

[54] PIPERIDINES MORPHOLINES, ETC., AND FUNGICIDAL COMPOSITIONS THEREOF

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[58] Field of Search 260/293.65, 293.72; 544/105, 178, 173; 546/141, 149, 153, 165, 164, 192, 150; 424/248, 267, 258; 542/429, 469

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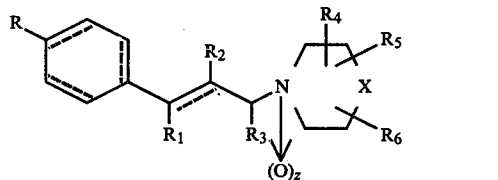
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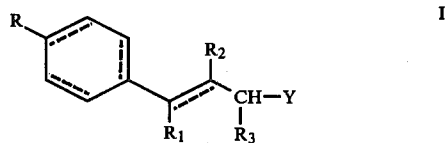
[57] ABSTRACT

Heterocyclic compounds characterized by the formula

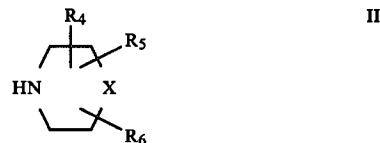


wherein R, R₁, R₂, R₃, R₄, R₅, R₆, X and z are as hereinafter set forth,

prepared, inter alia, by reacting a compound characterized by the formula



with an amine characterized by the formula



wherein R, R₁, R₂, R₃, R₄, R₅, R₆, X and Y are as hereinafter set forth,

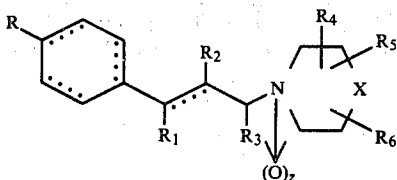
are described. The end products are useful as fungicidal agents.

140 Claims, No Drawings

PIPERIDINES MORPHOLINES, ETC., AND FUNGICIDAL COMPOSITIONS THEREOF

BRIEF SUMMARY OF THE INVENTION

The invention relates to heterocyclic compounds of the formula



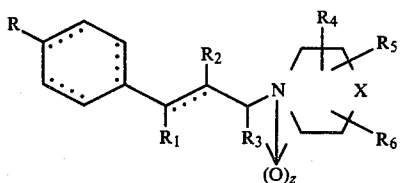
wherein R, R₁, R₂, R₃, R₄, R₅, R₆, X and z are as herein-after described.

In another aspect, the invention relates to fungicidal compositions and methods.

In yet another aspect, the invention relates to compounds useful as intermediates.

DETAILED DESCRIPTION OF THE INVENTION

The present invention comprises heterocyclic compounds of the formula



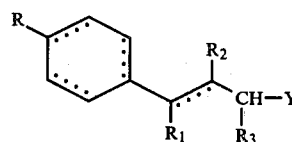
wherein R is alkyl of 4 to 12 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, mono(lower alkyl)-substituted cycloalkyl of 4 to 7 carbon atoms, cycloalkylalkyl of 4 to 12 carbon atoms, phenyl or aryl-(lower alkyl) of 7 to 12 carbon atoms; R₁, R₂ and R₃, independently, are hydrogen or alkyl of 1 to 8 carbon atoms; R₄, R₅ and R₆, independently, are hydrogen or alkyl of 1 to 8 carbon atoms, and two of R₄, R₅ and R₆ can each be bonded to the same carbon atom or together can form a fused alicyclic or aromatic 6-membered ring; provided that when R is tert.-butyl, at least one of R₁ and R₃ is alkyl of 2 to 8 carbon atoms or R₂ is hydrogen or alkyl of 2 to 8 carbon atoms or at least one of R₄, R₅ and R₆ is alkyl of 5 to 8 carbon atoms; X is methylene or an oxygen atom; z is zero or 1 and the dotted bonds can be hydrogenated, and acid addition salts of those compounds of formula I which are basic.

