

PATENT SPECIFICATION

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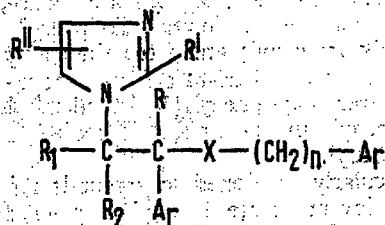
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(54) IMIDAZOLE DERIVATIVES

(71) We, JANSSEN PHARMACEUTICA N.V., a Belgian Body Corporate, of Turnhoutsebaan 30, Beerse, Belgium, 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 invention relates to novel imidazole derivatives and, more particularly to 1-(β-aryl)ethyl-imidazole ethers and amines which possess anti-fungal and anti-bacterial activity.

The present invention provides 1-(β-aryl)ethyl-imidazole ethers and amines having the following formula:



wherein:

R, R₁ and R₂ are each hydrogen or lower alkyl;

X is —O— or —NH—;

n is 0 or the integer 1 or 2;

- 5 Ar is phenyl, substituted phenyl, thienyl or halothienyl, said substituted phenyl containing a phenyl substituent which is halo, lower alkyl or lower alkoxy;

- 10 Ar' is phenyl, substituted phenyl or α -tetralyl, said substituted phenyl containing a phenyl substituent which is halo, lower alkyl, lower alkoxy, cyano, nitro or amino;

R' is hydrogen, methyl or ethyl; and

R'' is hydrogen or methyl;

- 15 provided that:

(i) when X is —NH—, then R is hydrogen;

(ii) when Ar' is a substituted phenyl containing a phenyl substituent which is nitro or amino, then X is —O— and n is 0;

- 20 (iii) when Ar' is β tetralyl, then X is —NH— and n is 0; and

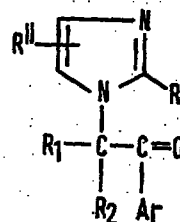
- (iv) when X is —O— and Ar' is phenyl or substituted phenyl containing a phenyl substituent which is halo, lower alkyl, lower alkoxy or cyano, then n is an integer of 1 or 2.

The pharmaceutically acceptable salts of the foregoing compounds (I) are also included within the scope of the present invention.

- 30 As used herein, the terms "lower alkyl" and "lower alkoxy" refer to straight or branch chained saturated hydrocarbons having from 1 to 6 carbons, such as, for example, methyl, ethyl, propyl, isopropyl, butyl, pentyl or hexyl, and, respectively, the corresponding alkoxy groups such as methoxy, ethoxy, propoxy and isopropoxy. The preferred lower alkyl and lower alkoxy groups are methyl and methoxy, respectively. The preferred substituted phenyls with regard to the group Ar are mono-, di- and tri-halophenyl, lower alkylphenyl and lower alkoxyphenyl; and from the group Ar' are mono-, di- and tri-halophenyl, mono- and di- (lower alkyl)phenyl, lower alkoxyphenyl, cyanophenyl, mono- and di-nitrophenyl and aminophenyl.

- 45 Particularly preferred compounds of the present invention are 1 - [β - (p-chlorobenzoyloxy)phenethyl]imidazole, 1 - [2,4-dichloro - β - (p-chlorobenzoyloxy)phenethyl]-imidazole, 1 - (2,4-dichloro - β - (2,4-dichlorobenzoyloxy)phenethyl)imidazole, 1-[2,4-dichloro - β - (2,6-dichlorobenzoyloxy)phenethyl]imidazole and 1 - [p-chloro - β - (2,6-dichlorobenzoyloxy)phenethyl]imidazole.

- 55 The amines of formula (I), i.e. the compounds in which —X— is —NH— may be obtained by the reductive amination of an appropriate 1 - (aroyl - methyl) - imidazole of formula (II):



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(II)

wherein R₁, R₂, R', R'' and Ar are as previously defined. Thus, the ketone of formula (II) may be treated with an appropriate amine of formula (III):



(III)

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wherein n and Ar' are as previously defined, in a suitable solvent, e.g., an aromatic hydrocarbon such as benzene, toluene or xylene.

Preferably, the amination is conducted under reflux conditions and in the presence of a small amount of an appropriate acid, e.g., p - toluenesulfonic acid. After the evolution of water has ceased, the aromatic hydrocarbon solvent is evaporated off and the residual product (IV) is transferred to a suitable solvent, preferably a lower alkanol solvent having up to 7 carbon atoms, and reduced to the corresponding amine (I-a), for example, by treatment with a suitable reducing agent, such as a complex metal hydride, e.g., potassium borohydride or sodium borohydride, or by catalytic hydrogenation, e.g., by contact with hydrogen and a palladium - on - charcoal catalyst. The amine product may be recovered from the reaction mixture according to conventional isolation procedures either as the free base, or, if so desired, in the form of an acid addition salt by treatment of the base with a suitable acid.

Thus, 1 - [2,4 - dichloro - β - (p-chlorobenzoyloxy)phenethyl]imidazole and 1 - [β - (p-chlorobenzoyloxy)phenethyl]imidazole may be prepared by reacting the sodium salt of α - (2,4 - dichlorophenyl)imidazole - 1-ethanol or of 1 - [β - hydroxyphenethyl]imidazole respectively with p - chlorobenzylchloride. 1 - [2,4 - Dichloro - β - (2,4-dichlorobenzoyloxy)phenethyl]imidazole may be prepared by reacting the sodium salt of α - (2,4 - dichlorophenyl)imidazole - 1 - ethanol with 2,4 - dichlorobenzylchloride. In similar manner 1 - [2,4 - dichloro - β - (2,6-dichlorobenzoyloxy)phenethyl]imidazole and 1 - [p-chloro - β - (2,6-dichlorobenzoyloxy)phenethyl]imidazole may be prepared by reacting the sodium salt of α - (2,4 - dichlorophenyl)imidazole - 1 - ethanol or of α - (p-

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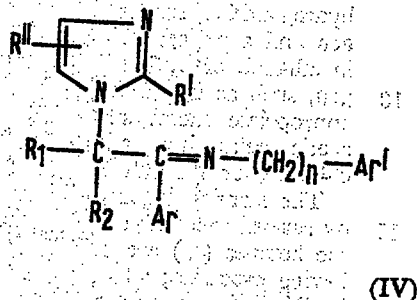
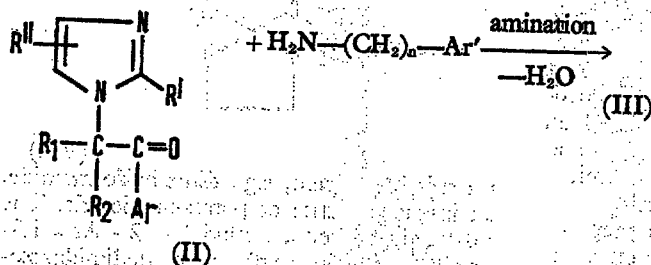
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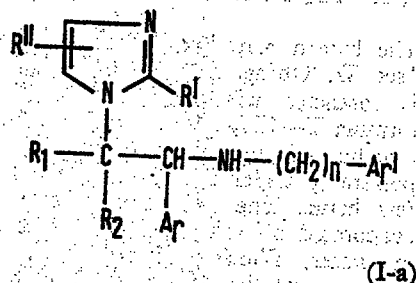
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chlorophenyl)imidazole - 1 - ethanol respectively with 2,6 - dichlorobenzylchloride. The compounds so prepared may be thereafter, if desired, converted into pharmaceutically acceptable salts.

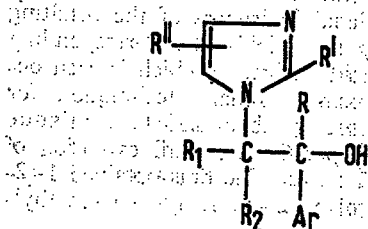
The foregoing reductive amination sequence may be further illustrated by the following schematic diagram:



reduction

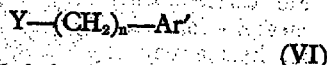


The ethers of formula (I), i.e. the compounds in which ---X--- is ---O--- , may be prepared by the O - alkylation of an appropriate α - Ar - imidazole - 1 - ethanol of formula (V):

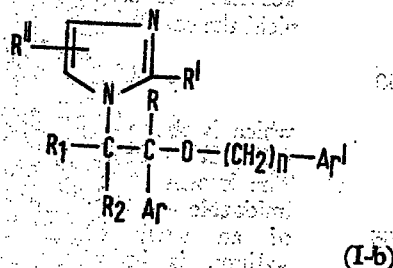
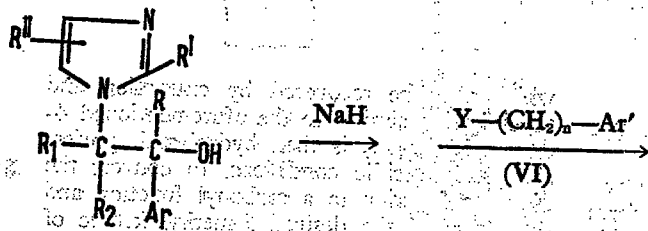


wherein R, R₁, R₂, R', R'' and Ar are as previously defined. Thus, the alcohol of formula (V) which has been preliminarily converted into its alkali metal salt form by treatment with a strong base such as an alkali

metal amide or hydride, may be contacted with an appropriate halide of formula (VI):



wherein n and Ar' are as previously defined, with the exception that Ar' is not aminophenyl and Y is halo, preferably chloro or bromo. Suitable solvents for the O - alkylation procedure include the aromatic hydrocarbons, e.g., benzene, toluene or xylene; the dialkylformamides, e.g., dimethylformamide or diethylformamide; ethers such as tetrahydrofuran or 1,2 - dimethoxyethane; and hexamethylphosphortriamide. Elevated temperatures may be advantageously employed to accelerate the rate of reaction. As with the amines of formula (I-a), the resulting ethers (I-b) may be recovered in the form of the free base or as an acid addition salt. The foregoing O - alkylation procedure may be illustrated by the following schematic diagram:



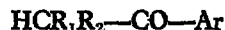
The formula (I) ethers, wherein Ar' is aminoethyl, may be obtained by reduction of the corresponding nitrophenyl ethers of formula (I-b) according to conventional procedures for reducing a nitro function to an amino function, for example, by catalytic hydrogenation, such as by contact with hydrogen and a palladium - on - charcoal catalyst in ethanol, or by contact with nascent hydrogen, such as is produced by the action of an appropriate metal and acid, e.g., zinc and acetic acid, iron and aqueous ammonium chloride, or tin and hydrochloric acid.

The starting ketones (II) may be prepared by several methods of synthesis. For example, the ketones (II) are obtainable from the following processes; wherein the symbols R₁, R₂, Y, R', R'' and Ar are as previously defined;

- A. The known material, N-acetyl-imidazole [see W. Otting, Ber. 89, 1940 (1956)] is contacted with a compound of the formula Y-CH₂-CO-Ar in a suitable organic solvent, e.g., acetonitrile, and preferably under reflux conditions for a few hours. The solvent is subsequently evaporated off and the residue dissolved in water, filtering if necessary. The aqueous solution is treated with an appropriate base, e.g., sodium bicarbonate solution, until about pH 9 to precipitate the corresponding ketone: 1 - Aroyl-methyl - imidazole. If desired, the resulting ketone may be dissolved in a suitable organic solvent and reprecipitated as an acid addition salt by conventional treatment with an acid; or
- B. 2 - R' - 4(5) - R'' - Imidazole and a halide of the formula



- are intimately contacted in a suitable solvent, e.g., dimethylformamide or lower alkanol containing up to 7 carbon atoms, from which mixture the desired ketone is precipitated by addition of water. Alternatively, a ketone of the formula



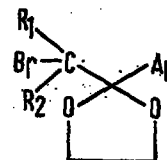
is first brominated with liquid bromine according to conventional techniques to yield the compound



which is then reacted with said 2 - R' - 4(5) - R'' - imidazole;

- C. The known material, ethyl 5 - methyl-imidazole - 4 - carboxylate, in the form of an alkali metal salt, preferably sodium, is intimately contacted under

reflux conditions with an appropriate 2-bromomethyl - 2 - Ar - 1,3 - dioxolan of the formula:

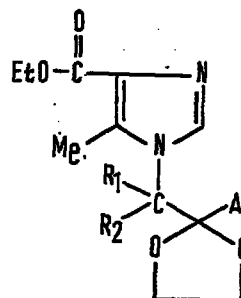


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(VII)

in a suitable solvent, e.g., dimethylformamide, and in the presence of potassium iodide. The thus-obtained product, ethyl 1 - (2 - Ar - 1,3-dioxolan - 2 - ylmethyl) - 5 - methylimidazole - 4 - carboxylate:

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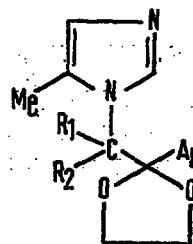


is then extracted from the reaction mixture with a suitable solvent, e.g., ether, the evaporation of which affords the ester, or, alternatively, the ester may be precipitated out by treating the extract with an acid such as nitric acid. Conventional hydrolysis of the resulting ester or ester salt yields the corresponding 4-carboxylic acid derivative which is then decarboxylated using standard techniques, for example, by heating (about 250°C) a mixture of the acid in paraffin oil until evolution of carbon dioxide ceases. The thus-obtained 1-(2-Ar - 1,3 - dioxolan - 2 - ylmethyl) - 5 - methyl-imidazole:

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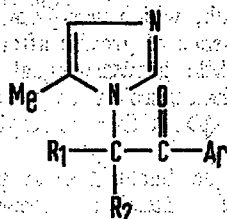
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which may be recovered by extraction and precipitation similar to the aforementioned 4-carboxylate ester, is then hydrolyzed, preferably under acidic conditions, to convert the dioxolan function to a carbonyl function and thereby yield the desired 5-methyl ketone of formula (II):

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The starting alcohols (V) are also obtainable from several methods of synthesis such as the following processes; wherein the symbols R, R₁, R₂, Y, R', R'' and Ar are as previously defined;

A. The carbonyl function of the ketones (II) is reduced to a carbinol function by contact with a suitable reducing agent, for example, sodium borohydride or lithium aluminum hydride in a suitable solvent, e.g., a lower alkanol containing up to 7 carbon atoms; or

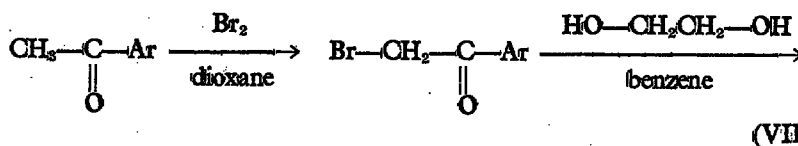
B. 2 - R' - 4(5) - R'' - Imidazole, in the form of an alkali metal salt, such as is obtained by treatment with sodium methoxide, is contacted with a compound of the formula Y - CR₁R₂ - CR(OH) - Ar in a suitable organic solvent, e.g., dimethylformamide. Subsequent addition of water to the reaction mixture precipitates the desired alcohol which is then isolated by conventional techniques; or

C. 2 - R' - 4(5) - R'' - Imidazole is contacted with a compound of the formula - Ar in a suitable organic solvent, e.g., a lower alkanol containing up to 7 carbon atoms, and in the presence of a small amount of organic base, e.g., pyridine, to yield, as a precipitate upon the addition of water, the corresponding alcohol of formula (V), in which R, R₁ and R₂ are all equal hydrogen.

Several of the reactant halides of formula (VII) have been reported in the literature [Feugas Cl., Bull. Soc. Chim. Fr., 1963(II), 2568; and Patel A.R., J. Pharm. Sc., 52(6), 588-593 (1963)]. Those that are not heretofore known may be easily prepared by first brominating a ketone of the formula:



wherein Ar is as previously defined, according to conventional bromination procedures and then reacting the thus obtained bromide with ethylene glycol in a suitable organic solvent, e.g., an aromatic hydrocarbon such as benzene, toluene or xylene, to which a small amount of *p*-toluenesulfonic acid may be added. The following diagrammatic scheme further illustrates the foregoing reactions:



Due to the available asymmetric carbons present in the compounds (I), it is evident that their existence in the form of stereochemical isomers (enantiomorphs) is possible. If desired, the resolution and isolation or the production of a particular form can be accomplished by application of the general principles known in the art. Said enantiomorphs are naturally intended to be included within the scope of this invention.

