonyl)- β -(4'-chlorobenzylsulfinyl)phenethyl]imidazole; and
 1-[4-(4-methoxybenzylsulfonyl)- β -(4'-chlorobenzylsulfinyl)phenethyl]imidazole.

EXAMPLE 13

Repeating the procedure recited in Example 8 on the products obtained in Examples 10 and 11 is productive of the following 1-[β -(R-sulfonyl)phenethyl]imidazoles:

1-[4-phenylthio- β -(3',4'-dichlorophenylsulfonyl)phenethyl]imidazole;
 1-[4-(4-chlorophenylthio)- β -(3',4'-dichlorophenylsulfonyl)phenethyl]imidazole;
 1-[4-phenylsulfonyl- β -(3',4'-dichlorophenylsulfonyl)phenethyl]imidazole;
 1-[4-(4-chlorophenylsulfonyl)- β -(3',4'-dichlorophenylsulfonyl)phenethyl]imidazole;
 1-[4-methylsulfonyl- β -(3',4'-dichlorophenylsulfonyl)phenethyl]imidazole;
 1-[4-t-butylsulfonyl- β -(3',4'-dichlorophenylsulfonyl)phenethyl]imidazole;
 1-[4-benzylsulfonyl- β -(3',4'-dichlorophenylsulfonyl)phenethyl]imidazole;
 1-[4-(4-chlorobenzylsulfonyl)- β -(3',4'-dichlorophenylsulfonyl)phenethyl]imidazole;
 1-[4-(4-methoxybenzylsulfonyl)- β -(3',4'-dichlorophenylsulfonyl)phenethyl]imidazole;
 1-[4-phenylsulfonyl- β -(3',4'-dichlorophenylsulfonyl)phenethyl]imidazole;
 1-[4-(4-chlorophenylsulfonyl)- β -(3',4'-dichlorophenylsulfonyl)phenethyl]imidazole;
 1-[4-phenylthio- β -(4'-chlorobenzylsulfonyl)phenethyl]imidazole;
 1-[4-(4-chlorophenylthio)- β -(4'-chlorobenzylsulfonyl)phenethyl]imidazole;
 1-[4-phenylsulfonyl- β -(4'-chlorobenzylsulfonyl)phenethyl]imidazole;
 1-[4-(4-chlorophenylsulfonyl)- β -(4'-chlorobenzylsulfonyl)phenethyl]imidazole;
 1-[4-methylsulfonyl- β -(4'-chlorobenzylsulfonyl)phenethyl]imidazole;
 1-[4-t-butylsulfonyl- β -(4'-chlorobenzylsulfonyl)phenethyl]imidazole;

- 1-[4-benzylsulfonyl- β -(4'-chlorobenzylsulfonyl)phenethyl]imidazole;
 1-[4-(4-chlorobenzylsulfonyl)- β -(4'-chlorobenzylsulfonyl)phenethyl]imidazole;
 1-[4-(4-methoxybenzylsulfonyl)- β -(4'-chlorobenzylsulfonyl)phenethyl]imidazole;
 1-[4-phenylsulfonyl- β -(4'-chlorobenzylsulfonyl)phenethyl]imidazole; and
 1-[4-(4-chlorophenylsulfonyl)- β -(4'-chlorobenzylsulfonyl)phenethyl]imidazole.

EXAMPLE 14

Repeating the procedure recited in Example 1, using reactants as dictated by the particular 1- $[\beta$ -(R-thio)phenethyl]imidazole desired, is productive of the following compounds which, where indicated, are further characterized as the acid addition salts by treatment in the conventional manner with the appropriate acid.