Unless stated to the contrary, the term "lower alkyl" as used herein denotes a straight-chain or branched-chain hydrocarbon group of 1 to 4 carbon atoms, such as, methyl, ethyl, propyl, isopropyl, butyl, isobutyl and tert.-butyl. Alkyl groups of 4 to 12 carbon atoms are straight-chain or branched-chain hydrocarbon groups, for example, butyl, isobutyl, tert.-butyl, neopentyl, 1,1-dimethylpropyl, 1,1-dimethylpentyl, 1,1-diethylpropyl, 1,1-dimethylbutyl, 1-isopropyl-3-methyl-but-1-yl, 1-ethyl-1-methylbutyl, dodecyl, and the like. The term "cycloalkylalkyl" includes, in particular, those groups in which the alkyl moiety is branched. The term "aryl-(lower alkyl)" includes not only groups which are mono- or di(lower alkyl)-substituted in the aryl ring but

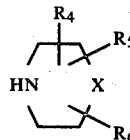
also groups which are mono- or di(lower alkyl)-substituted in the lower alkyl moiety. Exemplary of aryl-(lower alkyl) groups are benzyl, phenylethyl, (lower alkyl)-benzyl, for example, methylbenzyl and dimethylbenzyl, naphthylmethyl, 2-phenyl-propan-2-yl, 1-phenyl-1-ethyl, or the like.

Compounds of formula I which are basic form salts with organic and inorganic acids. Preferred salts are those formed with physiologically acceptable acids, including, in particular, the salts formed with hydrohalic acids, for example, hydrochloric acid and hydrobromic acid, phosphoric acid, nitric acid, monofunctional and bifunctional carboxylic acids and hydroxycarboxylic acids, for example, acetic acid, maleic acid, succinic acid, fumaric acid, tartaric acid, citric acid, salicylic acid, sorbic acid and lactic acid, and sulfonic acids, for example, 1,5-naphthalene-disulfonic acid. Salts of this type are prepared in a known manner.

The compounds of formula I and acid addition salts of those compounds which are basic can be prepared by (a) reacting a halide of the formula

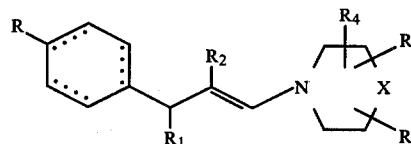


wherein R, R₁, R₂, R₃ and the dotted bonds are as previously described, and Y is chlorine, bromine or iodine, with an amine of the formula

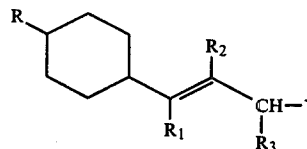


wherein R₄, R₅, R₆ and X are as previously described, or

(b) catalytically hydrogenating or reducing with formic acid the aliphatic double bond in a compound of the formula



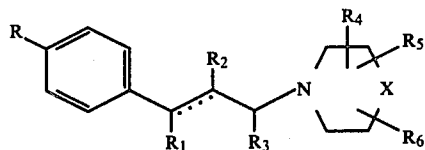
wherein R, R₁, R₂, R₄, R₅, R₆, X and the dotted bonds are as previously described, or (c) reacting a compound of the formula



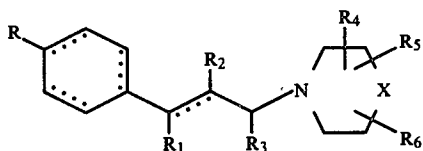
wherein R, R₁, R₂, R₃ and Y are as previously described, with an amine of formula III, or

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(d) catalytically hydrogenating a compound of the formula



wherein R, R₁, R₂, R₃, R₄, R₅, R₆, X and the dotted bond are as previously described, or
(e) treating a compound of the formula



VI

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(f) converting a compound of formula I which is basic into a salt with an acid in a known manner.