Depending upon the conditions employed during the course of the reactions, the novel compounds herein are obtained either in the form of the free bases or salts thereof. The salts are converted to the free bases in the usual manner, e.g., by reaction with alkali such as sodium or potassium hydroxide. The compounds in base form may be converted to their pharmaceutically acceptable salts by reaction with an appropriate acid, as, for example, an inorganic acid such as hydrohalic acid, i.e., hydrochloric, hydrobromic or hydroiodic acid; sulfuric, nitric or thiocyanic acid; a phosphoric acid; an organic acid such as

acetic, propionic, glycolic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, cinnamic, mandelic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, *p*-toluenesulfonic, salicylic, *p*-aminosalicylic, 2-phenoxybenzoic or 2-acetoxy benzoic acid.

The compounds of formula (I) and the pharmaceutically acceptable salts thereof are useful agents in combatting fungi and bacteria as demonstrated by their broad spectrum of anti-fungal and anti-bacterial action. The data given in the following tables illustrate such activity. The method employed in obtaining the tabulated data is that reported by Vanbreuseghem et al., *Chemotherapy*, 12, 107 (1967).

The tests on fungi were performed using Sabouraud's liquid medium (1 g. of neopeptone Difco and 2 g. of glucose Difco per 100 ml. distilled water) in 16 x 160 mm. test tubes, each containing 4.5 ml. of liquid medium, autoclaved at 120°C. for 15 minutes. The drug to be tested is primarily dissolved in

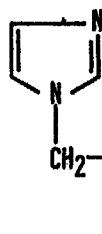
ethanol 50% at a concentration of 20 mg./ml. and afterwards diluted with sterile distilled water in order to obtain a concentration of 10 mg./ml. Successive decimal dilutions were made in distilled water. To each tube, containing 4.5 ml. of Sabouraud's liquid medium, 0.5 ml. of a dilution of the drug was added in order to obtain 1000 γ , 500 γ , 100 γ , 10 γ and 1 γ per ml. medium (the symbol " γ " equals "micrograms"). A control tube was prepared by adding 0.5 ml. distilled water to 4.5 ml. medium. The concentration of ethanol in the control tubes was the same as in those containing 1000 γ and 500 γ /ml. of the drug. The filamentous fungi were incubated at 25°C. for two to three weeks. A square block of 2 mm. side was cut and inoculated in the liquid medium. A three day old culture on Sabouraud's liquid medium was used for yeasts. The inoculum was 0.05 ml. per tube. All the cultures were made in duplicate and incubated at 25°C. for 14 days. The first readings were made after 7 days and the final ones after 14 days (the data given in Tables I and II are the final scores observed after 14 days for each compound at the concentration of 100 micrograms per milliliter culture). The score was

established assuming a maximum growth for the control tube which was given score 4. The complete absence of growth after 14 days was scored 0, while growths equal to 1/4, 1/2 and 3/4 of the controls were rated respectively 1, 2 and 3. (DIFCO is a Registered Trade Mark).

The tests on bacteria were performed on phenol red dextrose broth medium (Difco) and on trypton broth medium (Difco) using the same decimal dilution technique as for fungistatic tests (100 γ /ml. and 10 γ ml). The inoculum size are 0.1 ml. from a 24 hours culture diluted 1/10 in distilled water for *Streptococcus pyogenes* and 0.05 ml. for the other organisms. The results after 72 hours were rated as + or 0, corresponding to the presence or the absence of growth. The data given in Table III hereafter illustrate such anti-bacterial action.

It is understood that the compounds in the following tables are not listed for purposes of limiting the invention thereto, but only to exemplify the useful properties of all the compounds within the scope of formula (I), including the pharmaceutically acceptable acid addition salts thereof.

TABLE I



Ar	n	Ar'	salt	fungistatic activity (final score at 100 µg/ml)										
				1*	2	3	4	5	6	7	8	9	10	11
C ₆ H ₅	1	C ₆ H ₅	2 HCl	1	0	0	3	4	4	4	4	4	3	4
C ₆ H ₅	2	C ₆ H ₅	2 HNO ₃	1	0	0	3	3	4	4	4	4	3	3
C ₆ H ₅	0	C ₆ H ₅	2 HCl	1	0	0	3	3	4	4	4	4	4	3
C ₆ H ₅	0	C ₁₀ H ₁₁ **	2 HNO ₃	0	0	0	2	0	4	0	4	4	0	3
C ₆ H ₅	1	4-Cl-C ₆ H ₄	2 HCl	0	0	0	1	0	3	1	4	1	0	1
C ₆ H ₅	2	C ₆ H ₅	2 HCl	0	0	0	2	3	4	4	4	4	3	4
C ₆ H ₅	1	2-Cl-C ₆ H ₄	2 HCl	0	0	0	1	0	4	0	4	4	0	2
4-CH ₃ -C ₆ H ₄	1	4-Cl-C ₆ H ₄	2 HCl	0	0	0	0	0	2	0	0	0	0	0
4-Cl-C ₆ H ₄	1	4-OCH ₃ -C ₆ H ₄	2 HCl	0	0	0	1	0	4	1	4	4	4	1
4-CH ₃ -C ₆ H ₄	1	4-OCH ₃ -C ₆ H ₄	2 HCl	0	0	0	1	2	4	3	4	4	4	2
4-CH ₃ -C ₆ H ₄	2	C ₆ H ₅	2 HNO ₃	0	0	0	2	1	4	2	4	4	4	2
4-Cl-C ₆ H ₄	0	C ₆ H ₅	2 HCl	0	0	0	1	0	3	1	4	4	0	0
4-Cl-C ₆ H ₄	1	2-Cl-C ₆ H ₄	2 HCl	0	0	0	0	0	2	0	0	4	3	1
4-Cl-C ₆ H ₄	2	C ₆ H ₅	2 HNO ₃	0	0	0	1	0	0	0	4	4	0	0

TABLE I Continued

Ar	n	Ar'	salt	fungistatic activity (final score at 100 µg/ml)										
				1*	2	3	4	5	6	7	8	9	10	11
C ₆ H ₅	1	4-CH ₃ -C ₆ H ₄	2 HCl	0	0	0	3	0	4	3	4	4	1	1
C ₆ H ₅	1	4-OCH ₃ -C ₆ H ₄	2 HCl	0	0	0	3	3	4	4	4	4	3	2
4-Cl-C ₆ H ₄	1	4-CH ₃ -C ₆ H ₄	2 HCl	4	1	1	4	4	4	4	4	4	4	4
4-Cl-C ₆ H ₄	0	C ₁₀ H ₁₁ **	2 HCl.3H ₂ O	0	0	0	1	0	3	0	0	3	0	0
4-F-C ₆ H ₄	1	C ₆ H ₅	2 HNO ₃	1	0	0	2	1	3	3	4	4	3	3
4-F-C ₆ H ₄	1	2-Cl-C ₆ H ₄	2HNO ₃	0	0	0	2	0	3	0	4	3	3	2
4-F-C ₆ H ₄	1	4-OCH ₃ -C ₆ H ₄	2 HNO ₃	0	0	0	3	2	4	2	4	4	2	2
4-F-C ₆ H ₄	2	C ₆ H ₅	2 HNO ₃	0	0	0	2	2	3	3	4	3	1	3
4-F-C ₆ H ₄	1	4-CH ₃ -C ₆ H ₄	2 HNO ₃	0	0	0	2	1	3	0	4	3	0	1
4-F-C ₆ H ₄	0	C ₁₀ H ₁₁ **	2 HNO ₃	0	0	0	2	0	2	1	4	4	0	1
4-F-C ₆ H ₄	1	4-Cl-C ₆ H ₄	2 HNO ₃	0	0	0	1	0	1	0	0	0	0	1
C ₄ H ₉ S***	1	4-Cl-C ₆ H ₄	2 HCl	0	0	0	0	0	2	1	4	0	0	0

*) 1 = *Microsporum canis*
 2 = *Trichophyton mentagrophytes*
 3 = *Trichophyton rubrum*
 4 = *Phialophora verrucosa*
 5 = *Cryptococcus neoformans*
 6 = *Candida tropicalis*

**) C₁₀H₁₁ = α-tetralyl

7 = *Candida albicans*
 8 = *Mucor*
 9 = *Aspergillus fumigatus*
 10 = *Sporotrichum schenckii*
 11 = *Saprolegnia*

***) C₄H₉S = 2 thienyl

TABLE II-a



Ar	R	n	Ar'	base or salt	fungistatic activity (final score at 100 µg/ml)										
					1*	2	3	4	5	6	7	8	9	10	11
C ₆ H ₅	H	1	4-Cl-C ₆ H ₄	HNO ₃	0	0	0	0	0	1	0	1	0	0	0
4-Cl-C ₆ H ₄	H	1	4-Cl-C ₆ H ₄	HNO ₃	0	0	0	0	0	0	0	0	0	0	0
4-F-C ₆ H ₄	H	1	4-Cl-C ₆ H ₄	HNO ₃	0	0	0	1	0	1	0	0	0	0	0
2,4-(Cl) ₂ -C ₆ H ₃	H	1	4-Cl-C ₆ H ₄	HNO ₃	0	0	0	0	0	0	0	0	0	0	0
2-Cl-C ₆ H ₄	H	1	4-Cl-C ₆ H ₄	HNO ₃	0	0	0	0	0	0	0	0	0	0	0
2,4-(Cl) ₂ -C ₆ H ₃	H	1	2,4-(Cl) ₂ -C ₆ H ₃	HNO ₃	0	0	0	2	0	1	1	4	0	0	0
4-F-C ₆ H ₄	H	1	2,4-(Cl) ₂ -C ₆ H ₃	HNO ₃	0	0	0	0	0	0	0	0	0	0	0
4-CH ₃ -C ₆ H ₄	H	1	2,4-(Cl) ₂ -C ₆ H ₃	HNO ₃	0	0	0	0	0	1	0	0	0	0	0
2-CH ₃ -C ₆ H ₄	H	1	2,4-(Cl) ₂ -C ₆ H ₃	HNO ₃	0	0	0	0	0	1	0	2	0	0	0
2-CH ₃ -C ₆ H ₄	H	1	4-Cl-C ₆ H ₄	HNO ₃	0	0	0	0	0	1	1	0	0	0	0
4-CH ₃ -C ₆ H ₄	H	1	4-Cl-C ₆ H ₄	HNO ₃	0	0	0	0	0	1	0	1	0	0	0
2-Cl-C ₆ H ₄	H	1	2,4-(Cl) ₂ -C ₆ H ₃	HNO ₃	0	0	0	0	0	1	0	1	0	0	0

TABLE II-a (Continued)

Ar	R	n	Ar'	base or salt	fungistatic activity (final score at 100 µg/ml)										
					1*	2	3	4	5	6	7	8	9	10	11
4-Cl-C ₆ H ₄	H	1	2,4-(Cl) ₂ -C ₆ H ₃	HNO ₃	0	0	0	0	0	0	0	1	0	0	0
4-Cl-C ₆ H ₄	H	1	2-Cl-C ₆ H ₄	HNO ₃	0	0	0	0	0	0	0	0	0	0	0
4-F-C ₆ H ₄	H	1	2-Cl-C ₆ H ₄	HNO ₃	0	0	0	1	0	0	0	4	0	0	0
4-Br-C ₆ H ₄	H	1	4-Cl-C ₆ H ₄	HNO ₃	0	0	0	0	0	1	0	0	0	0	0
2-OCH ₃ -C ₆ H ₄	H	1	2,4-(Cl) ₂ -C ₆ H ₃	HNO ₃	0	0	0	0	0	2	0	4	0	0	0
4-CH ₃ -C ₆ H ₄	H	1	2-Cl-C ₆ H ₄	HNO ₃	0	0	0	0	0	3	0	4	0	0	0
2-CH ₃ -C ₆ H ₄	H	1	2-Cl-C ₆ H ₄	HNO ₃	0	0	0	1	1	3	1	4	0	0	0
2-OCH ₃ -C ₆ H ₄	H	1	2-Cl-C ₆ H ₄	HNO ₃	0	0	0	1	2	3	1	4	0	0	0
2-Cl-C ₆ H ₄	H	1	2-Cl-C ₆ H ₄	HNO ₃	0	0	0	0	0	2	0	1	0	0	0
2,4-(Cl) ₂ -C ₆ H ₃	H	1	2-Cl-C ₆ H ₄	HNO ₃	0	0	0	0	0	0	0	0	0	0	0
4-Br-C ₆ H ₄	H	1	2-Cl-C ₆ H ₄	HNO ₃	0	0	0	1	0	0	0	0	0	0	0
C ₆ H ₅	CH ₃	1	4-Cl-C ₆ H ₄	HNO ₃	0	0	0	0	0	1	0	0	0	0	0
C ₆ H ₅	CH ₃	1	2,4-(Cl) ₂ -C ₆ H ₃	HNO ₃	0	0	0	0	0	3	1	0	0	0	1
4-Cl-C ₆ H ₄	CH ₃	1	4-Cl-C ₆ H ₄	HNO ₃	0	0	0	2	0	2	0	0	0	0	0
4-Cl-C ₆ H ₄	CH ₃	1	2,4-(Cl) ₂ -C ₆ H ₃	HNO ₃	0	0	0	2	0	2	1	1	2	0	1
C ₄ H ₂ CIS**	H	1	2-Cl-C ₆ H ₄	HNO ₃	0	0	0	0	0	0	0	0	0	0	0

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TABLE II-a (Continued)

Ar	R	n	Ar'	base or salt	fungistatic activity (final score at 100 µg/ml)										
					1*	2	3	4	5	6	7	8	9	10	11
2,4-(Cl) ₂ -C ₆ H ₃	H	1	2-CH ₃ -C ₆ H ₄	HNO ₃	0	0	0	0	0	2	0	4	0	0	0
2,4-(Cl) ₂ -C ₆ H ₃	H	1	2,6-(Cl) ₂ -C ₆ H ₃	HNO ₃	0	0	0	0	0	2	0	3	0	0	0
C ₆ H ₅	H	1	C ₆ H ₅	HNO ₃	0	0	0	1	0	3	1	3	0	0	1
2,4-(Cl) ₂ -C ₆ H ₃	H	1	3-OCH ₃ -C ₆ H ₄	HNO ₃	0	0	0	0	0	3	0	2	0	0	0
4-Cl-C ₆ H ₄	H	1	2-CH ₃ -C ₆ H ₄	HNO ₃	0	0	0	0	0	1	0	1	0	0	0
4-Cl-C ₆ H ₄	H	1	2,6-(Cl) ₂ -C ₆ H ₃	HNO ₃	0	0	0	0	0	0	1	1	0	0	0
2,4-(Cl) ₂ -C ₆ H ₃	H	0	4-NO ₂ -C ₆ H ₄	HNO ₃	0	0	0	0	0	1	0	3	0	0	1
2,4-(Cl) ₂ -C ₆ H ₃	H	1	4-OCH ₃ -C ₆ H ₄	HNO ₃	0	0	0	0	0	1	0	1	0	0	0
4-Cl-C ₆ H ₄	H	1	4-CH ₃ -C ₆ H ₄	HCl.H ₂ O	0	0	0	0	0	2	0	3	0	0	0
2,4-(Cl) ₂ -C ₆ H ₃	H	1	2-F-C ₆ H ₄	HNO ₃	0	0	0	0	0	1	0	1	0	0	0
2,4-(Cl) ₂ -C ₆ H ₃	H	1	4-F-C ₆ H ₄	HNO ₃	0	0	0	0	0	0	0	1	0	0	0
2,4-(Cl) ₂ -C ₆ H ₃	H	0	2,4-(NO ₂) ₂ -C ₆ H ₃	HNO ₃	1	0	0	1	1	2	2	3	4	2	2
2,4-(Cl) ₂ -C ₆ H ₃	H	0	4-NH ₂ -C ₆ H ₄	base	0	0	0	2	1	3	1	3	4	2	2
1-[p-chloro-β-(2,6-dichlorobenzyloxy) phenethyl]-2-ethylimidazole nitrate					0	0	0	0	0	4	4	4	4	0	1
1-[p-chloro-β-(2,4-dichlorobenzyloxy) phenethyl]-2-ethylimidazole nitrate					0	0	0	0	0	4	4	4	3	0	1
1-p-chloro-β-(2,4-dichlorobenzyloxy) phenethyl]-2-methylimidazole nitrate					0	0	0	0	0	4	3	2	0	0	0
1-p-[chloro-β-(2,6-dichlorobenzyloxy) phenethyl]-2-methylimidazole nitrate					0	0	0	0	0	3	3	2	3	0	0
1-[β-(p-chlorobenzyloxy)-α,α-dimethylphenethyl]-imidazole					0	0	0	0	0	0	0	0	0	0	0

*) For the meanings of 1 to 11, see the footnote of the table relating to the corresponding amine-derivatives.