- 1 - [2,4 - dichloro - β - (4' - nitro - 3' - trifluoromethylphenylthio)phenethyl] - imidazole, nitrate salt, decomp. 127.5—130.5°C.;
 1-[4-trifluoromethyl- β -(4'-tert-butylphenylthio)phenethyl]imidazole, oxalate salt, M.P. 161—162°C.;
 1-[2,4-dimethyl- β -(3',4'-dichlorophenylthio)phenethyl]imidazole, nitrate salt, decomp. 165.5—166°C.;
 1-[4-methoxy- β -(3',4'-dichlorophenylthio)phenethyl]imidazole, oxalate salt, M.P. 145.5°C.;
 1-[4-methoxy- β -(4'-tert-butylphenylthio)phenethyl]imidazole, oxalate salt, M.P. 139.5—141.5°C.;
 1-[2,4-dimethoxy- β -(3',4'-dichlorophenylthio)phenethyl]imidazole, nitrate salt, decomp. 155.5—158°C.;
 1-[4-nitro- β -(pentachlorophenylthio)phenethyl]imidazole, nitrate salt, decomp. 163.5—165.5°C.;
 1-[2,4-dichloro- β -(n-butoxyphenylthio)phenethyl]imidazole, oxalate salt, m.p. 143—144°C.;
 1-[4-cyano- β -(pentachlorophenylthio)phenethyl]imidazole, nitrate salt, m.p. 182.5—183.5°C. (foaming);
 1-[4-n-butylthio- β -(4'-chlorophenylthio)phenethyl]imidazole; and
 1-[4-methylthio- β -(3',4'-dichlorophenylthio)phenethyl]imidazole.

EXAMPLE 15

Repeating the procedure recited in Example 2, using reactants as dictated by the particular 1- $[\beta$ -(R-thio)phenethyl]imidazole desired, is productive of the following compounds which, where indicated, are further characterized as the acid addition salts by treatment in the conventional manner with the appropriate acid:

- 1-[2,4-difluoro- β -(n-nonylthio)phenethyl]imidazole, oxalate salt, M.P. 79.5—84°C.;
 1-[2,4-dimethyl- β -(4'-chlorobenzylthio)phenethyl]imidazole, oxalate salt, decomp. 80.5—83°C.;
 1-[4-methoxy- β -(3-phenylpropylthio)phenethyl]imidazole, oxalate salt, M.P. 75—83°C.;
 1-[4-methoxy- β -(n-dodecylthio)phenethyl]imidazole; oxalate salt, m.p. 90—93°C.;
 1-[2,4-dichloro- β -(1'-naphthylmethylthio)phenethyl]imidazole, oxalate salt, coalesces 86°C., foams 86—121.5°C.;
 1-[4-chloro- β -(ethylthio)phenethyl]imidazole, oxalate salt, M.P. 157—158°C.;
 1-[2,4-dichloro- β -(n-undec-10-enylthio)phenethyl]imidazole, oxalate salt, M.P. 82—107°C.;
 1 - [2,4 - dichloro - β - (3 - (4' - methylphenyl)prop - 2 - enylthio) - phenethyl] - imidazole, nitrate salt, m.p. 133.5—137°C.;
 1 - (2,4 - dichloro - β - (3 - (4' - tert - butylphenyl)prop - 2 - enylthio)phenethyl]imidazole, nitrate salt, m.p. 147—153.5°C.;
 1-[2,4-dichloro- β -(4-phenylbut-3-enylthio)phenethyl]imidazole;
 1 - [2,4 - dichloro - β - (3 - (4' - chlorophenyl)propylthio)phenethyl]imidazole, oxalate salt, m.p. 111—113°C.;
 1-[2,4-dichloro- β -(prop-2-ynylthio)phenethyl]imidazole;
 1-[4-methylthio- β -(3',4'-dichlorobenzylthio)phenethyl]imidazole;
 1-[4-n-butylthio- β -(4'-chlorobenzylthio)phenethyl]imidazole;
 1-[2,4-dichloro- β -(n-hexylthio)phenethyl]imidazole;
 1-[2,4-dibromo- β -(n-hexylthio)phenethyl]imidazole;
 1-[2,4-dibromo- β -(n-octylthio)phenethyl]imidazole;
 1-[2,4-difluoro- β -(n-octylthio)phenethyl]imidazole; and
 1-[2,4-difluoro- β -(n-decylthio)phenethyl]imidazole.

EXAMPLE 16

1-[4-chloro- β -(4'-chlorophenylthio)phenethyl]imidazole nitrate (1 g.) in 100 ml. of dichloromethane is shaken with excess dilute potassium carbonate solution until the salt is completely dissolved. The organic layer is then separated, washed with water and dried over magnesium sulfate.