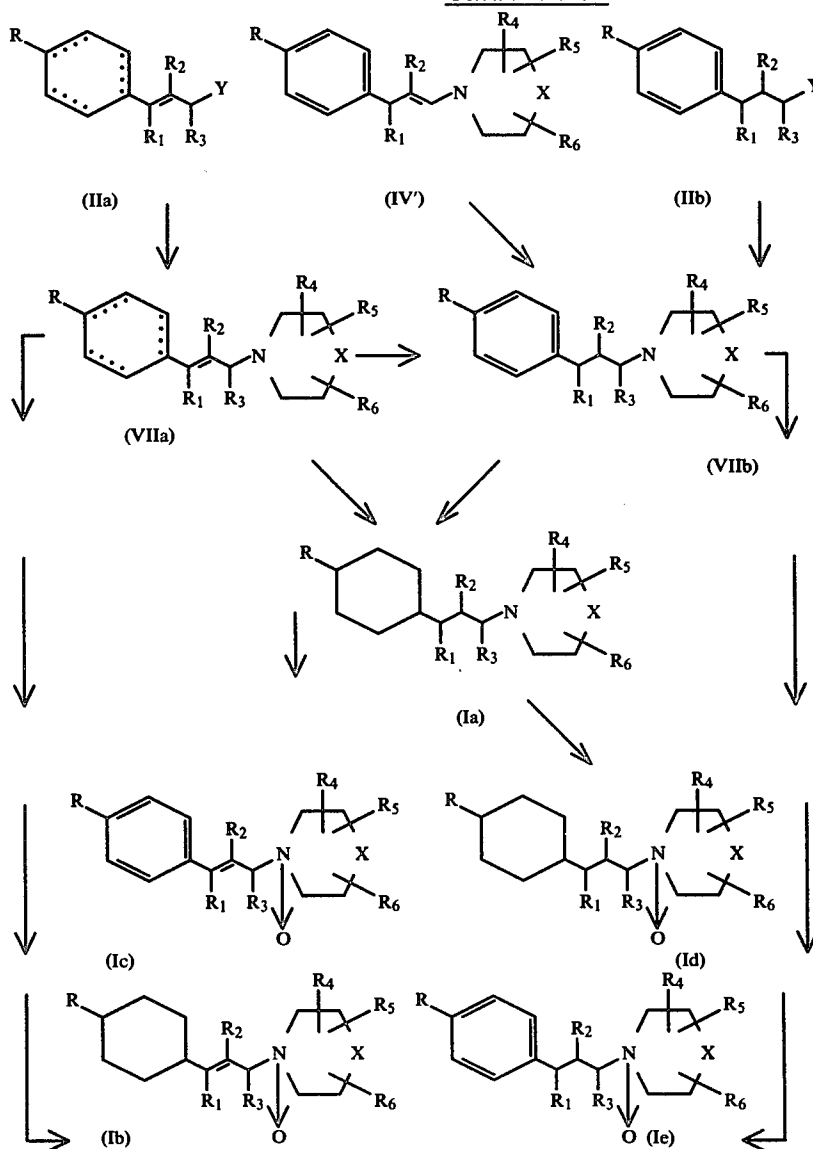
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The Roman numerals mentioned in the following text relate to the structural formulas given earlier and/or to the structural formulas given in the following Formula Schemes and/or to the structural formulas given in the description in connection with the preparation of the starting materials. Some of the formulas given in the text are elaborated in Formula Schemes A and B. Thus, for example, formula I hereinbefore includes all of the formulas given in Formula Scheme A with the exception of formulas IIa, IIb and IV. In Formula Schemes A and B, the symbols R, R₁, R₂, R₃, R₄, R₅, R₆, X and Y and the dotted bonds are as previously described. In Formula Scheme B, Et is ethyl and Ac is acetyl.