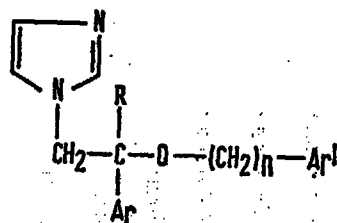
**) C₄H₂CIS = 5-chloro-2-thienyl.

Compound*	fungistatic activity (final score at 100 µg/ml)										
	1	2	3	4	5	6	7	8	9	10	11
A	0	0	0	1	0	3	0	4	2	0	0
B	2	0	0	1	0	4	4	0	3	1	1
C	0	0	0	3	0	3	0	4	3	0	3
D	0	0	0	0	0	0	0	4	0	0	0
E	0	0	0	4	1	4	2	4	3	2	2
F	1	0	1	2	1	4	2	4	3	0	2
G	1	0	0	0	0	4	1	4	0	0	0
H	0	0	0	1	1	4	4	4	0	0	0
I	0	0	0	3	3	4	3	4	4	0	3
J	0	0	0	0	1	2	2	1	0	0	0
K	0	0	0	1	0	3	1	2	1	0	2
L	1	0	0	2	1	4	2	2	3	0	1
M	0	0	0	3	3	4	4	3	1	2	3
N	0	0	0	0	0	3	0	1	0	0	0
O	0	0	0	1	0	4	0	2	0	0	0
P	0	0	0	1	1	3	0	1	0	0	0
Q	0	0	0	3	2	4	1	4	0	3	2
R	0	0	0	3	3	4	2	4	3	1	3
S	0	0	0	2	1	4	3	4	1	0	2
T	0	0	0	1	0	2	0	1	0	0	0
U	0	0	0	0	0	3	0	2	0	0	0
V	0	0	0	2	0	3	1	2	0	0	1
W	0	0	0	2	0	3	1	3	0	0	0
X	0	0	0	3	2	4	4	2	1	0	3
Y	0	0	0	3	2	4	4	4	3	1	4
Z	0	0	0	0	0	4	1	4	1	0	0
AA	0	0	0	1	2	4	2	4	0	0	1
BB	0	0	0	2	0	2	0	3	0	1	1
CC	0	0	0	1	0	2	0	3	0	0	3
DD	0	0	0	1	0	2	0	1	1	1	1

*Compound
Name

- A 1-(*p*-chloro- β -(2,4-dichlorobenzyloxy)phenethyl]-5-methylimidazole nitrate
- B 1-[*p*-chloro- β -(2,4-dichlorobenzyloxy)phenethyl]-2,4-dimethylimidazole nitrate
- C (+)-1-[2,4-dichloro- β -(2,4-dichlorobenzyloxy)-phenethyl]imidazole nitrate
- D (-)-1-[2,4-dichloro- β -(2,4-dichlorobenzyloxy)-phenethyl]imidazole nitrate
- E 1-[2,4,6-trichloro- β -(2,4-dichlorobenzyloxy)-phenethyl]imidazole nitrate
- F 1-[2,4,6-trichloro- β -(2,6-dichlorobenzyloxy)-phenethyl]imidazole nitrate
- G 1-[2,4-dichloro- β -(3,4-dimethylbenzyloxy)-phenethyl]imidazole nitrate
- H 1-[2,4-dichloro- β -(*p*-iodobenzyloxy)phenethyl]imidazole nitrate
- I 1-[2,4-dichloro- β -(2-methoxy-4-nitrobenzyloxy)-phenethyl]imidazole nitrate
- J α -[1-(2,4-dichlorophenyl)-2-(1-imidazolyl)-ethoxy]-*p*-tolunitrile nitrate
- K 1-[3,4-dichloro- β -(2,4-dichlorobenzyloxy)-phenethyl]imidazole nitrate
- L 1-[3,4-dichloro- β -(2,6-dichlorobenzyloxy)-phenethyl]imidazole nitrate
- M 1-[3,4-dichloro- β -(3,4-dichlorobenzyloxy)-phenethyl]imidazole nitrate
- N 1-[2,4-dichloro- β -(3,4-dichlorobenzyloxy)-phenethyl]imidazole nitrate
- O 1-[*o*-chloro- β -(3,4-dichlorobenzyloxy)phenethyl]imidazole nitrate
- P 1-[β -(3,4-dichlorobenzyloxy)-*p*-fluorophenethyl]imidazole nitrate
- Q 1-[3,4-dichloro- β -(*p*-chlorobenzyloxy)phenethyl]imidazole nitrate
- R 1-[2,6-dichloro- β -(2,4-dichlorobenzyloxy)-phenethyl]imidazole nitrate
- S 1-[2,6-dichloro- β -(2,6-dichlorobenzyloxy)-phenethyl]imidazole nitrate
- T 1-[2,6-dichloro- β -(*p*-chlorobenzyloxy)phenethyl]imidazole nitrate
- U 1-[2,5-dichloro- β -(*p*-chlorobenzyloxy)phenethyl]imidazole nitrate
- V 1-[2,5-dichloro- β -(2,6-dichlorobenzyloxy)-phenethyl]imidazole nitrate
- W 1-[2,5-dichloro- β -(2,4-dichlorobenzyloxy)-phenethyl]imidazole nitrate
- X 1-[2,5-dichloro- β -(2,5-dichlorobenzyloxy)-phenethyl]imidazole nitrate
- Y 1-[β -(*p*-*tert*-butylbenzyloxy)-2,4-dichlorophenethyl]imidazole nitrate
- Z 1-[2,4-dichloro- β -(*p*-cumenylmethoxy)phenethyl]imidazole nitrate
- AA 1-[2,6-dichloro- β -(*p*-methoxybenzyloxy)phenethyl]imidazole nitrate
- BB 1-[*p*-chloro- β -(2,6-dichlorobenzyloxy)- α,α -dimethylphenethyl]imidazole nitrate
- CC 1-[*p*-chloro- β -(*p*-fluorobenzyloxy)- α,α -dimethylphenethyl]imidazole nitrate
- DD 1-[*p*-chloro- β -(2,4-dichlorobenzyloxy)- α,α -dimethylphenethyl]imidazole nitrate

TABLE III-a



Ar	R	n	Ar'	base or salt	bactericidal activity (final score at 10 $\mu\text{gr/ml}$)		
					1*	2	3
C_6H_5	H	1	4-Cl- C_6H_4	HNO_3	0	0	0
4-Cl- C_6H_4	H	1	4-Cl- C_6H_4	HNO_3	0	0	0
4-F- C_6H_4	H	1	4-Cl- C_6H_4	HNO_3	0	0	0
2,4-Cl ₂ - C_6H_3	H	1	4-Cl- C_6H_4	HNO_3	0	0	0
2-Cl- C_6H_4	H	1	4-Cl- C_6H_4	HNO_3	0	0	0
2,4-Cl ₂ - C_6H_3	H	1	2,4-Cl ₂ - C_6H_3	HNO_3	0	0	—
4-F- C_6H_4	H	1	2,4-Cl ₂ - C_6H_3	HNO_3	0	+	0
4-CH ₃ - C_6H_4	H	1	2,4-Cl ₂ - C_6H_3	HNO_3	0	+	0
2-CH ₃ - C_6H_4	H	1	2,4-Cl ₂ - C_6H_3	HNO_3	0	0	0
2-CH ₃ - C_6H_4	H	1	4-Cl- C_6H_4	HNO_3	0	0	0
4-CH ₃ - C_6H_4	H	1	4-Cl- C_6H_4	HNO_3	0	0	0
2-Cl- C_6H_4	H	1	2,4-Cl ₂ - C_6H_3	HNO_3	0	0	0
4-Cl- C_6H_4	H	1	2,4-Cl ₂ - C_6H_3	HNO_3	0	0	0

TABLE III-a (Continued)

Ar	R	n	Ar'	base or salt	bactericidal activity (final score at 10 μ gr/ml)		
					1*	2	3
4-Cl-C ₆ H ₄	H	1	2-Cl-C ₆ H ₄	HNO ₃	0	0	0
4-F-C ₆ H ₄	H	1	2-Cl-C ₆ H ₄	HNO ₃	0	0	0
4-Br-C ₆ H ₄	H	1	4-Cl-C ₆ H ₄	HNO ₃	0	0	0
2-OCH ₃ -C ₆ H ₄	H	1	2,4-Cl ₂ -C ₆ H ₃	HNO ₃	0	0	0
4-CH ₃ -C ₆ H ₄	H	1	2-Cl-C ₆ H ₄	HNO ₃	0	0	0
2-CH ₃ -C ₆ H ₄	H	1	2-Cl-C ₆ H ₄	HNO ₃	0	0	0
2-OCH ₃ -C ₆ H ₄	H	1	2-Cl-C ₆ H ₄	HNO ₃	0	0	0
2-Cl-C ₆ H ₄	H	1	2-Cl-C ₆ H ₄	HNO ₃	0	0	0
2,4-Cl ₂ -C ₆ H ₃	H	1	2-Cl-C ₆ H ₄	HNO ₃	0	0	0
4-Br-C ₆ H ₄	H	1	2-Cl-C ₆ H ₄	HNO ₃	0	0	0
C ₆ H ₅	CH ₃	1	4-Cl-C ₆ H ₄	HNO ₃	0	0	—
C ₆ H ₅	CH ₃	1	2,4-Cl ₂ -C ₆ H ₃	HNO ₃	0	0	—
4-Cl-C ₆ H ₄	CH ₃	1	4-Cl-C ₆ H ₄	HNO ₃	0	0	—
4-Cl-C ₆ H ₄	CH ₃	1	2,4-Cl ₂ -C ₆ H ₃	HNO ₃	0	0	—
5-Cl-C ₄ H ₂ S**)	H	1	2-Cl-C ₆ H ₄	HNO ₃	0	0	—
2,4-Cl ₂ -C ₆ H ₃	H	1	2-CH ₃ -C ₆ H ₄	HNO ₃	0	0	0
2,4-Cl ₂ -C ₆ H ₃	H	1	2,6-Cl ₂ -C ₆ H ₃	HNO ₃	0	0	0
C ₆ H ₅	H	1	C ₆ H ₅	HNO ₃	0	+	0
2,4-Cl ₂ -C ₆ H ₃	H	1	3-OCH ₃ -C ₆ H ₄	HNO ₃	0	0	0

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TABLE III-a (Continued)

Ar	R	n	Ar'	base or salt	bactericidal activity (final score at 10 μ gr/ml)		
					1*	2	3
4-Cl-C ₆ H ₄	H	1	2-CH ₃ -C ₆ H ₄	HNO ₃	0	0	0
4-Cl-C ₆ H ₄	H	1	2, 6-Cl ₂ -C ₆ H ₃	HNO ₃	0	0	0
2, 4-Cl ₂ -C ₆ H ₃	H	0	4-NO ₂ -C ₆ H ₄	HNO ₃	0	0	0
2, 4-Cl ₂ -C ₆ H ₃	H	1	4-OCH ₃ -C ₆ H ₄	HNO ₃	0	0	0
4-Cl-C ₆ H ₄	H	1	4-CH ₃ -C ₆ H ₄	HCl.H ₂ O	0	0	0
2, 4-Cl ₂ -C ₆ H ₃	H	1	2-F-C ₆ H ₄	HNO ₃	0	0	0
2, 4-Cl ₂ -C ₆ H ₃	H	1	4-F-C ₆ H ₄	HNO ₃	0	0	0
2, 4-Cl ₂ -C ₆ H ₃	H	0	2, 4-(NO ₂) ₂ -C ₆ H ₃	HNO ₃	0	+	0
2, 4-Cl ₂ -C ₆ H ₃	H	0	4-NH ₂ -C ₆ H ₄	base	0	+	0

O : no growth

— : test not performed

- *) 1. Erysipelothrix insidiosa
 2. Staphylococcus hemolyticus
 3. Streptococcus pyogenes

**) thienyl

TABLE III-b

Compound*	bactericidal activity (final score at 10 μ g/ml)		
	1	2	3
A	0	0	0
B	0	+	0
C	0	0	0
D	0	0	0
E	0	0	0
F	0	0	0
G	0	0	0
H	0	+	0
I	0	+	0
J	0	+	+
K	—	—	—
L	0	0	0
M	+	+	0
N	0	0	0
O	0	0	0
P	0	0	0
Q	0	+	0
S	0	+	0
U	0	0	0
V	0	0	0
W	0	0	0
X	0	+	+
Y	0	0	0
Z	0	0	0
AA	0	+	0
BB	0	0	0
DD	0	+	0

* for compound name, see Table II-b

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In view of the aforementioned anti-fungal and anti-bacterial activities, this invention provides valuable compositions comprising the amines and ethers (I) or the acid addition salts thereof as the active ingredient in a solvent or a solid, semi-solid or liquid diluent or carrier, and, in addition, it provides an effective method of combatting fungus or bacterial growth by the use of an effective anti-fungal or anti-bacterial amount of such amines and ethers (I) or salts thereof. The subject compounds can be used in suitable solvents or diluents, in the form of emulsions, suspensions, dispersions or ointments, on suitable solid or semi-solid carrier substances, in ordinary or synthetic soaps, detergents or dispersion media, if desired, together with other compounds having arachnidicidal, insecticidal, ovicidal, fungicidal and/or bactericidal effects, or together with inactive additives.

Solid carrier substances which are suitable for the preparation of compositions in powder form include various inert, porous and pulverous distributing agents of inorganic or organic nature, such as, for example, tricalcium phosphate, calcium carbonate, in the form of prepared chalk or ground limestone, kaolin, bole, bentonite, talcum, kieselguhr and boric acid; powdered cork, sawdust, and other fine pulverous materials of vegetable origin are also suitable carrier substances.

The active ingredient is mixed with these carrier substances, for example, by being ground therewith; alternatively, the inert carrier substance is impregnated with a solution of the active component in a readily volatile solvent and the solvent is thereafter eliminated by heating or by filtering with suction at reduced pressure. By adding wetting and/or dispersing agents, pulverous preparations can also be made readily wettable with water, so that suspensions can be obtained.

Inert solvents used for the production of liquid preparations should preferably not be readily inflammable and should be as far as possible odorless and as far as possible non-toxic to warm-blooded animals or plants in the relevant surroundings. Solvents suitable for this purpose are high-boiling oils, for example, of vegetable origin, and lower-boiling solvents with a flash point of at least 30°C., such as, for example, isopropanol, dimethylsulfoxide, hydrogenated naphthalenes and alkylated naphthalenes. It is, of course, also possible to use mixtures of solvents. Solutions can be prepared in the usual way, if necessary, with assistance of solution promoters. Other liquid forms which can be used consist of emulsions or suspensions of the active compound in water or suitable inert solvents, or also concentrates for preparing such emulsions, which can be directly adjusted to the required concentration. For this purpose, the active ingredient is, for example, mixed with a dispersing or emulsifying agent. The active component can also be

dissolved or dispersed in a suitable inert solvent and mixed simultaneously or subsequently with a dispersing or emulsifying agent.

It is also possible to use semi-solid carrier substances of a cream ointment, paste or wax-like nature, into which the active component can be incorporated, if necessary, with the aid of solution promoters and/or emulsifiers. Vaseline and other cream bases are examples of semi-solid carrier substances. (VASELINE is a Registered Trade Mark).

Furthermore, it is possible for the active component to be used in the form of aerosols. For this purpose, the active component is dissolved or dispersed, if necessary, with the aid of suitable inert solvents as carrier liquids, such as difluorodichloromethane, which at atmospheric pressure boils at a temperature lower than room temperature, or in other volatile solvents. In this way, solutions under pressure are obtained which, when sprayed, yield aerosols which are particularly suitable for controlling or combatting fungi and bacteria, e.g., in closed chambers and storage rooms, and for application to vegetation for eradicating or for preventing infections by fungi or bacteria.

The compounds of Formula I and compositions thereof can be applied by conventional methods. For example, a fungus or bacterial growth or a material to be treated or to be protected against attack by fungus or bacterium can be treated with the subject compounds and the compositions thereof by dusting, sprinkling, spraying, brushing, dipping, smearing, impregnating or other suitable means.

When the compounds of Formula I are employed in combination with suitable carriers, e.g., in solution, suspension, dust, powder, ointment or emulsion, a high activity over a very high range of dilution is observed. For example, concentrations of the active ingredient ranging from 0.1 to 10 percent by weight, based on the weight of composition employed, have been found effective in combatting fungi or bacteria. Of course, higher concentrations may also be employed as warranted by the particular situation.