Evaporation of the solvent yields 1-[4-chloro- β -(4'-chlorophenylthio)phenethyl]-imidazole as a gum.

In similar manner, the acid addition salts of all compounds of Formula (I) can be converted to the corresponding compounds in base form, for example,

1-[2,4-dichloro- β -(3',4'-dichlorophenylthio)phenethyl]imidazole;

1-[2,4-dichloro- β -(2',4'-dichlorobenzylthio)phenethyl]imidazole;

1-[2,4-dichloro- β -(n-heptylthio)phenethyl]imidazole;

1-[2,4-dichloro- β -(4'-chlorophenylthio)phenethyl]imidazole;

1-[2,4-dichloro- β -(4'-chlorobenzylthio)phenethyl]imidazole, and so forth.

EXAMPLE 17

Nitric acid (70%; d=1.42) is added dropwise to a stirred solution of 2.5 g. of 1-[4-chloro- β -(4'-chlorophenylthio)phenethyl]imidazole in 40 ml. anhydrous ether until precipitation is complete. The product is filtered off, washed with ether and dried. Recrystallization from ethyl acetate yields 1-[4-chloro- β -(4'-chlorophenylthio)phenethyl]imidazole nitrate, m.p. 136.5—137.5°C.

In similar manner, all compounds of Formula (I) in base form can be converted to the acid addition salts by treatment in the conventional manner with the appropriate acid.

EXAMPLE 18

The anti-bacterial activity of certain compounds of the present invention and of Keflin* is illustrated in the following procedure.

Streptococcus faecalis, a gram(+) bacteria, is cultured at 37°C. in Brain-Heart Infusion Broth (Difco—Trade Mark). After 24 hours the culture is diluted to a concentration of 1×10^8 cells/ml. with the growth medium. Of this suspension, 0.05 ml. is added to various dilutions of the test compounds.

The test compounds are dissolved in dimethyl sulfoxide, ethanol or water at a concentration of 10 mg./ml. and thereafter diluted with sterile water to give a stock solution having a concentration of 100 μ g./ml. From this stock solution, appropriate dilutions are made. Approximately 4 ml. of each dilution is added to a sterile test tube and 0.05 ml. of the above prepared inoculum is then added to each tube. Incubation is then carried out for 24 hours and the minimal inhibitory concentration (MIC), which is the concentration at which no visible growth occurs, is then determined.

* sodium salt of 7-(thiophene-2-acetamido) cephalosporanic acid.

TABLE 1

Compound	Minimal Inhibitory Concentration μ g./ml.
Keflin	33
1-[3,4-dichloro- β -(3',4'-dichlorophenylthio)-phenethyl]imidazole nitrate	10
1-[2,4-dichloro- β -(4'-chlorobenzylthio)-phenethyl]imidazole nitrate	10
1-[4-chloro- β -(4'-chlorophenylthio)-phenethyl]imidazole nitrate	3.3

EXAMPLE 19

The anti-fungal activity of certain compounds of the present invention and of Miconazole* is illustrated in the following procedure.

* 1-[2,4-dichloro- β -(2',4'-dichlorobenzylthio)phenethyl]imidazole nitrate.

Trichophyton rubrum is cultured on Sabourad Dextrose agar (Difco) at room temperature for 14 days. The fungi mat is then removed from the agar slant and homogenized to a fine suspension in Sabourad Dextrose Broth. This suspension is diluted to a uniform concentration (OD of 0.1 at 600 nm) and 0.05 ml. is added to various dilutions of the test compounds.

The test compounds are dissolved in dimethyl sulfoxide, ethanol or water at a concentration of 10 mg./ml. and thereafter diluted with sterile water to give a concentration of 100 μ g./ml. From this stock solution appropriate dilutions were made. Approximately 4 ml. of each dilution is added to a sterile test tube and 0.05 ml. of

the above prepared inoculum is then added to each tube. Incubation is carried out for 7 to 14 days depending on the growth in the negative control.

The minimal inhibitory concentration (MIC), which is the concentration at which no visible growth occurs, is then determined for each test compound and for Miconazole.