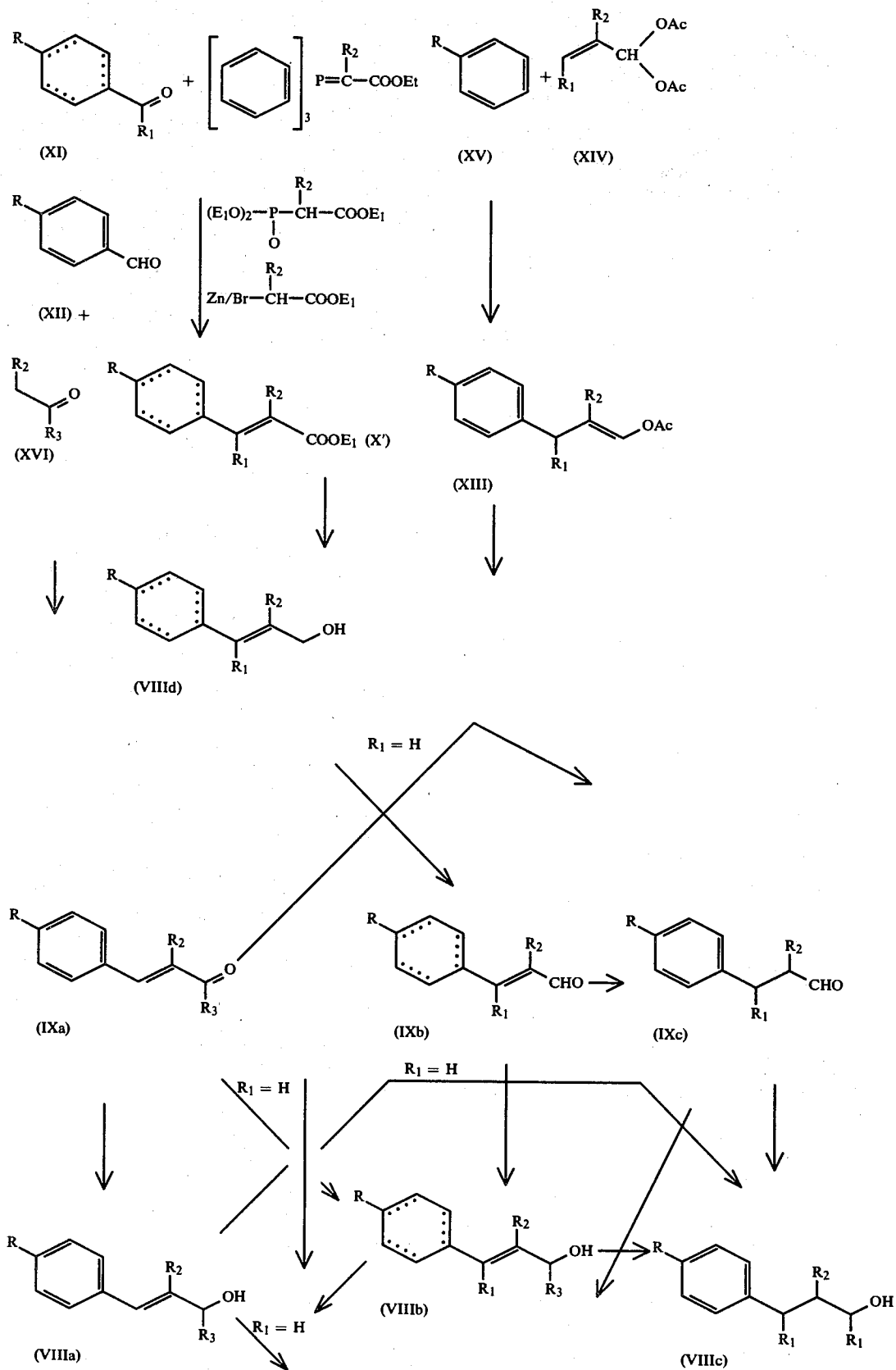
VII

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Formula Scheme A

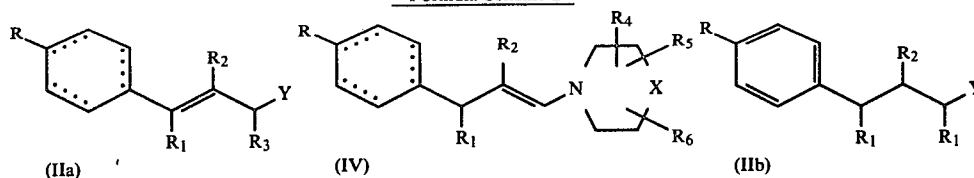


Formula Scheme B



-continued

Formula Scheme B



According to process embodiment (a), a halide of formula II is reacted with an amine of formula III in an inert solvent, preferably an ether, such as, diethyl ether, tetrahydrofuran or dioxane, in the presence of a base, for example, triethylamine or an excess of the amine of formula III.

When a halide of formula IIa is used as the starting material, diethyl ether is preferably used as the inert solvent. A particularly suitable reaction temperature lies in the range of from about 0° C. to about the reflux temperature of the reaction mixture. The reaction is preferably carried out at the boiling point of the reaction mixture.

When a halide of formula IIb is reacted with an amine of formula III, a high boiling alcohol is preferably used as the inert solvent. Ethylene glycol or glycerol is particularly preferred. The reaction is preferably carried out at a temperature in the range of from about 50° C. to about 150° C. In a particularly preferred aspect, the reaction is carried out using ethylene glycol as the inert solvent and at a temperature of 100°-110° C.

According to process embodiment (b), a compound of formula IV is catalytically hydrogenated or is reduced with formic acid. Particularly suitable catalysts are noble metal catalysts, for example, platinum, palladium (optionally precipitated onto charcoal) and Raney nickel. Palladium-on-charcoal is the preferred catalyst. Suitable inert solvents for the catalytic hydrogenation are hydrocarbons, such as, benzene, toluene or xylene, and alcohols, such as, methanol or ethanol. Toluene is the preferred inert solvent. The catalytic hydrogenation is advantageously carried out at a temperature in the range of from about 0° C. to about 50° C., preferably at room temperature. The reduction of a compound of formula IV with formic acid is preferably carried out in the absence of a solvent. Formic acid is added dropwise to a compound of formula IV at a temperature in the range of from about 0° C. to about 100° C., preferably at 50° to 70° C., if necessary while cooling.