The following examples XIV to XXV are intended to illustrate, but not to limit, the scope of the present invention. Unless otherwise stated, all parts are by weight.

EXAMPLE I

A mixture of 11 parts of N-acetylamidazole and 19 parts of phenacylbromide in 40 parts of acetonitrile is stirred and refluxed for 2 hours. The solvent is evaporated *in vacuo*. The residue is taken up in hot water and the solution is cooled and filtered. To the aqueous filtrate is added a solution of sodium carbonate in water till pH 9: the product is precipitated immediately. It is filtered off and recrystallized twice: first from hot water and then from a mixture of diisopropylether and 2-propanol,

yielding 1 - (benzoylmethyl)imidazole; m.p. 114—117°C.

By repeating the procedure of Example I and replacing phenacylbromide by an equivalent amount of the appropriate ketone, the following compounds are obtained:

1 - [(4 - methylbenzoyl)methyl]imidazole; m.p. 133—134°C.

1 - (4 - methylbenzoylmethyl)imidazole hydrochloride; m.p. 210.5—216°C.

1 - (4 - chlorobenzoylmethyl)imidazole hydrochloride; m.p. 228—229°C.

EXAMPLE II

To a solution of 20.4 parts of imidazole in 40 parts of methanol are added 23.3 parts of *o*-chlorophenacylbromide and the whole is stirred for 2 hours at 0°C. The solvent is evaporated *in vacuo*. The residue is poured onto water. The product, 2' - chloro - 2 - (1-imidazolyl)acetophenone, is extracted with chloroform. From the residual free base, the hydrochloride salt is prepared in the usual manner, yielding, after two recrystallizations: first from a mixture of 2-propanol and diisopropylether and then from a mixture of methanol and diisopropylether, 2' - chloro - 2 - (1 - imidazolyl)acetophenone hydrochloride; m.p. 186.5—189°C.

EXAMPLE III

To a solution of 276 parts of *p*-fluoroacetophenone in 400 parts of dioxane and 640 parts of dry ether are added dropwise 320 parts of bromine, while cooling on ice and stirring. The mixture is then brought to room temperature and the solvent is removed *in vacuo*, till an internal temperature of 110°C. is obtained. The residue is cooled on an ice-salt bath and there are added 640 parts of acetone. At a temperature of 0°C; there is added a solution of 528 parts of imidazole in 640 parts of methanol, while stirring. The whole is further stirred for 3 hours while cooling. The solvent is removed at atmospheric pressure till 125°C internal temperature. To the residue are added, after cooling, 750 parts of chloroform and 500 parts of water. The chloroform layer is separated, stirred for 30 minutes, washed with water, dried, filtered and evaporated. From the residue containing 1 - (*p*-fluorophenacyl)imidazole, the hydrochloride salt is prepared in the usual manner. The crude salt is recrystallized twice from a mixture of 2-propanol, methanol and diisopropylether. The free base is again liberated by treatment with an equivalent amount of sodium hydroxide and after recrystallization from a mixture of 2-propanol and diisopropylether, about 178 parts of 1-(*p*-fluorophenacyl)imidazole are obtained; m.p. 149—155°C.

By repeating the procedure of Example III and replacing *p*-fluoroacetophenone by an equivalent amount of an appropriate methyl-aryl-

ketone or by 2-methylpropiofenone, the following compounds are obtained:

3' - chloro - 2 - (1 - imidazolyl)acetophenone nitrate; mp. 179.7°C.

4' - bromo - 2 - (1 - imidazolyl)acetophenone; mp. 164°C.

2',4' - dichloro - 2 - (1 - imidazolyl)acetone nitrate; mp. 164.5°C.

2 - (1 - imidazolyl) - 2' - methylacetophenone nitrate; mp. 165.5—167°C.

2 - (1 - imidazolyl) - 2' - methoxyacetophenone hydrochloride; mp. 208°C.

(1 - imidazolylmethyl) - 2 - thienylketone nitrate; mp. 136°C.

2 - (1 - imidazolyl) - 2 - methylpropiofenone nitrate; mp. 167.5°C.

EXAMPLE IV

To a cooled (5°—15°C) slurry of 120 parts of imidazole in 125 parts of dimethylformamide is added portionwise 82 parts of 2-(5-chloro - 2 - thienyl)acetyl bromide in 125 parts of dimethylformamide. After the addition is complete, the whole is stirred on ice for 2 hours. The reaction mixture is poured onto water, whereupon the product, (5 - chloro - 2 - thienyl) - (1 - imidazolylmethyl)ketone is precipitated. It is filtered off and taken up in 750 parts of chloroform, washed with water and the chloroform evaporated. The residue is triturated in ether and filtered off again, yielding the free base, m.p. 104—106°C. From this fraction, 4.4 parts are converted into the nitrate salt, yielding, after recrystallization of the crude solid salt from ethanol, 3.7 parts of (5 - chloro - 2 - thienyl) - (1 - imidazolylmethyl)ketone nitrate; mp. 161.5°C.

By repeating the procedure of Example IV and replacing imidazole by an equivalent amount of the appropriate imidazole when required and the 2 - (5 - chloro - 2 - thienyl)acetyl bromide by an equivalent amount of an appropriate acetophenone or propiofenone, the following compounds are obtained:

4' - chloro - 2 - (1 - imidazolyl)isobutyrophenone nitrate; mp. 178.2°C.

4' - chloro - 2 - (2 - methyl - 1 - imidazolyl)acetophenone; mp. 209.5°C.

4' - chloro - 2 - (2 - ethyl - 1 - imidazolyl)acetophenone; mp. 160°C.

4' - chloro - 2 - (2,4 - dimethyl - 1 - imidazolyl)acetophenone; mp. 185.8°C.

2',4' - dichloro - 2 - (2 - methyl - 1 - imidazolyl)acetophenone

2' - methoxy - 2 - (2 - methyl - 1 - imidazolyl)acetophenone

(5 - chloro - 2 - thienyl) - (2 - methyl - 1 - imidazolylmethyl)ketone

4' - bromo - 2 - (2 - ethyl - 1 - imidazolyl)acetophenone

2 - (2 - ethyl - 1 - imidazolyl) - 2' - methylacetophenone

(2 - ethyl - 1 - imidazolylmethyl) - 2 - thienylketone

- 2 - (2 - ethyl - 1 - imidazolyl) - 2 - methyl-
propiofenone
2 - (2,4 - dimethyl - 1 - imidazolyl)aceto-
phenone
5 4' - methyl - 2 - (2,4 - dimethyl - 1 - imid-
azolyl)acetophenone
2' - methoxy - 2 - (2,4 - dimethyl - 1 - imid-
azolyl)acetophenone
10 2',4' - dichloro - 2 - (2,4 - dimethyl - 1 -
imidazolyl)acetophenone
2',4',6' - trichloro - 2 - (2,4 - dimethyl - 1 -
imidazolyl)acetophenone

EXAMPLE V

- To a stirred and hot (60—80°C) solution
of 155 parts of *p*-chloroacetophenone in 250
parts of propylene glycol are added dropwise
160 parts of bromine and the whole is further
stirred overnight. The reaction mixture is
poured onto diluted sodium hydroxide solution
and the product is extracted with benzene.
The extract is dried and evaporated *in vacuo*.
The oily residue is distilled, yielding 220 parts
of oily 2 - (bromomethyl) - 2 - (*p* - chloro-
phenyl) - 4 - methyl - 1,3 - dioxolane; bp.
25 131—133°C. at 1.25 mm. pressure. On
trituration the distillate in 400 parts of 2-
propanol while cooling, the oil solidifies. It
is filtered off and recrystallized from
2-propanol, yielding 2-(bromomethyl)-2-(*p*-
chlorophenyl) - 4 - methyl - 1,3 - dioxolane;
30 mp. 71°C.

- Following the procedure of Example V and
replacing the acetophenone and the glycol used
therein by an equivalent amount of an appropri-
ate ketone and resp. an appropriate glycol,
35 the following compounds are obtained:

- 2 - (bromomethyl) - 2 - *o* - tolyl - 1,3 - dioxo-
lane; bp. 113—115°C at 0.8 mm. pressure.
2 - (bromomethyl) - 2 - *p* - tolyl - 1,3 - dioxo-
40 lane; bp. 135—137°C at 2.5 mm. pressure.
2 - (bromomethyl) - 2 - (2,5 - dichlorophenyl)-
1,3-dioxolane; mp. 61.5°C.
2 - (bromomethyl) - 2 - *m* - tolyl - 1,3 - dioxo-
lane; mp. 59°C.
45 2 - (bromomethyl) - 2 - (*o* - methoxyphenyl)-
1,3-dioxolane; mp. 99—100°C.
2 - (bromomethyl) - 2 - (*p* - fluorophenyl)-
1,3-dioxolane; mp. 50°C.

EXAMPLE VI

- 50 37.8 Parts of methyl-2-thienyl-ketone are
brominated with 48 parts of bromine in 48
parts of dioxane and 96 parts of dry ether,
while cooling and stirring. The solvent is
removed *in vacuo*. To the residue is added
55 60 parts of ethylene glycol in 160 parts of
toluene and a few crystals of *p*-toluenesulfonic
acid. The whole is stirred and refluxed in an
apparatus equipped with a watertrap for 15
hours. The reaction mixture is cooled and the
60 toluene layer is separated, washed once with
potassium carbonate solution and once with

water, dried, filtered and evaporated *in vacuo*.
The oily residue is distilled *in vacuo* from
potassium carbonate, yielding 2 - (bromo-
methyl) - 2 - (2 - thienyl) - 1,3 - dioxolane;
bp. 95°C. at 0.6 mm. pressure.

Repeating the procedure of Example VI
and replacing the acetophenone and the glycol
used therein by an equivalent amount of an
appropriate ketone and an appropriate glycol,
the following dioxolanes are prepared:

- 2 - bromomethyl - 2 - (*o* - chlorophenyl) - 1,3-
dioxolane, bp. 130°C at 0.8 mm. pressure.
2 - (bromomethyl) - 2 - (*m* - methoxyphenyl)-
1,3-dioxolane; mp. 61°C.
2 - (bromomethyl) - 2 - (2,3,4 - trichloro-
phenyl)-1,3-dioxolane; mp. 59.5°C.
2 - bromomethyl - 2 - (*m* - chlorophenyl)-
1,3 - dioxolane; bp. 149°C at 0.2 mm.
pressure.

EXAMPLE VII

To a solution of 23 parts of sodium in 600
parts of ethanol are added 154 parts of ethyl
5 - methylimidazole - 4 - carboxylate. Then
440 parts of ethanol are evaporated off and
to the warm residue are added 1600 parts of
2 - diisopropylether. Upon cooling, the sodium
salt is precipitated. It is filtered off, yielding
the sodium salt of ethyl 5-methylimidazole-4-
carboxylate.

A mixture of 17.7 parts of ethyl 5-methyl-
imidazole-4-carboxylate, sodium salt, 35 parts
of 2 - bromomethyl - 2 - (*p* - chlorophenyl)-
1,3-dioxolane [described in Patel A. R., J.
Pharm. Sci., 52(6), 588—592 (1963)], 22.5
parts of potassium iodide, 30 parts of
dimethylformamide and 4 parts of toluene is
stirred and refluxed for 12 hours. The reaction
mixture is cooled and 400 parts of ether are
added. The organic phase is washed three
times with water, dried and an excess of con-
centrated nitric acid is added. The precipitated
nitrate salt is filtered off and recrystallized
from a mixture of 40 parts of absolute ethanol
and 400 parts of diisopropyl ether, yielding
ethyl 1 - [2 - (*p* - chlorophenyl) - 1,3 - di-
oxolan - 2 - ylmethyl] - methylimidazole - 4-
carboxylate nitrate; mp. 130.3°C.

A mixture of 2 parts of ethyl 1 - [2 - (*p*-
chlorophenyl) - 1,3 - dioxolan - 2 - ylmethyl] -
5 - methylimidazole - 4 - carboxylate nitrate
and 7.5 parts of sodium hydroxide solution
10N is stirred and refluxed for 15 minutes.
Then 20 parts of water are added, followed by
the addition of 4.5 parts of acetic acid, where-
upon the product is precipitated. It is filtered
off and recrystallized from 80 parts of ethanol,
yielding 1 - [2 - (*p* - chlorophenyl) - 1,3-
dioxolan - 2 - ylmethyl] - 5 - methylimid-
azole-4-carboxylic acid; mp. 258.3°C.

To 40 parts of paraffin oil are added portion-
wise 25 parts of 1 - [2 - (*p* - chlorophenyl)-
1,3 - dioxolan - 2 - ylmethyl] - 5 - methyl-
imidazole-4-carboxylic acid at 250°C. The

mixture is heated to 270°C, till no more carbon dioxide is evolved. The reaction mixture is cooled and 240 parts of ether are added. The solution is filtered and to the filtrate is added an excess of concentrated nitric acid solution. The precipitated nitrate salt is filtered off and recrystallized from a mixture of 120 parts of ethanol and 340 parts of diisopropylether, yielding 1-[2-(*p*-chlorophenyl)-1,3-dioxolan-2-ylmethyl]-5-methylimidazole nitrate; mp. 153.6°C.

A mixture of 13 parts of 1-[2-(*p*-chlorophenyl)-1,3-dioxolan-2-ylmethyl]-5-methylimidazole, 100 parts of acetic acid and 50 parts of dilute hydrochloric acid is stirred and refluxed for 18 hours. The solvents are evaporated off and to the residue is added successively 100 parts of water and an excess of sodium hydroxide, whereupon the product, 4'-chloro-2-(5-methyl-1-imidazolyl)acetophenone, is precipitated. It is filtered off and recrystallized from dimethylformamide 10% (50 parts), yielding 6.5 parts of 4'-chloro-2-(5-methyl-1-imidazolyl)acetophenone; mp. 123°C.

EXAMPLE VIII

The procedure of Example VII demonstrates a method of preparing the 5-methylimidazolyl ketones of formula (II). By repeating such procedure, except that an equivalent quantity of each of the dioxolan derivatives obtained in Examples V and VI is substituted for the 2-bromomethyl-2-(*p*-chlorophenyl)-1,3-dioxolan used in Example VII, the following ketones are obtained as respective products:

(1-imidazolylmethyl)-2-thienylketone;
2'-chloro-2-(5-methyl-1-imidazolyl)acetophenone;
2'-methyl-2-(5-methyl-1-imidazolyl)acetophenone;
4'-methyl-2-(5-methyl-1-imidazolyl)acetophenone;
3'-methoxy-2-(5-methyl-1-imidazolyl)acetophenone;
2',5'-dichloro-2-(5-methyl-1-imidazolyl)acetophenone;
3'-methyl-2-(5-methyl-1-imidazolyl)acetophenone;
2',3',4'-trichloro-2-(5-methyl-1-imidazolyl)acetophenone;
2'-methoxy-2-(5-methyl-1-imidazolyl)acetophenone;
3'-chloro-2-(5-methyl-1-imidazolyl)acetophenone; and
4'-fluoro-2-(5-methyl-1-imidazolyl)acetophenone.

EXAMPLE IX

The procedure of Example VII is repeated except that an equivalent quantity of each of the following known dioxolane derivatives:

2-bromomethyl-2-phenyl-1,3-dioxolane;
2-bromomethyl-2-(*p*-bromophenyl)-1,3-dioxolane;
2-bromomethyl-2-(*p*-methoxyphenyl)-1,3-dioxolane; and
2-(2-bromoisopropyl)-2-phenyl-1,3-dioxolane,

is substituted for the 2-bromomethyl-2-(*p*-chlorophenyl)-1,3-dioxolane used therein to yield the following respective 5-methylimidazolyl ketones of formula (II):

2-(5-methyl-1-imidazolyl)acetophenone;
4-bromo-2-(5-methyl-1-imidazolyl)acetophenone;
4-methoxy-2-(5-methyl-1-imidazolyl)acetophenone; and
2-(5-methyl-1-imidazolyl)-2-methylpropiofenone.

EXAMPLE X

To a suspension of 40 parts of 1-(*p*-chlorobenzoylmethyl)imidazole in 120 parts of methanol are added portionwise 4 parts of sodium borohydride while cooling on ice and while stirring. After 30 minutes, the reaction mixture is stirred and refluxed for one hour and 100 parts of water are added. The methanol is removed at atmospheric pressure. Then there are added 16 parts of concentrated hydrochloric acid solution and the whole is stirred and refluxed for 5 minutes. After cooling on ice-bath, an excess of ammonium hydroxide solution is added, whereupon the alcohol product is precipitated. It is filtered off, washed with water and recrystallized from a mixture of dimethylformamide and water, yielding α -(*p*-chlorophenyl)imidazole-1-ethanol; mp. 180°C.