The results obtained are listed in Table I.

TABLE I

	Compound	Minimal Inhibitory Concentration $\mu\text{g./ml.}$	
10	Miconazole	10	10
	1-[2,4-dichloro- β -(2',4'-dichlorobenzylthio)-phenethyl]imidazole nitrate	3	
	1-[2,4-dichloro- β -(4'-chlorobenzylthio)-phenethyl]imidazole nitrate	3	
15	1-[2,4-dichloro- β -(n-heptylthio)phenethyl]-imidazole oxalate	3	15

Example 20

The following formulations are typical of topical, oral and parenteral dosage forms for the compounds of the present invention:

20	Cream:		20
	a compound of the present invention	1.0 g.	
	stearic acid	10.0 g.	
	Span 60 (Trade Mark for commercial surfactant)	5.2 g.	
	Span 80 (Trade Mark for commercial surfactant)	1.0 g.	
25	propylene glycol	5.0 g.	25
	methyl paraben	0.05 g.	
	propyl paraben	0.01 g.	
	distilled water qs. to	100.0 g.	

The constituents are mixed at 60°C. and cooled with agitation to produce a smooth cream.

	Tablet:		
	a compound of the present invention	100 mg.	
	lactose USP	80 mg.	
	cornstarch	16 mg.	
35	polyvinylpyrrolidone	5.6 mg.	35
	magnesium stearate	0.4 mg.	
		200.0 mg.	

The constituents are mixed and granulated with an appropriate solvent, e.g. methanol, dried, then formed into tablets using suitable tableting equipment.

40	Suppository:		40.
	a compound of the present invention	0.1 g.	
	polyethylene glycol 1000	1.0 g.	
	polyethylene glycol 4000	0.1 g.	
		1.2 g.	

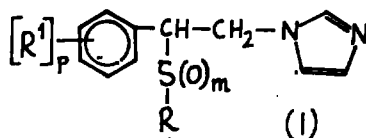
The constituents are mixed together at 50°C., then poured into molds and allowed to cool to room temperature.

	Injectable Solution:		
	a compound of the present invention	0.5 g.	
	propylene glycol	30.0 g.	
	sodium chloride	0.8 g.	
50	distilled water qs. to	100 ml.	50

A solution of the active compound hereof in the propylene glycol is mixed with the sodium chloride in water, brought to final volume, and filtered through 0.2 μ membrane filter and packaged under sterile conditions.

WHAT WE CLAIM IS:—

1. A compound of the formula:



and the acid addition salts thereof,
wherein:

R is alkyl, alkenyl, aralkenyl, substituted aralkenyl, alkynyl, cycloalkyl, cycloalkyl alkyl, aralkyl, substituted aralkyl, aryl or substituted aryl, said substituted aralkenyl and substituted aralkyl containing at least one substituent on the aryl moiety selected from halo, lower alkyl, lower alkoxy, trifluoromethyl, nitro and cyano and said substituted aryl containing at least one substituent selected from halo, lower alkyl, lower alkoxy, trifluoromethyl, nitro, amino, acylamino and cyano;

R¹ is hydrogen, halo, lower alkyl, lower alkoxy, trifluoromethyl, nitro, cyano, thio-cyanato or the group



in which R² is alkyl, cycloalkyl, aralkyl, substituted aralkyl, aryl or substituted aryl, said substituted aralkyl and said substituted aryl containing at least one substituent on the aryl moiety selected from halo, lower alkyl, lower alkoxy, trifluoromethyl, nitro and cyano;

m, n and p are independently selected from the integers zero, 1 and 2;
provided that the value of m cannot be greater than the value of n except when R¹ is the group



and R² is aryl or substituted aryl.

2. A compound of Claim 1 wherein m is zero.

3. A compound of Claim 2 wherein R¹ is halo and R is alkyl, alkenyl, aralkenyl, halo substituted aralkenyl, aralkyl, halo substituted aralkyl, aryl or halo substituted aryl.