According to process embodiment (c), a compound of formula V is reacted with an amine of formula III under the conditions described earlier in connection with process embodiment (a).

According to process embodiment (d), a compound of formula VI is catalytically hydrogenated. Platinum or palladium is preferably used as the catalyst, with water or alcohol being used as the solvent. In order to avoid a possible hydrogenolysis, at least one equivalent of acid, preferably hydrochloric acid, is added to the catalytic hydrogenation mixture. When a perhydrogenation is desired, the catalytic hydrogenation is carried out utilizing platinum in glacial acetic acid with the addition of perchloric acid. The aromatic ring is completely hydrogenated under these conditions.

According to process embodiment (e), a compound of formula VII is treated with hydrogen peroxide or a peracid. When a compound of formula Ia, VIIa or VIIb (see Formula Scheme A) is used as the starting material, the treatment is carried out with hydrogen peroxide. In

this case, an alcohol, such as, methanol, ethanol or isopropanol, is used as the solvent, with isopropanol being preferred. The treatment with hydrogen peroxide is preferably carried out at a temperature in the range of from about 0° C. to about 50° C., especially at 40° C. When a compound of formula Ia or VIIb is used as the starting material, the treatment is preferably carried out with a peracid, such as peracetic acid, perbenzoic acid, m-chloroperbenzoic acid, peradipic acid, etc., or with hydrogen peroxide in a corresponding acid or acid anhydride. A halogenated hydrocarbon, such as, methylene chloride, chloroform or ethylene chloride, is preferably used as the solvent when a peracid is used. Suitable treatment temperatures are the same as those mentioned earlier in connection with the treatment with hydrogen peroxide.

A preferred class of compounds of formula I comprises those wherein R is 1,1-dimethylpropyl. Also preferred are those compounds of formula I wherein R is phenyl.

Preferred compounds of formula I are:

- 1-[3-(p-Tert.amyl-phenyl)-2-methyl-propyl]-piperidine,
- 1-[3-(p-tert.amyl-phenyl)-2-methyl-propyl]-3-methyl-piperidine,
- 1-[3-(p-tert.amyl-phenyl)-2-methyl-propyl]-3,5-dimethyl-piperidine,
- 4-[3-(p-tert.amyl-phenyl)-2-methyl-propyl]-2,6-dimethyl-morpholine,
- 1-[3-(4-tert.amyl-cyclohexyl)-2-methyl-propyl]-piperidine,
- 1-[3-(4-tert.amyl-cyclohexyl)-2-methyl-propyl]-3-methyl-piperidine,
- 1-[3-(4-tert.amyl-cyclohexyl)-2-methyl-propyl]-3,5-dimethyl-piperidine,
- 4-[3-(4-tert.amyl-cyclohexyl)-2-methyl-propyl]-2,6-dimethyl-morpholine,
- 4-[3-(4-tert.amyl-cyclohexyl)-2-methyl-2-propenyl]-2,6-dimethyl-morpholine,
- 1-[3-(4-tert.amyl-cyclohexyl)-2-methyl-2-propenyl]-piperidine,
- 1-[3-(4-tert.amyl-cyclohexyl)-2-methyl-2-propenyl]-3-methyl-piperidine,
- 1-[3-(4-tert.amyl-cyclohexyl)-2-methyl-2-propenyl]-3,5-dimethyl-piperidine,
- 1-[3-(p-tert.amyl-phenyl)-2,3-dimethyl-2-propenyl]-piperidine,
- 1-[3-(p-tert.amyl-phenyl)-2,3-dimethyl-2-propenyl]-3-methyl-piperidine,
- 1-[3-(p-tert.amyl-phenyl)-2,3-dimethyl-2-propenyl]-3,5-dimethyl-piperidine,
- 4-[3-(p-tert.amyl-phenyl)-2,3-dimethyl-2-propenyl]-2,6-dimethyl-morpholine,
- 1-[3-(p-tert.amyl-phenyl)-2,3-dimethyl-propyl]-piperidine,
- 1-[3-(p-tert.amyl-phenyl)-2,3-dimethyl-propyl]-3-methyl-piperidine,

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