The procedure of Example X is repeated except that an equivalent amount of an appropriate starting ketone is substituted therein, to yield as respective products, the following alcohols, some of which have been converted to the indicated acid addition salt by treatment in the conventional manner with the appropriate acid.

α -(*o*-chlorophenyl)imidazole-1-ethanol nitrate; mp. 143°C.
 α -(*p*-fluorophenyl)imidazole-1-ethanol; mp. 146.5°C.
 α -(2,4-dichlorophenyl)imidazole-1-ethanol; mp. 136.5°C.
 α -*o*-tolylimidazole-1-ethanol nitrate; mp. 131°C.
 α -*p*-tolylimidazole-1-ethanol; mp. 155°C.
 α -(phenyl)imidazole-1-ethanol;
 α -(*m*-chlorophenyl)imidazole-1-ethanol; mp. 109.8°C.

α - (*p* - bromophenyl)imidazole - 1 - ethanol; mp. 188.5°C.

α - (*o* - methoxyphenyl)imidazole - 1 - ethanol hydrochloride; mp. 171.5°C.

5 α - (5 - chloro - 2 - thienyl)imidazole - 1 - ethanol; mp. 131.5°C.

α - (2 - thienyl)imidazole - 1 - ethanol;
 β, β - dimethyl - α - phenylimidazole - 1 - ethanol; mp. 139°C.

10 α - (*p* - chlorophenyl) - β, β - dimethylimidazole - 1 - ethanol; mp. 187.5°C.

α - (*p* - chlorophenyl) - 2 - methyl - 1 - imidazoleethanol; mp. 165.5°C.

15 α - (*p* - chlorophenyl) - 5 - methylimidazole - 1 - ethanol; mp. 194°C.

α - (*p* - chlorophenyl) - 2,4 - dimethylimidazole - 1 - ethanol; mp. 128.8°C.

α - (*p* - chlorophenyl) - 2 - ethyl - 1 - imidazoleethanol; mp. 151.5°C.

EXAMPLE XI

20 To a sodium methoxide solution, prepared from 9.2 parts of sodium in 140 parts of methanol, are added successively 27.2 parts of imidazole and 100 parts of dimethylformamide. The solvent is removed at atmospheric pressure while stirring. At an internal temperature of 130°C (all of the methanol has been removed), there are added 47 parts of
25 α - chloro - methyl - α - methylbenzyl alcohol. The whole is stirred at 130°C for one hour. After the addition of 500 parts of water, the alcohol product is crystallized. It is filtered off and recrystallized from toluene, yielding
30 α - methyl - α - phenylimidazole - 1 - ethanol, mp. 119.5°C.

35 By repeating the procedure of Example XI and replacing α - chloromethyl - α - methylbenzyl alcohol by an equivalent amount of
40 α - chloromethyl - α - methyl - (*p* - chlorobenzyl)alcohol, the following compound is obtained:

α - (*p* - chlorophenyl) - α - methylimidazole - 1 - ethanol; mp. 140°C.

EXAMPLE XII

45 To a suspension of 4.5 parts of sodium methoxide solution 30% in 15 parts of dimethylformamide and 16 parts of benzene are added 2 parts of imidazole. The solvent is distilled off till an internal temperature of 130°C is reached. Then there is added a solution of
50 5.4 parts of α - (bromomethyl) - 3,4 - dichlorobenzyl alcohol in 5.5 parts of benzene (temperature: 130° to 115°C), and the solvent is distilled off. The temperature is brought again to 130°C and then cooled slowly to 40°C. Diisopropylether (32 parts) is added, followed by the addition of 50 parts of water and upon cooling, the product is crystallized. It is filtered off, washed with ether and boiled for a few
55 minutes in a mixture of 25 parts of dimethylformamide and 5 parts of water. The product is crystallized again at room temperature and
60

separated, yielding α - (3,4 - dichlorophenyl)imidazole - 1 - ethanol; mp. 148.7°C.

By repeating the procedure of Example XII and replacing the α - (bromomethyl) - 3,4 - dichlorobenzyl alcohol therein by an equivalent amount of an appropriate starting alcohol, the following compounds are prepared:

α - (2,5 - dichlorophenyl)imidazole - 1 - ethanol; mp. 145.3°C.

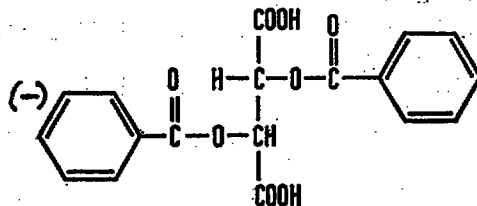
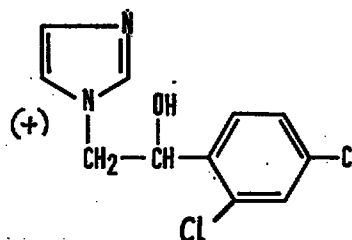
α - (2,6 - dichlorophenyl)imidazole - 1 - ethanol; mp. 131.6°C.

α - (2,4,6 - trichlorophenyl)imidazole - 1 - ethanol; mp. 151.8°C.

EXAMPLE XIII

This example demonstrates the resolution of a typical formula (V) alcohol into its optical isomers.

154.8 parts of α - (2,4 - dichlorophenyl)imidazole - 1 - ethanol (obtained from Example X) are suspended in 960 parts of acetone at 50°C. The addition of 107.4 parts of dibenzoyl D-tartaric acid dissolved in 120 parts of acetone results in a one-phase system. This solution is filtered at 50°C. The temperature is allowed to fall to 20°C (2 hours) and the product is removed by filtration (filtrate A). It is washed with 400 parts acetone. The product consists of the diastereoisomeric salt of (+) - α - (2,4 - dichlorophenyl)imidazole - 1 - ethanol with dibenzoyl D-tartaric acid. The compound is a one-to-one addition product, since analytical data correspond to the following structure:



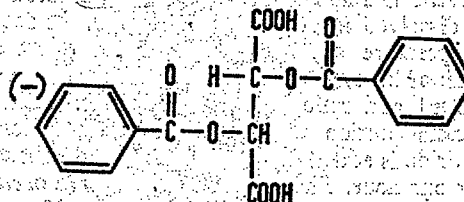
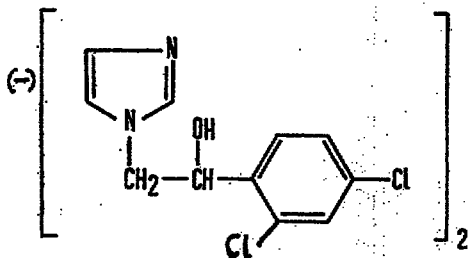
The yield of the dibenzoyl D-tartaric acid compound with (+) - α - (2,4 - dichlorophenyl)imidazole - 1 - ethanol (1:1) amounts to 101 parts (54.3%); α_D^{20} - 20° (c=1, methanol). Liberation of the corresponding free base by conventional treatment of the salt with strong alkali affords 33.5 parts of (+) - α - (2,4 - dichlorophenyl)imidazole - 1 - ethanol; mp.

112—115.2°C. This is the dextro-rotatory enantiomer, having a specific rotation of $\alpha_D^{20} +100^\circ$ ($c=1$, methanol).

The original mother-liquor (filtrate A) therefore contains 34.8 parts of (+) - α - (2,4-dichlorophenyl)imidazole - 1 - ethanol; 77.4 parts of (-) - α - (2,4 - dichlorophenyl)imidazole-1-ethanol; and 49 parts of dibenzoyl D-tartaric acid. Acidification with 2-propanol/HCl causes deposition of the hydrochloride salts of (+) - α - (2,4 - dichlorophenyl)imidazole-1 - ethanol and of (-) - α - (2,4 - dichlorophenyl)imidazole - 1 - ethanol. The yield amounts to 84 parts and the material has a specific rotation of $\alpha_D^{20} -18^\circ$ ($c=1$, methanol); therefore an excess of the (-) form with respect to the (+) form is indicated.

Nonetheless, a part of ($\pm$) - α - (2,4 - dichlorophenyl)imidazole - 1 - ethanol remains in solution, (because, after filtration of the hydrochloride it is possible to isolate from the filtrate another 14 parts of ($\pm$) - α - (2,4-dichlorophenyl)imidazole - 1 - ethanol. The latter is filtered and the filtrate is evaporated and the residue is dissolved in water. This aqueous solution is made alkaline and extracted with chloroform. The solvent is evaporated and the residue is crystallized from acetone, yielding 14 parts of ($\pm$) - α - (2,4 - dichlorophenyl)imidazole-1-ethanol. The specific rotation of the latter is $\alpha_D^{20} -80^\circ$ ($c=1$, methanol). This means that this 14 parts consists of 10% of (+) - α - (2,4 - dichlorophenyl)imidazole-1-ethanol and 90% of (-) - α - (2,4 - dichlorophenyl)imidazole - 1 - ethanol (assuming -100° to be the specific rotation of the pure enantiomer).

The following manipulations describe the optical purification of this (-)-enriched fraction. Addition of 3 parts of dibenzoyl D-tartaric acid to a solution of 111 parts (taken from the above-mentioned 14 parts) in 80 parts of acetone causes deposition of a crystalline salt, consisting of dibenzoyl D-tartaric acid salt of (-) - α - (2,4 - dichlorophenyl)imidazole-1-ethanol (1:2). The specific rotation is $\alpha_D^{20} -100^\circ$ ($c=1$, methanol). This salt corresponds, upon analytical data, to the following structure:



A sample of 7 parts of this diastereoisomeric salt gives, after liberation of the free base, 3 parts of (-) - α - (2,4 - dichlorophenyl)imidazole - 1 - ethanol; mp. 111.4—113.4°C; with a specific rotation of $\alpha_D^{20} -99^\circ$ ($c=1$, methanol).

EXAMPLE XIV

A solution of 18.6 parts of 1-(benzoylmethyl)imidazole and 14.5 parts of β -phenethylamine in 160 parts of dry benzene containing a little amount of *p*-toluenesulphonic acid is stirred and refluxed in an apparatus equipped with a water trap. After 24 hours the theoretical amount of water is evolved. The solvent is removed *in vacuo*. The residue is dissolved in 120 parts of ethanol and this solution is hydrogenated at an initial pressure of 4.5 kg/cm² at room temperature in the presence of 3 parts of palladium-on-charcoal catalyst 5%. After the calculated amount of hydrogen is taken up, hydrogenation is stopped. The solution is filtered and the solvent is removed *in vacuo*. The residue is dissolved in acetone and to this solution is added an excess of nitric acid solution (conc.) in diisopropylether: the nitrate salt separates out as an oil. The solvent is decanted and to the residue is added a new volume of acetone together with a little amount of diisopropylether whereupon the solid salt crystallizes out. It is filtered off, washed with acetone and recrystallized from a mixture of methanol, acetone and diisopropylether, yielding 1 - (β - phenethylamino)phenethylimidazole dinitrate; mp. 164.5—168°C.

By repeating the procedure of Example XIV and replacing β -phenethylamine by an equivalent amount of an appropriate amine, the following imidazole amines are obtained:

- 1 - (β - anilinophenethyl)imidazole dihydrochloride; mp. 217.5—230°C (dec.).
- 1 - [β - (1 - tetralinylamino)phenethyl]imidazole nitrate; mp. 139—143°C.

EXAMPLE XV

A solution of 18.6 parts of 1 - (benzoylmethyl) - imidazole and 12.9 parts of benzylamine in 80 parts of benzene containing a little amount (about 0.5 parts) of *p*-toluenesulphonic acid is stirred and refluxed for 4 hours. (The reaction vessel is provided with a reflux-condensor and water-separator). The

5 solvent is removed *in vacuo* and the residue is dissolved in 120 parts of ethanol. At room temperature a first portion of 3.8 parts of sodium borohydride is added and the whole is stirred and refluxed for 30 minutes. Then a second portion of 3.8 parts of sodium borohydride is added and again stirred and refluxed for one hour. The solvent is removed *in vacuo*.
10 To the residue is added successively 100 parts of water and 70 parts of a concentrated hydrochloric acid solution (pH: 2—3). This solution is stirred and refluxed for one hour. After cooling on ice, it is filtered and the filtrate is made alkaline (strongly) with a 10N sodium hydroxide solution and the free base is
15 extracted with methylene chloride. The extract is washed with water, dried, filtered and evaporated *in vacuo*. The residue free base is

dissolved in acetone and to this solution is added an excess of 2-propanol previously saturated with gaseous hydrogen chloride. On further addition of diisopropylether, the hydrochloride salt is precipitated. It is filtered off and recrystallized twice: first from a mixture of methanol and diisopropylether and then from a mixture of ethanol and diisopropylether, yielding 1-(β -benzylaminophenethyl)-imidazole dihydrochloride; mp. 263.5—266.5°C.

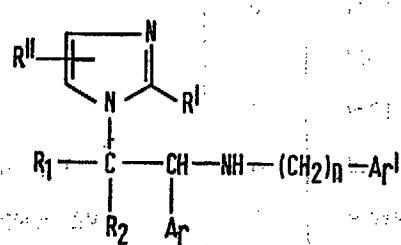
The reductive amination procedure of Example XV is repeated except that an equivalent quantity of an appropriate ketone and an equivalent quantity of an appropriate amine are substituted therein as starting materials to yield the following imidazole amines:

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R'	R''	R ₁	R ₂	Ar	n	Ar'	salt m.p. (°C)
H	H	H	H	Ph	1	<i>p</i> -Cl-Ph	2HCl 264.5—266.5
H	H	H	H	Ph	2	Ph	2HCl 167—171
H	H	H	H	Ph	1	<i>m</i> -Cl-Ph	2HCl 251—255
H	H	H	H	Ph	1	<i>o</i> -Cl-Ph	2HCl 239.5—251.5
H	H	H	H	<i>p</i> -Me-Ph	1	<i>p</i> -Cl-Ph	2HCl 264—265
H	H	H	H	<i>p</i> -Cl-Ph	1	<i>p</i> -MeO-Ph	2HCl 232—250
H	H	H	H	<i>p</i> -Me-Ph	1	<i>p</i> -MeO-Ph	2HCl 246—248
H	H	H	H	<i>p</i> -Me-Ph	2	Ph	2HNO ₃ 148—154
H	H	H	H	<i>p</i> -Cl-Ph	1	Ph	2HCl 213—215
H	H	H	H	<i>p</i> -Cl-Ph	0	Ph	2HCl 201—221 (dec.)
H	H	H	H	<i>p</i> -Cl-Ph	1	<i>o</i> -Cl-Ph	2HCl 224—227
H	H	H	H	<i>p</i> -Cl-Ph	1	<i>o</i> -Cl-Ph	2HNO ₃ 194—197.5
H	H	H	H	<i>p</i> -Cl-Ph	2	Ph	2HNO ₃ 145.5—148
H	H	H	H	Ph	1	<i>p</i> -Me-Ph	2HCl 260—261

R'	R''	R ₁	R ₂	Ar	n	Ar'	salt m.p. (°C)
H	H	H	H	Ph	1	<i>p</i> -MeO—Ph	2HCl 258—259
H	H	H	H	<i>p</i> -Cl—Ph	1	<i>p</i> -Me—Ph	2HCl 279—288
H	H	H	H	<i>p</i> -Cl—Ph	0	1-tetralinyl	2HCl 193—196 3H ₂ O
H	H	H	H	<i>p</i> -F—Ph	1	Ph	2HNO ₃ 210—212
H	H	H	H	<i>p</i> -F—Ph	1	O—Cl—Ph	2HNO ₃ 205.5—207.5
H	H	H	H	<i>p</i> -F—Ph	1	<i>p</i> -MeO—Ph	2HNO ₃ 164.5—183 (dec.)
H	H	H	H	<i>p</i> -F—Ph	2	Ph	2HNO ₃ 152—153.5
H	H	H	H	<i>p</i> -F—Ph	1	<i>p</i> -Me—Ph	2HNO ₃ 208—209
H	H	H	H	<i>p</i> -F—Ph	0	1-tetralinyl	2HNO ₃ 122—136
H	H	H	H	<i>p</i> -F—Ph	1	<i>p</i> -Cl—Ph	2HNO ₃ 213.5
H	H	H	H	2-thienyl	1	<i>p</i> -Cl—Ph	2HCl 263.5
H	H	H	H	5-Cl-2-thienyl	1	<i>p</i> -Me—Ph	2HNO ₃
H	H	H	H	5-Cl-2-thienyl	2	Ph	2HCl
H	H	H	H	2-thienyl	0	Ph	2HNO ₃
H	H	H	H	<i>o</i> , <i>p</i> -di-Cl—Ph	1	<i>p</i> -Me—Ph	2HNO ₃
H	H	H	H	<i>o</i> -MeO—Ph	1	<i>p</i> -MeO—Ph	2HCl
H	H	H	H	<i>p</i> -Br—Ph	0	Ph	2HCl
H	H	Me	Me	Ph	1	<i>p</i> -Cl—Ph	2HNO ₃
H	H	Me	Me	Ph	1	Ph	2HCl
H	H	Me	Me	Ph	0	1-tetralinyl	2HNO ₃