4. A compound of Claim 3 wherein [R¹]ₚ is mono halo or dihalo and R is alkyl containing 1 to 12 carbon atoms, 2-alkenyl, phenyl-2-alkenyl, chloro substituted phenyl 2-alkenyl, benzyl, chloro or fluoro substituted benzyl, phenyl or chloro substituted phenyl.

5. A compound of Claim 4 wherein [R¹]ₚ is 2,4-dichloro, 2,4-dibromo or 2,4-difluoro.

6. The compound of Claim 5 which is 1-[2,4-dichloro-β-(n-pentylthio)phenethyl]imidazole and the acid addition salts thereof.

7. The compound of Claim 5 which is 1-[2,4-dichloro-β-(n-heptylthio)phenethyl]imidazole and the acid addition salts thereof.

8. The compound of Claim 5 which is 1-[2,4-dichloro-β-(n-octylthio)phenethyl]-imidazole and the acid addition salts thereof.

9. The compound of Claim 5 which is 1-[2,4-dichloro-β-(n-nonylthio)phenethyl]-imidazole and the acid addition salts thereof.

10. The compound of Claim 5 which is 1-[2,4-dichloro-β-(n-hexylthio)phenethyl]imidazole and the acid addition salts thereof.

11. The compound of Claim 5 which is 1-[2,4-dibromo-β-(n-hexylthio)phenethyl]imidazole and the acid addition salts thereof.

12. The compound of Claim 5 which is 1-[2,4-dibromo-β-(n-heptylthio)phenethyl]imidazole and the acid addition salts thereof.

13. The compound of Claim 5 which is 1-[2,4-dibromo-β-(n-octylthio)phenethyl]imidazole and the acid addition salts thereof.

14. The compound of Claim 5 which is 1-[2,4-difluoro-β-(n-octylthio)phenethyl]-imidazole and the acid addition salts thereof.

15. The compound of Claim 5 which is 1-[2,4-difluoro-β-(n-nonylthio)phenethyl]imidazole and the acid addition salts thereof.



16. The compound of Claim 5 which is 1-[2,4-difluoro- β -(n-decylthio)phenethyl]imidazole and the acid addition salts thereof.

17. The compound of Claim 5 which is 1-[2,4-dichloro- β -(2-octenylthio)phenethyl]imidazole and the acid addition salts thereof.

5 18. The compound of Claim 5 which is 1-[2,4-dichloro- β -3-phenyl-2-propenylthio)phenethyl]imidazole and the acid addition salts thereof. 5

19. The compound of Claim 5 which is 1-[2,4-dichloro- β -(3-(4'-chlorophenyl)-2-propenylthio)phenethyl]imidazole and the acid addition salts thereof.

10 20. The compound of Claim 5 which is 1-[2,4-dichloro- β -(4'-chlorobenzylthio)phenethyl]imidazole and the acid addition salts thereof. 10

21. The compound of Claim 5 which is 1-[2,4-dichloro- β -(4'-fluorobenzylthio)phenethyl]imidazole and the acid addition salts thereof.

22. The compound of Claim 5 which is 1-[2,4-dichloro- β -(2',4'-dichlorobenzylthio)phenethyl]imidazole and the acid addition salts thereof.

15 23. The compound of Claim 5 which is 1-[2,4-dichloro- β -(3',4'-dichlorobenzylthio)phenethyl]imidazole and the acid addition salts thereof. 15

24. The compound of Claim 5 which is 1-[2,4-dibromo- β -(4'-chlorobenzylthio)phenethyl]imidazole and the acid addition salts thereof.

20 25. The compound of Claim 5 which is 1-[2,4-dichloro- β -(4'-chlorophenylthio)phenethyl]imidazole and the acid addition salts thereof. 20

26. The compound of Claim 5 which is 1-[2,4-dichloro- β -(3',4'-dichlorophenylthio)phenethyl]imidazole and the acid addition salts thereof.

27. The compound of Claim 5 which is 1-[2,4-dichloro- β -(2',4'-dichlorophenylthio)phenethyl]imidazole and the acid addition salts thereof.

25 28. The compound of Claim 5 which is 1-[2,4-dichloro- β -(3',4',5'-trichlorophenylthio)phenethyl]imidazole and the acid addition salts thereof. 25

29. The compound of Claim 5 which is 1-[2,4-dibromo- β -(3',4'-dichlorophenylthio)phenethyl]imidazole and the acid addition salts thereof.

30 30. A composition useful for inhibiting the growth of fungi or bacteria which comprises a compound of claim 1 in admixture with a suitable carrier. 30

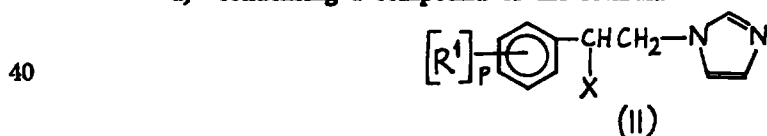
31. The composition of Claim 30 for pharmaceutical use wherein the carrier is a pharmaceutically acceptable non-toxic carrier.

32. The composition of Claim 31 wherein the compound of Formula (I) is present in an amount ranging between 0.1 and 10.0 weight percent of the composition.

35 33. A method of inhibiting the growth of fungi or bacteria which comprises applying to a host object containing, or subject to attack by, fungi or bacteria, a fungicidally or bacteriocidally effective amount of a compound of claim 1. 35

34. A process for the preparation of compounds of claim 1 which comprises:

a) condensing a compound of the formula

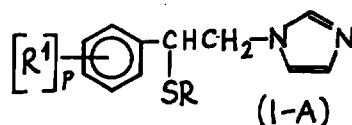


wherein R¹ and p are defined as above and X is a leaving group, with a compound of the formula



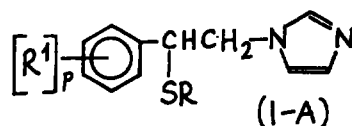
45 35. A method of inhibiting the growth of fungi or bacteria which comprises applying to a host object containing, or subject to attack by, fungi or bacteria, a fungicidally or bacteriocidally effective amount of a compound of claim 1. 45

wherein R is defined as above, to produce a 1-[β -(R-thio)phenethyl]imidazole of the formula



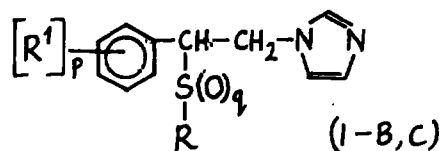
wherein R, R¹ and p are defined as above; or

b) oxidizing a compound of the formula





wherein R, R¹ and p are defined as above to produce a corresponding compound of the formula



wherein R, R¹ and p are defined as above and q is 1 or 2; or

c) converting a compound of Formula (I) to an acid addition salt thereof or converting an acid addition salt of a compound of Formula (I) to a free base.

35. A compound of claim 1 or acid addition salt thereof as exemplified herein.

36. A method according to claim 33 as described herein.

37. A process for preparing a compound of claim 1 or an acid addition salt thereof, as described herein.

38. A compound according to claim 1 or acid addition salt thereof when prepared by a process according to claim 34 or claim 37.

39. An antifungal or antibacterial composition comprising a compound according to any one of claims 2 to 29, 35 and 38.

40. An antifungal or antibacterial composition as exemplified herein.

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(11)

ERRATA

SPECIFICATION No. 1,485,719

- Page 2, line 19, *after 10 insert ring*
Page 2, line 22, *for 2-hexynyl read 3-hexynyl*
Page 6, line 28, *delete prepared by*
Page 8, line 19, *for β -3',4' read β -(3',4'*
Page 8, line 46, *for 4-butyl read 4-t-butyl*
Page 10, line 57, *for thiocyano read thio-*
cyanato
Page 13, line 37, *for phenethyl)imidazole read*
phenethyl]imidazole
Page 13, line 53, *for propionaylaminophenyl-*
thio read propionylaminophenylthio
Page 14, line 52, *for -4-)4'- read -4-(4'-*
Page 16, line 39, *for phenethyl)imidazole*
read phenethyl]imidazole
Page 17, line 51, *for 1-(2,4 read 1-[2,4*
Page 18, line 26, *for proceudre read pro-*
cedure
Page 21, line 15, *for dicholor read dichloro*
THE PATENT OFFICE
7th November, 1977