R'	R''	R ₁	R ₂	Ar	n	Ar'	salt m.p. (°C)
H	H	Me	Me	Ph	2	Ph	2HCl
H	H	Me	Me	Ph	1	<i>p</i> -Me-Ph	2HNO ₃
H	H	Me	Me	Ph	1	<i>p</i> -MeO-Ph	2HNO ₃
Me	H	H	H	<i>o</i> - <i>p</i> -di-Cl-Ph	1	<i>p</i> -MeO-Ph	base
Me	H	H	H	<i>o</i> -MeO-Ph	2	Ph	base
Me	H	H	H	<i>p</i> -Cl-Ph	1	<i>o</i> -Cl-Ph	base
Me	H	H	H	<i>o</i> , <i>p</i> -di-Cl-Ph	1	<i>p</i> -Me-Ph	base
Me	H	H	H	<i>p</i> -Cl-Ph	0	1-tetralinyl	base
Et	H	H	H	<i>o</i> -Me-Ph	1	<i>p</i> -MeO-Ph	base
Et	H	H	H	<i>p</i> -Br-Ph	2	Ph	base
Et	H	H	H	2-thienyl	1	<i>p</i> -Cl-Ph	base
Et	H	H	H	5-Cl-2-thienyl	1	<i>p</i> -Me-Ph	base
Et	H	Me	Me	Ph	2	Ph	base
Me	4-Me	H	H	Ph	0	Ph	2HCl
Me	4-Me	H	H	Ph	2	Ph	2HNO ₃
Me	4-Me	H	H	Ph	0	1-tetralinyl	2HNO ₃
Me	4-Me	H	H	<i>p</i> -Cl-Ph	1	<i>p</i> -MeO-Ph	2HCl
Me	4-Me	H	H	<i>p</i> -Cl-Ph	1	<i>p</i> -Me-Ph	2HCl
Me	4-Me	H	H	<i>p</i> -Me-Ph	1	<i>o</i> -Cl-Ph	2HNO ₃
Me	4-Me	H	H	<i>p</i> -MeO-Ph	1	Ph	2HNO ₃
Me	4-Me	H	H	<i>o</i> , <i>p</i> -di-Cl-Ph	2	Ph	2HNO ₃

R'	R''	R ₁	R ₂	Ar	n	Ar'	salt m.p. (°C)
Me	4—Me	H	H	<i>o, m, p</i> -tri-Cl—Ph	1	Ph	2HNO ₃
H	5—Me	H	H	Ph	0	Ph	2HCl
H	5—Me	H	H	Ph	2	Ph	SHNO ₃
H	5—Me	H	H	Ph	0	1-tetralinyl	2HNO ₃
H	5—Me	H	H	<i>p</i> -Cl—Ph	1	<i>p</i> -MeO—Ph	2HCl
H	5—Me	H	H	<i>p</i> -Cl—Ph	1	<i>p</i> -Me—Ph	2HCl
H	5—Me	H	H	<i>o, m, p</i> -tri-Cl—Ph	1	Ph	2HNO ₃
H	5—Me	H	H	2-thienyl	1	<i>p</i> -Cl—Ph	2HCl
H	5—Me	Me	Me	Ph	1	Ph	2HCl

EXAMPLE XVI

5 A solution of 140 parts of imidazole, 240 parts of 2-phenylethylene oxide, 400 parts of denatured absolute ethanol and 8 parts of pyridine is heated to reflux (an exothermic reaction occurs, requiring ice-bath moderation). Upon completion of the exotherm (about 15—30 minutes), the mixture is allowed to cool to 10 50°C. Then there are added 240 parts of diisopropylether and the whole is poured onto 1000 parts of water. The crude product is filtered off after cooling, triturated in ice-cold acetone, filtered off again, washed with ice-cold acetone and then with ether, to yield 15 1 - (β - hydroxyphenethyl)imidazole; m.p. 149—150°C.

20 80 Parts of 1 - (β - hydroxyphenethyl)-imidazole are dissolved in 250 parts of dry hexamethylphosphortriarnide at about 40°C, while anti-foam is added. This solution is

added, over a one hour period to 22 parts of a sodium hydride dispersion in 100 parts of dry hexamethylphosphortriarnide, while cooling at 5—15°C. Upon completion, the whole 25 is allowed to come to room temperature (about 30 minutes). After stirring for one hour at 45—50°C., the mixture is cooled to 5°C. and there is added portionwise 80 parts of *p*-chlorobenzoyl chloride, while keeping the tem- 30 perature below 25°C. The whole is stirred for 30 minutes at room temperature, further heated to 45°C. and then allowed to come to room temperature (about one hour). After the addition of 1500 parts of water, the ether 35 product, 1 - [β - (*p* - chlorobenzyloxy)-phenethyl]imidazole, is extracted three times with ether. The combined extracts are washed with water and there is added an excess of 40 nitric acid. After cooling, the precipitated nitrate salt is filtered off, triturated twice in

50% acetone/ether and dried *in vacuo*, yielding 1 - [β - (*p* - chlorobenzoyloxy)phenethyl]imidazole nitrate; m.p. 132–134°C.

By repeating the procedure of Example XVI and replacing 1 - (β - hydroxyphenethyl)imidazole and *p*-chlorobenzyl chloride by an equivalent amount of an appropriate imidazole alcohol and respectively an equivalent amount of the appropriate benzyl halide, the following compounds are prepared:

1 - [*p* - chloro - β - (2,4 - dichlorobenzoyloxy)phenethyl] - 2 - methylimidazole nitrate; mp. 117°C.

1 - [*p* - chloro - β - (2,6 - dichlorobenzoyloxy)phenethyl] - 2-methylimidazole nitrate; mp. 162.5°C.

1 - [*p* - chloro - β - (2,6 - dichlorobenzoyloxy)phenethyl] - 2 - ethylimidazole nitrate; mp. 146°C.

1 - [*p* - chloro - β - (2,4 - dichlorobenzoyloxy)phenethyl] - 2-ethylimidazole nitrate; mp. 134.5°C.

1 - [2,4 - dichloro - β - (*o* - methoxybenzoyloxy)phenethyl] - 2 - methylimidazole;

1 - [2 - methoxy - β - (*p* - methylbenzoyloxy)phenethyl] - 2-methylimidazole;

1 - [*p* - chloro - β - (*p* - chlorobenzoyloxy)phenethyl] - 2-methylimidazole;

1 - [2 - methoxy - β - (phenethyloxy)phenethyl] - 2-methylimidazole;

1 - [2 - (*o* - chlorobenzoyloxy) - 2 - (5 - chloro - 2 - thienyl)ethyl] - 2 - methylimidazole;

1 - [*p* - chloro - β - (*p* - fluorobenzoyloxy)phenethyl] - 2-ethylimidazole;

1 - [*p* - bromo - β - (phenoxy)phenethyl] - 2-ethylimidazole;

1 - [2 - methyl - β - (phenethyloxy)phenethyl] - 2-ethylimidazole;

1 - [2 - (*o* - chlorobenzoyloxy) - 2 - (2-thienyl)ethyl] - 2-ethylimidazole;

1 - [β - (*p* - chlorobenzoyloxy) - $\alpha\alpha$ - dimethylphenethyl] - 2-ethylimidazole;

1 - [*p* - chloro - β - (*p* - nitrophenoxy)phenethyl] - 2-ethylimidazole; and

1 - [2,4 - dichloro - β - (2,4 - dinitrophenoxy)phenethyl] - 2-ethylimidazole.

EXAMPLE XVII

To a stirred and refluxing solution of 40 parts of benzene and 35 parts of dimethylformamide (both solvents previously dried azeotropically) are added successively 1.6 parts of sodium hydride and 7.7 parts of α - (2,4-dichlorophenyl) - imidazole - 1 - ethanol, (cooling on ice is necessary). After the addition is complete, stirring and refluxing is continued for 30 minutes. Then there are added 7.8 parts of 2,6-dichlorobenzyl chloride and the whole is stirred at reflux for another 3 hours. The reaction mixture is poured onto water and the product 1 - [2,4 - dichloro - β - (2,6 - dichlorobenzoyloxy)phenethyl]imidazole, is ex-

tracted with benzene. The extract is washed twice with water, dried, filtered and evaporated *in vacuo*. The base residue is dissolved in a mixture of acetone and diisopropylether and to this solution is added an excess of concentrated nitric acid solution. The precipitated nitrate salt is filtered off and recrystallized from a mixture of methanol and diisopropylether, yielding 1 - [2,4 - dichloro - β - (2,6-dichlorobenzoyloxy)phenethyl]imidazole nitrate; mp. 179°C.

By repeating the procedure of Example XVII and replacing α - (2,4 - dichlorophenyl)imidazole-1-ethanol by an equivalent amount of the appropriate imidazole alcohol and replacing 2,6-dichlorobenzyl chloride by an equivalent quantity of the appropriate benzyl halide, the following compounds are obtained:

1-(β -benzyloxyphenylethyl)imidazole nitrate; mp. 93°C.

1 - [2,4 - dichloro - β - (*m* - methoxybenzoyloxy)phenethyl]imidazole nitrate; mp. 115.5°C.

1 - [2,4 - dichloro - β - (*o* - fluorobenzoyloxy)phenethyl]imidazole nitrate; mp. 146.5°C.

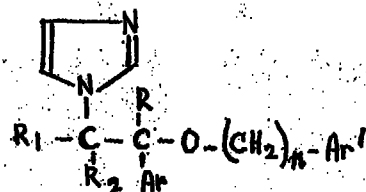
1 - [2,4 - dichloro - β - (*p* - fluorobenzoyloxy)phenethyl]imidazole nitrate; mp. 141°C.

1 - [2,4 - dichloro - β - (*p* - methoxybenzoyloxy)phenethyl]imidazole nitrate; mp. 148°C.

EXAMPLE XVIII

A suspension of 5 parts of α - (*p* - chlorophenyl)imidazole-1-ethanol and 1.1 parts of sodium hydride in 27 parts of dry tetrahydrofuran is stirred and refluxed for 2 hours, after which the evolution of hydrogen is ceased. Then there are added 30 parts of dimethylformamide and 4.8 parts of *p*-chlorobenzyl chloride and the whole is stirred and refluxed for 2 hours. The tetrahydrofuran is evaporated at atmospheric pressure and the dimethylformamide solution is poured onto water. The product is extracted with benzene. The extract is washed with water, dried, filtered and evaporated *in vacuo*. The residue is washed with petroleum ether. The latter is decanted and from the residual oily free base, 1-[*p*-chloro- β - (*p* - chlorobenzoyloxy)phenethyl]imidazole, the nitrate salt is prepared in the usual manner from nitric acid in 2-propanol. The crude solid salt is filtered off and recrystallized from a mixture of 2-propanol and diisopropylether, yielding 1 - [*p* - chloro - β - (*p* - chlorobenzoyloxy)phenethyl]imidazole nitrate; mp. 155°C.

The O-alkylation procedure of Example XVIII is repeated except that an equivalent quantity of an appropriate alcohol and an equivalent quantity of an appropriate halide are substituted therein as starting materials to yield the following imidazole ethers:



R	R ₁	R ₂	Ar	n	Ar'	m.p. (°C) b.p./mm.	salt
H	H	H	<i>p</i> -F—Ph	1	<i>p</i> -Cl—Ph	123	HNO ₃
H	H	H	<i>o</i> , <i>p</i> -di-Cl—Ph	1	<i>p</i> -Cl—Ph	162	HNO ₃
H	H	H	<i>o</i> -Cl—Ph	1	<i>p</i> -Cl—Ph	127	HNO ₃
H	H	H	<i>o</i> , <i>p</i> -di-Cl—Ph	1	<i>o</i> , <i>p</i> -di-Cl—Ph	170.5	HNO ₃
H	H	H	<i>p</i> -F—Ph	1	<i>o</i> , <i>p</i> -di-Cl—Ph	120	HNO ₃
H	H	H	<i>p</i> -Me—Ph	1	<i>o</i> , <i>p</i> -di-Cl—Ph	130.5	HNO ₃
H	H	H	<i>o</i> -Me—Ph	1	<i>o</i> , <i>p</i> -di-Cl—Ph	139.5	HNO ₃
H	H	H	<i>o</i> -Me—Ph	1	<i>p</i> -Cl—Ph	129.5	HNO ₃
H	H	H	<i>p</i> -Me—Ph	1	<i>p</i> -Cl—Ph	121.5	HNO ₃
H	H	H	<i>o</i> -Cl—Ph	1	<i>o</i> , <i>p</i> -di-Cl—Ph	128.5	HNO ₃
H	H	H	<i>p</i> -Cl—Ph	1	<i>o</i> , <i>p</i> -di-Cl—h	110.5	HNO ₃
H	H	H	<i>o</i> -MeO—Ph	1	<i>o</i> , <i>p</i> -di-Cl—Ph	132	HNO ₃
Me	H	H	Ph	1	<i>p</i> -Cl—Ph	167.5	HNO ₃
Me	H	H	Ph	1	<i>o</i> , <i>p</i> -di-Cl—Ph	179.5	HNO ₃
Me	H	H	<i>p</i> -Cl—Ph	1	<i>p</i> -Cl—Ph	167	HNO ₃
Me	H	H	<i>p</i> -Cl—Ph	1	<i>o</i> , <i>p</i> -di Cl—Ph	162.5	HNO ₃

R	R ₁	R ₂	Ar	n	Ar'	m.p. (°C) b.p./mm.)	salt
H	H	H	<i>o</i> , <i>p</i> -di-Cl-Ph	1	<i>p</i> -Me-Ph	129.5	HNO ₃
H	H	H	<i>p</i> -Cl-Ph	1	<i>o</i> -Cl-Ph	125	HNO ₃
H	H	H	<i>p</i> -F-Ph	1	<i>o</i> -Cl-Ph	95.5	HNO ₃
H	H	H	<i>p</i> -Cl-Ph	2	Ph		HNO ₃
H	H	H	<i>o</i> -Me-Ph	2	<i>p</i> -Cl-Ph		HNO ₃
H	H	H	<i>o</i> -MeO-Ph	2	<i>p</i> -Me-Ph		HNO ₃
Me	H	H	Ph	2	Ph		HNO ₃
Me	H	H	<i>p</i> -Cl-Ph	2	<i>p</i> -MeO-Ph		HNO ₃
H	H	H	<i>p</i> -F-Ph	2	<i>o</i> , <i>p</i> -di-Cl-Ph		HNO ₃
H	H	H	2-thienyl	1	<i>p</i> -Me-Ph		HNO ₃
H	H	H	2-thienyl	2	Ph		HNO ₃
H	H	H	5-Cl-2-thienyl	1	<i>o</i> -F-Ph		HNO ₃
H	H	H	5-Cl-2-thienyl	2	<i>p</i> -MeO-Ph		HNO ₃
H	H	H	<i>o</i> -Me-Ph	0	<i>p</i> -NO ₂ -Ph		HNO ₃
H	H	H	<i>p</i> -Br-Ph	1	<i>p</i> -Cl-Ph	159	HNO ₃
H	H	H	<i>p</i> -Me-Ph	1	<i>o</i> -Cl-Ph	124.5	HNO ₃
H	H	H	<i>o</i> -Me-Ph	1	<i>o</i> -Cl-Ph	162.5	HNO ₃
H	H	H	<i>o</i> -MeO-Ph	1	<i>o</i> -Cl-Ph	156	HNO ₃
H	H	H	<i>o</i> -Cl-Ph	1	<i>o</i> -Cl-Ph	161.5	HNO ₃
H	H	H	<i>o</i> , <i>p</i> -di-Cl-Ph	1	<i>o</i> -Cl-Ph	151	HNO ₃

R	R ₁	R ₂	Ar	n	Ar'	m.p.(°C) b.p./mm.)	salt
H	H	H	<i>p</i> -Br-Ph	1	<i>o</i> -Cl-Ph	124.5	HNO ₃
H	H	H	5-Cl-2-thienyl	1	<i>o</i> -Cl-Ph	125	HNO ₃
H	H	H	<i>p</i> -Cl-Ph	1	<i>o</i> -Me-Ph	140.5	HNO ₃
H	H	H	<i>p</i> -Cl-Ph	1	2, 6-di-Cl-Ph	143	HNO ₃
H	H	H	<i>p</i> -Cl-Ph	1	<i>p</i> -Me-Ph	134.5	HCl.H ₂ O
H	Me	Me	Ph	1	<i>p</i> -Cl-Ph	(190—200 0.4)	base
H	H	H	<i>m, p</i> -di-Cl-Ph	1	<i>o, p</i> -di-Cl-Ph	142.2	HNO ₃
H	H	H	<i>m, p</i> -di-Cl-Ph	1	2, 6-di-Cl-Ph	158.2	HNO ₃
H	H	H	<i>m, p</i> -di-Cl-Ph	1	<i>m, p</i> -di-Cl-Ph	149.9	HNO ₃
H	H	H	<i>o, p</i> -di-Cl-Ph	1	<i>m, p</i> -di-Cl-Ph	177.6	HNO ₃
H	H	H	<i>o</i> -Cl-Ph	1	<i>m, p</i> -di-Cl-Ph	140	HNO ₃
H	H	H	<i>p</i> -F-Ph	1	<i>m, p</i> -di-Cl-Ph	108	HNO ₃
H	H	H	<i>m, p</i> -di-Cl-Ph	1	<i>p</i> -Cl-Ph	138.1	HNO ₃
H	H	H	2, 6-di-Cl-Ph	1	<i>o, p</i> -di-Cl-Ph	168.7	HNO ₃
H	H	H	2, 6-di-Cl-Ph	1	2, 6-di-Cl-Ph	178.7	HNO ₃
H	H	H	2, 6-di-Cl-Ph	1	<i>p</i> -Cl-Ph	144.6	HNO ₃
H	H	H	<i>o, p</i> -di-Cl-Ph	1	<i>o, p</i> -di-Cl-Ph	79.4	base
H	H	H	2, 5-di-Cl-Ph	1	<i>p</i> -Cl-Ph	178.5	HNO ₃
H	H	H	2, 5-di-Cl-Ph	1	2, 6-di-Cl-Ph	203.6	HNO ₃
H	H	H	2, 5-di-Cl-Ph	1	<i>o, p</i> -di-Cl-Ph	173.2	HNO ₃

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R	R ₁	R ₂	Ar	n	Ar'	m.p.(°C) b.p./mm.)	salt
H	H	H	2,5-di-Cl-Ph	1	2,5-di-Cl-Ph	178.7	HNO ₃
H	H	H	<i>o</i> , <i>p</i> -di-Cl-Ph	1	<i>p</i> -Cl-Ph	86.9	base
H	H	H	<i>o</i> , <i>p</i> -di-Cl-Ph	1	<i>p</i> -tert. Bu-Ph	135.6	HNO ₃
H	H	H	<i>o</i> , <i>p</i> -di-Cl-Ph	1	<i>p</i> -isoPr-Ph	133.7	HNO ₃
H	H	H	2,6-di-Cl-Ph	1	<i>p</i> -MeO-Ph	144.8	HNO ₃
H	Me	Me	<i>p</i> -Cl-Ph	1	2,6-di-Cl-Ph	172.3	HNO ₃
H	Me	Me	<i>p</i> -Cl-Ph	1	<i>p</i> -F-Ph	123.2	HNO ₃
H	Me	Me	<i>p</i> -Cl-Ph	1	<i>o</i> , <i>p</i> -di-Cl-Ph	119.6	HNO ₃
H	H	H	<i>m</i> -Cl-Ph	1	<i>o</i> , <i>p</i> -di-Cl-Ph	179.2	HNO ₃
H	H	H	<i>m</i> -Cl-Ph	1	2,6-di-Cl-Ph	116.6	HNO ₃
H	Me	Me	<i>p</i> -Cl-Ph	1	<i>p</i> -Cl-Ph	101.1	HNO ₃
H	H	H	<i>o</i> , <i>p</i> -di-Cl-Ph	1	<i>o</i> , <i>m</i> , <i>p</i> -triCl-Ph	190.5	HNO ₃
H	H	H	<i>o</i> , <i>p</i> -di-Cl-Ph	1	2,4,6-triCl-Ph	180.1	HNO ₃
H	H	H	2,4,6-triCl-Ph	1	<i>o</i> , <i>p</i> -di-Cl-Ph	162.9	HNO ₃
H	H	H	2,4,6-triCl-Ph	1	2,6-di-Cl-Ph	180.3	HNO ₃
H	H	H	<i>o</i> , <i>p</i> -di-Cl-Ph	1	<i>m</i> , <i>p</i> -di-Me-Ph	138.2	HNO ₃
H	H	H	<i>o</i> , <i>p</i> -di-Cl-Ph	1	<i>p</i> -I-Ph	177.6	HNO ₃
H	H	H	<i>o</i> , <i>p</i> -di-Cl-Ph	1	<i>p</i> -CN-Ph	176.2	HNO ₃
H	Me	Me	Ph	1	<i>o</i> -Me-Ph		HCl
H	Me	Me	Ph	1	<i>p</i> -F-Ph		HNO ₃

R	R ₁	R ₂	Ar	n	Ar'	m.p. (°C) b.p./mm.)	salt
H	Me	Me	Ph	1	<i>o</i> , <i>p</i> -di-Cl—Ph		HCl
H	Me	Me	Ph	1	<i>p</i> -MeO—Ph		HCl
H	Me	Me	Ph	1	Ph		HNO ₃
H	Me	Me	Ph	1	Ph		HCl
H	Me	Me	Ph	0	<i>p</i> -NO ₂ —Ph		HNO ₃
H	Me	Me	Ph	0	<i>o</i> , <i>p</i> -di-NO ₂ —Ph		HNO ₃
H	Me	Me	Ph	2	<i>p</i> -Cl—Ph		HCl
H	H	H	2, 4, 6-triCl—Ph	1	Ph		HNO ₃
H	H	H	2, 4, 6-triCl—Ph	1	<i>m</i> , <i>p</i> -di-Me—Ph		HNO ₃
H	H	H	2, 4, 6-triCl—Ph	1	<i>p</i> -I—Ph		HNO ₃
H	H	H	2, 4, 6-triCl—Ph	1	<i>p</i> -CN—Ph		HNO ₃

EXAMPLE XIX

5 To a stirred and warm mixture of 1.66 parts of sodium hydride 50% in 45 parts of tetrahydrofuran are added portionwise 7.9 parts of α - (*p* - chlorophenyl) - 5 - methylimidazole-1-ethanol at 50°C. Upon completion, stirring is continued for 3 hours at reflux temperature. Then there are added 7.3 parts of 2,4-dichlorobenzyl chloride and stirring and refluxing is continued for 5 hours. The reaction mixture is cooled and 240 parts of ether are added. The ethereal phase is washed four times with water, dried and upon the addition of an excess of concentrated nitric acid, the salt is precipitated. It is filtered off, triturated with ethyl acetate and recrystallized from a mixture of 2-propanol and diisopropylether (1:9

by volume), yielding 1 - [*p* - chloro - β - (2,4-dichlorobenzoyloxy)phenethyl] - 5 - methylimidazole nitrate; mp. 150.7°C.

By repeating the procedure of Example XIX and replacing α - (*p* - chlorophenyl) - 5 - methylimidazole - 1 - ethanol by an equivalent amount of α - (*p* - chlorophenyl) - 2,4 - dimethylimidazole - 1 - ethanol or by an equivalent quantity of 2 - ethyl - 4(5) - methylimidazole - 1 - ethanol [Windaus et al., Ber. 5513, 3706 (1922)], the following compounds are prepared:

1 - [*p* - chloro β - (2,4 - dichlorobenzoyloxy)phenethyl] - 2,4 - dimethylimidazole nitrate; mp. 145.1°C;

1 - [*p* - chloro - β - (2,4 - dichlorobenzoyloxy)-phenethyl] - 2 - ethyl - 4 - methylimidazole nitrate

5 and the corresponding 5-methylimidazole ethers and the 2,4-dimethylimidazole ethers of formula (I-b).

EXAMPLE XX

A mixture of 8.7 parts of α - (2,4 - dichlorophenyl)imidazole - 1 - ethanol hydrochloride and 3.4 parts of sodium hydride in 40 parts of benzene and 35 parts of dimethylformamide is stirred while cooling on ice (solvents are previously dried azeotropically). First there are added 3 parts of manganese dioxide, followed by the addition of 8 parts of *p*-nitrofluorobenzene and the whole is stirred for 3 hours at room temperature. The reaction mixture is filtered over Hyflo and water is added. The product is extracted with benzene. The extract is dried, filtered and evaporated *in vacuo*. From the residual free base, the nitrate salt is prepared in the conventional manner in acetone. The precipitated solid salt is filtered off and recrystallized from a mixture of methanol and diisopropylether, yielding 1 - [2,4-dichloro - β - (*p* - nitrophenoxy)phenethyl]imidazole nitrate; mp. 167°C. (HYFLO is a Registered Trade Mark).

By repeating the procedure of Example XX and replacing *p* - nitrofluorobenzene by an equivalent amount of 2,4-dinitrochlorobenzene, the compound 1 - [2,4 - dichloro - β - (2,4-dinitrophenoxy)phenethyl]imidazole nitrate is obtained; mp. 167.5°C.

EXAMPLE XXI

To a stirred and refluxing mixture of 13.5 parts of iron, 10 parts of ammonium chloride and 150 parts of water are added portionwise 20 parts of 1 - [2,4 - dichloro - β - (*p* - nitrophenoxy)phenethyl]imidazole nitrate and the whole is further stirred and refluxed for 6 hours. The reaction mixture is cooled on an ice-bath and methylene chloride is added. The whole is filtered over hyflo. From the filtrate, the methylene chloride layer is separated, dried, filtered and evaporated *in vacuo*. The residue is recrystallized from diisopropylether, yielding 1 - [β - (*p* - aminophenoxy) - 2,4-dichlorophenethyl]imidazole; mp. 94°C.

By substituting an equivalent amount of 1 - [*p* - chloro - β - (*p* - nitrophenoxy)phenethyl]-2-ethylimidazole in the nitro-to-amine reduction procedure of Example XVIII, there is obtained as product 1 - [*p* - chloro - β - *p* - aminophenoxy)phenethyl]-2-ethylimidazole.

The nitro-to-amine reduction procedure of Example XXI is repeated using an equivalent amount of each of the two nitro derivatives obtained in Example XVIII as starting materials, namely, 1 - [β - (*p* - nitrophenoxy) - α,α - dimethylphenethyl]imidazole nitrate and 1 - [β - (*o,p* - dinitrophenoxy) - α,α - dimethylphenethyl]imidazole nitrate, to yield,

as respective products, the corresponding *p*-aminophenoxy and *o,p*-diaminophenoxy derivatives.

EXAMPLE XXII

To a stirred mixture of 10.32 parts of (+)- α - (2,4 - dichlorophenyl)imidazole-1-ethanol in 75 parts of tetrahydrofuran are added portionwise 2.1 parts of sodium hydride 50% and the whole is stirred and refluxed for one hour. Then there are added 44 parts of dimethylformamide, followed by the addition of 8.7 parts of 2,4-dichlorobenzyl chloride in 22 parts of dimethylformamide. Upon completion, stirring is continued at reflux temperature for 2 hours. The tetrahydrofuran is distilled off *in vacuo* and the residue is poured onto 200 parts of water. The product is extracted several times with xylene (successively 160, 80 and 40 parts). The combined extracts are dried over magnesium sulfate, filtered and evaporated. The residue is dissolved in 36 parts of tetrahydrofuran and the solution is acidified with a concentrated nitric acid solution. The nitrate salt crystallizes at room temperature. It is filtered off and dried, yielding (+)-1 - [2,4 - dichloro - β - (2,4 - dichlorobenzoyloxy)phenethyl]imidazole nitrate; mp. 135.3°C.; $\alpha_D^{20} + 59^\circ$ ($c=1$, methanol).

EXAMPLE XXIII

To a stirred mixture of 10.32 parts of (-)- α - (2,4 - dichlorophenyl)imidazole-1-ethanol, in 75 parts of tetrahydrofuran are added portionwise 2.1 parts of sodium hydride 50% and the whole is stirred and refluxed for one hour. Then there are added 44 parts of dimethylformamide, followed by the addition of 8.7 parts of 2,4 - dichlorobenzyl chloride in 22 parts of dimethylformamide. Upon completion, stirring is continued at reflux temperature for 2 hours. The tetrahydrofuran is distilled off *in vacuo* and the residue is poured onto 200 parts of water. The product is extracted several times with xylene (successively 160, 80 and 40 parts). The combined extracts are dried over magnesium sulfate, filtered and evaporated. The residue is dissolved in 36 parts of tetrahydrofuran and the solution is acidified with a concentrated nitric acid solution. The nitrate salt crystallizes at room temperature upon the addition of 32 parts of diisopropylether. The salt is filtered off and dried, yielding (-)-1 - [2,4 - dichloro - β - (2,4 - dichlorobenzoyloxy)phenethyl]imidazole nitrate; mp. 135°C.; $\alpha_D^{20} - 58^\circ$ ($c=1$, methanol).

EXAMPLE XXIV

The procedure described in Example XVIII illustrates a general O-alkylation technique which may be employed in preparing ethers of formula (I-b). Such ethers, obtained in the form of a nitrate salt, may be treated with alkali to yield the corresponding free base form. By following such procedure, except that equivalent amounts of appropriate re-

actants are initially employed, the following respective products are obtained:

- 1 - [β - (3,4 - dimethylbenzyloxy)phenethyl] - imidazole;
- 5 1 - [β - (p - iodobenzyloxy) - p - methylphenethyl]imidazole;
- 1 - [β - (p - iodobenzyloxy) - β - methylphenethyl]imidazole;
- 10 1 - [β - (2 - methoxy - 4 - nitrobenzyloxy)phenethyl]imidazole;
- 1 - [β - (p - cyanobenzyloxy) - o - methoxyphenethyl]imidazole;
- 1 - [β - (p - cyanobenzyloxy) - p - chlorophenethyl]imidazole; and
- 15 1 - [β - (2,3,4 - trichlorobenzyloxy) - o - methylphenethyl]imidazole.

EXAMPLE XXV

A. 188 parts of α -phenyl-1-imidazole-ethanol are dissolved in 600 parts of 2-propanol. To this solution is added a solution of 118 parts of (+) - camphor - 10 - sulfonic acid monohydrate in 200 parts of 2-propanol. The formed precipitate is filtered off, yielding the crude (-) - α - phenyl - 1 - imidazole-ethanol - (+) - camphorsulfonate; α_D^{20} -11° (c=1, methanol). (Note: the filtrate contains the (+) - α - phenyl - 1 - imidazoleethanol (+) - camphorsulfonate). 163 Parts of the crude (-) - α - phenyl - 1 - imidazoleethanol (+) - camphorsulfonate are recrystallized from 1000 parts of water, yielding pure (-) - α - phenyl - 1 - imidazoleethanol (+) camphorsulfonate; α_D^{20} -15° (c=1, methanol). The latter pure camphorsulfonate salt is dissolved in water and after making alkaline with ammonium hydroxide the precipitated free base is filtered off, yielding (-) - α - phenyl - 1 - imidazole-ethanol; mp. 147.8-152.2°C.; α_D^{20} -42° (c=1, methanol).

40 B. A mixture of 5.5 parts of sodium hydride and 25 parts of hexamethylphosphoramide (previously dried over sodium hydride) is cooled to 10°C. While keeping the temperature below 15°C., there is added a solution of 45 20 parts of (-) - α - phenyl - 1 - imidazoleethanol in 65 parts of hexamethylphosphoramide. Upon completion, the whole is stirred first for 30 minutes at room temperature and then for one hour at a temperature between 50 45° and 50°C. The mixture is cooled again to 5°C. and there are added 20 parts of p-chlorobenzyl chloride. After stirring for 30 minutes at room temperature, the mixture is warmed to 50°C. and further allowed to cool again to room temperature, while stirring. 55 Then 500 parts of water are added and the product is extracted three times with toluene (respectively 240, 160 and 80 parts). The combined extracts are washed with 250 parts 60 of water, dried over magnesium sulfate and evaporated. The residue is taken up in 40 parts of toluene and concentrated nitric acid is added. The precipitated nitrate salt is

sucked off and washed with diisopropylether, yielding (-) - 1 - [β - (p - chlorobenzyloxy)phenethyl]imidazole nitrate with a specific rotation of α_D^{20} -86° (c=1, methanol). A sample of 10 parts is recrystallized from benzene and stirred in diisopropylether, yielding 9 parts of (-) - 1 - [β - (p - chlorobenzyloxy)phenethyl]imidazole nitrate; mp. 78°C.; α_D^{20} -85°.

EXAMPLE XXVI

The compositions according to this invention are employed in those forms which are customarily used for fungus or bacteria control, for example, as suspensions, dusting powders, solutions or ointments. The following will further illustrate the invention, the parts being by weight unless otherwise specified:

(1) Suspension:

1 kg. ... 1 - [β - (p - chlorobenzyloxy)phenethyl]imidazole
2 l. ... technical xylene
350 ml. ... Atlox 4855 (surface active agent—Registered Trade Mark of Atlas Powder Co., Wilmington, Del.)
Water ... dilute to desired concentration of active ingredient.

The 1 - [β - (p - chlorobenzyloxy)phenethyl]imidazole forms a stable aqueous suspension when dissolved in the xylene and is emulsified by means of the surface active agent.

(2) Dusting Powder: 20 Parts of 1 - [2,4-dichloro - β - (p - chlorobenzyloxy)phenethyl]imidazole are ground with 360 parts of talcum in a ball mill, then 8 parts of olein are added and grinding is continued, and finally the mixture is mixed with 4 parts of slaked lime. The powder which is formed can be sprayed satisfactorily and has good adhesive power. It can be used for dusting or for plant protection purposes.

(3) Solution: 5 Parts of 1 - [p - chloro - β - (2,6 - dichlorobenzyloxy)phenethyl]imidazole are dissolved in 95 parts of alkylated naphthalene and used as a spray for the treatment of fungus-infected subjects or on walls, floors or other objects to prevent infection by fungi.

(4) Ointment: 10 Parts of 1 - [2,4 - dichloro - β - (2,4 - dichlorobenzyloxy)phenethyl]imidazole nitrate are dissolved in a warm, liquefied mixture of 400 parts of polyethylene glycol 400 and 590 parts of polyethylene glycol 1500. The solution is stirred during cooling, and used as an ointment for treatment against fungi and bacteria.

WHAT WE CLAIM IS:—

1. 1 - (β - Aryl)ethyl - imidazole derivatives having the formula:

actants are initially employed, the following respective products are obtained:

- 1 - [β - (3,4 - dimethylbenzyloxy)phenethyl] - imidazole;
- 5 1 - [β - (*p* - iodobenzyloxy) - *p* - methylphenethyl]imidazole;
- 1 - [β - (*p* - iodobenzyloxy) - β - methylphenethyl]imidazole;
- 10 1 - [β - (2 - methoxy - 4 - nitrobenzyloxy) - phenethyl]imidazole;
- 1 - [β - (*p* - cyanobenzyloxy) - *o* - methoxyphenethyl]imidazole;
- 1 - [β - (*p* - cyanobenzyloxy) - *p* - chlorophenethyl]imidazole; and
- 15 1 - [β - (2,3,4 - trichlorobenzyloxy) - *o* - methylphenethyl]imidazole.

EXAMPLE XXV

A. 188 parts of *dl*- α -phenyl-1-imidazole-ethanol are dissolved in 600 parts of 2-propanol. To this solution is added a solution of 118 parts of (+) - camphor - 10 - sulfonic acid monohydrate in 200 parts of 2-propanol. The formed precipitate is filtered off, yielding the crude (-) - α - phenyl - 1 - imidazole-ethanol - (+) - camphorsulfonate; $\alpha_D^{20} - 11^\circ$ ($c=1$, methanol). (Note: the filtrate contains the (+) - α - phenyl 1 - imidazoleethanol (+) - camphorsulfonate). 163 Parts of the crude (-) - α - phenyl - 1 - imidazoleethanol (+) - camphorsulfonate are recrystallized from 1000 parts of water, yielding pure (-) - α - phenyl - 1 - imidazoleethanol (+) camphorsulfonate; $\alpha_D^{20} - 15^\circ$ ($c=1$, methanol). The latter pure camphorsulfonate salt is dissolved in water and after making alkaline with ammonium hydroxide the precipitated free base is filtered off, yielding (-) - α - phenyl - 1 - imidazole-ethanol; mp. 147.8—152.2°C.; $\alpha_D^{20} - 42^\circ$ ($c=1$, methanol).

B. A mixture of 5.5 parts of sodium hydride and 25 parts of hexamethylphosphoramide (previously dried over sodium hydride) is cooled to 10°C. While keeping the temperature below 15°C., there is added a solution of 20 parts of (-) - α - phenyl - 1 - imidazole-ethanol in 65 parts of hexamethylphosphoramide. Upon completion, the whole is stirred first for 30 minutes at room temperature and then for one hour at a temperature between 45° and 50°C. The mixture is cooled again to 5°C. and there are added 20 parts of *p*-chlorobenzyl chloride. After stirring for 30 minutes at room temperature, the mixture is warmed to 50°C. and further allowed to cool again to room temperature, while stirring. Then 500 parts of water are added and the product is extracted three times with toluene (respectively 240, 160 and 80 parts). The combined extracts are washed with 250 parts of water, dried over magnesium sulfate and evaporated. The residue is taken up in 40 parts of toluene and concentrated nitric acid is added. The precipitated nitrate salt is

sucked off and washed with diisopropylether, yielding (-) - 1 - [β - (*p* - chlorobenzyloxy)phenethyl]imidazole nitrate with a specific rotation of $\alpha_D^{20} - 86^\circ$ ($c=1$, methanol). A sample of 10 parts is recrystallized from benzene and stirred in diisopropylether, yielding 9 parts of (-) - 1 - [β - (*p* - chlorobenzyloxy)phenethyl]imidazole nitrate; mp. 78°C.; $\alpha_D^{20} - 85^\circ$.

EXAMPLE XXVI

The compositions according to this invention are employed in those forms which are customarily used for fungus or bacteria control, for example, as suspensions, dusting powders, solutions or ointments. The following will further illustrate the invention, the parts being by weight unless otherwise specified:

(1) Suspension:

1 kg. ... 1 - [β - (*p* - chlorobenzyloxy)phenethyl]imidazole
2 l. ... technical xylene
350 ml. ... Atlox 4855 (surface active agent—Registered Trade Mark of Atlas Powder Co., Wilmington, Del.)
Water ... dilute to desired concentration of active ingredient.

The 1 - [β - (*p* - chlorobenzyloxy)phenethyl]imidazole forms a stable aqueous suspension when dissolved in the xylene and is emulsified by means of the surface active agent.

(2) Dusting Powder: 20 Parts of 1 - [2,4 - dichloro - β - (*p* - chlorobenzyloxy)phenethyl]imidazole are ground with 360 parts of talcum in a ball mill, then 8 parts of olein are added and grinding is continued, and finally the mixture is mixed with 4 parts of slaked lime. The powder which is formed can be sprayed satisfactorily and has good adhesive power. It can be used for dusting or for plant protection purposes.

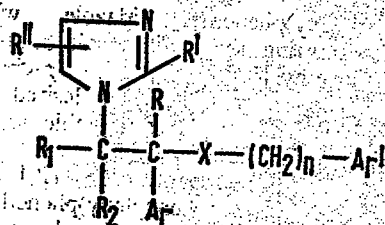
(3) Solution: 5 Parts of 1 - [*p* - chloro - β - (2,6 - dichlorobenzyloxy)phenethyl]imidazole are dissolved in 95 parts of alkylated naphthalene and used as a spray for the treatment of fungus-infected subjects or on walls, floors or other objects to prevent infection by fungi.

(4) Ointment: 10 Parts of 1 - [2,4 - dichloro - β - (2,4 - dichlorobenzyloxy)phenethyl]imidazole nitrate are dissolved in a warm, liquefied mixture of 400 parts of polyethylene glycol 400 and 590 parts of polyethylene glycol 1500. The solution is stirred during cooling, and used as an ointment for treatment against fungi and bacteria.

WHAT WE CLAIM IS:—

1. 1 - (β - Aryl)ethyl - imidazole derivatives having the formula:





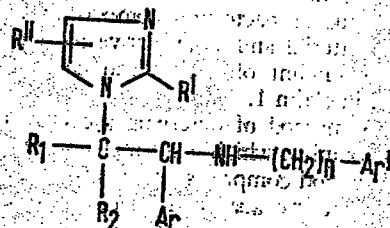
and the pharmaceutically acceptable salts thereof wherein:

- 5 R_1 , R_2 and R_3 are each hydrogen or lower alkyl;
- X is $-\text{O}-$ or $-\text{NH}-$;
- n is 0 or the integer 1 or 2;
- Ar is a phenyl, substituted phenyl, thienyl or halothieryl, said substituted phenyl containing a phenyl substituent which is halo,
- 10 lower alkyl or lower alkoxy;
- Ar' is phenyl, substituted phenyl or α -tetralyl, said substituted phenyl containing a phenyl substituent which is halo, lower alkyl, lower alkoxy, cyano, nitro or amino;
- 15 R' is hydrogen, methyl or ethyl; and
- R'' is hydrogen or methyl;

provided that:

- 20 (i) when X is $-\text{NH}-$, then R is hydrogen;
- (ii) when Ar' is a substituted phenyl containing a phenyl substituent which is nitro or amino, then X is $-\text{O}-$ and n is 0;
- 25 (iii) when Ar' is α -tetralyl, then X is $-\text{NH}-$ and n is 0; and
- (iv) when X is $-\text{O}-$ and Ar' is phenyl or substituted phenyl containing a phenyl substituent which is halo, lower alkyl, lower alkoxy or cyano, then n is an
- 30 integer of 1 or 2.

2. 1 - (β -Aryl)ethyl - imidazole derivatives having the formula:



35 and the pharmaceutically acceptable salts thereof wherein:

- 40 R_1 and R_2 are each hydrogen or lower alkyl;
- n is 0 or the integer 1 or 2;
- Ar is phenyl, substituted phenyl, thienyl or halothieryl, said substituted phenyl containing a phenyl substituent which is halo, lower alkyl or lower alkoxy;

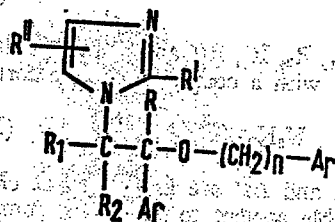
Ar' is phenyl, substituted phenyl or α -tetralyl, said substituted phenyl containing a phenyl substituent which is halo, lower alkyl, lower alkoxy or cyano;

45 R' is hydrogen, methyl or ethyl; and

R'' is hydrogen or methyl;

provided that, when Ar' is α -tetralyl, then n is 0.

3. 1 - (β -aryl)ethyl - imidazole derivatives having the formula:



and the pharmaceutically acceptable salts thereof wherein:

- 55 R_1 , R_2 and R_3 are each hydrogen or lower alkyl;
- n is 0 or the integer 1 or 2;
- Ar is phenyl, substituted phenyl, thienyl or halothieryl, said substituted phenyl containing a phenyl substituent which is halo, lower alkyl or lower alkoxy;
- 60 Ar' is phenyl, substituted phenyl or α -tetralyl, said substituted phenyl containing a phenyl substituent which is halo, lower alkyl, lower alkoxy, cyano, nitro or amino;
- 65 R' is hydrogen, methyl or ethyl; and
- R'' is hydrogen or methyl;

provided that:

- 70 (i) when Ar' is a substituted phenyl containing a phenyl substituent which is nitro or amino, then n is 0; and
- (ii) when Ar' is phenyl or substituted phenyl containing a phenyl substituent which is halo, lower alkyl, lower alkoxy or cyano, then n is the integer 1 or 2.
- 75 4. 1 - [β - (p - chlorobenzoyloxy)phenethyl]imidazole, and the pharmaceutically acceptable salts thereof.

5. 1 - [2,4 - dichloro - β - (p - chlorobenzoyloxy)phenethyl]imidazole and the pharmaceutically acceptable salts thereof.

6. 1 - [2,4 - dichloro - β - (2,4 - dichlorobenzoyloxy)phenethyl]imidazole and the pharmaceutically acceptable salts thereof.

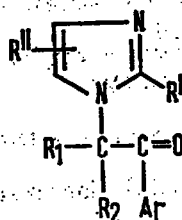
7. 1 - [2,4 - dichloro - β - (2,6 - dichlorobenzoyloxy)phenethyl]imidazole and the pharmaceutically acceptable salts thereof.

8. 1 - [p - chloro - β - (2,6 - dichlorobenzoyloxy)phenethyl]imidazole and the pharmaceutically acceptable salts thereof.

9. A process for preparing a 1-(β -aryl)ethyl-imidazole derivative as claimed in claim

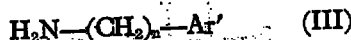


1. which process comprises reacting a compound of the formula:

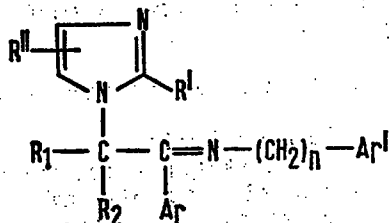


(II)

5 wherein R_1 , R_2 , R' , R'' and Ar are as defined in claim 1 with a compound of the formula

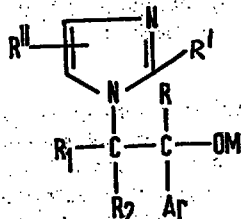


wherein n and Ar' are as defined in claim 1 in a suitable solvent to prepare a compound of the formula



(IV)

and reducing said compound IV to a compound of the formula I above wherein X is NH ; or reacting a compound of the formula



(Va)

15 wherein R_1 , R_2 , R' , R'' and Ar are as defined in claim 1 and M is an alkali metal, with a compound of the formula



20 wherein Y is halo and n and Ar' are as defined in claim 1 with the exception that Ar' is not aminophenyl in the presence of a suitable solvent, to prepare a compound of the formula I above, wherein X is ---O--- ; and, if desired preparing a pharmaceutically acceptable salt of said compound I.

25 10. A process for preparing 1 - [β - (p -

chlorobenzoyloxy)phenethyl]imidazole which comprises reacting the sodium salt of 1 - [β -hydroxyphenethyl]imidazole with p -chlorobenzoylchloride, and, thereafter if desired preparing a pharmaceutically acceptable salt of the product so formed.

11. A process for preparing 1 - [2,4 - dichloro - β - (p - chlorobenzoyloxy)phenethyl]imidazole which comprises reacting the sodium salt of α - (2,4 - dichlorophenyl)imidazole-1-ethanol with p -chlorobenzoylchloride, and, thereafter if desired preparing a pharmaceutically acceptable salt of the product so formed.

12. A process for preparing 1 - [2,4-dichloro - β - (2,4 - dichlorobenzoyloxy)phenethyl]imidazole which comprises reacting the sodium salt of α - (2,4 - dichlorophenyl)imidazole-1-ethanol with 2,4-dichlorobenzoylchloride, and, thereafter if desired preparing a pharmaceutically acceptable salt of the product so formed.

13. A process for preparing 1 - [2,4-dichloro - β - (2,6 - dichlorobenzoyloxy)phenethyl]imidazole which comprises reacting the sodium salt of α - (2,4 - dichlorophenyl)imidazole-1-ethanol with 2,6-dichlorobenzoylchloride, and, thereafter if desired preparing a pharmaceutically acceptable salt of the product so formed.

14. A process for preparing 1 - [p -chloro - β - (2,6 - dichlorobenzoyloxy)phenethyl]imidazole which comprises reacting the sodium salt of α - (p - chlorophenyl)imidazole-1-ethanol with 2,6 - dichlorobenzoylchloride and, thereafter if desired preparing a pharmaceutically acceptable salt of the product so formed.

15. A process for the preparation of a compound as claimed in claim 1 substantially as hereinbefore described with reference to any one of the examples XIV to XXV.

16. A compound as claimed in any one of claims 1 to 8 whenever prepared by a process as claimed in any one of claims 9 to 15.

17. A composition for deterring the growth of a fungus or bacterium comprising an inert carrier material and as an active ingredient an effective amount of a chemical compound as claimed in claim 1.

18. A method of deterring the growth of a micro-organism which is a fungus or bacterium which method comprises subjecting said micro-organism to the action of an effective amount of a chemical compound as claimed in claim 1.

BOULT, WADE & TENNANT,
111 & 112, Hatton Garden,
London, E.C.1,
Chartered Patent Agents,
Agents for the Applicants.

