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2,935,439

METHOD OF INHIBITING GROWTH OF FUNGI

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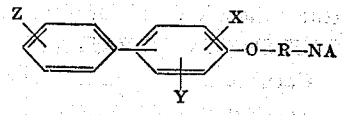
No Drawing. Application November 25, 1957 Serial No. 698,379

7 Claims. (Cl. 167—30)

This invention relates to a method of inhibiting growth of fungi and especially to the method of controlling the growth of fungi by applying to the fungus growth an effective amount of an aryl ether of an aminoalkanol as defined hereinafter.

The basic ethers and salts thereof as more fully defined hereinafter are very effective fungicides and they completely inhibit the growth of such common fungi as *Trichophyton mentagrophytes* and *Candida albicans* in dilutions of 1:10,000 and higher. Suitable carriers for the fungicidal ethers and salts thereof are water, dusting powder such as talc, and other commonly known excipients and vehicles.

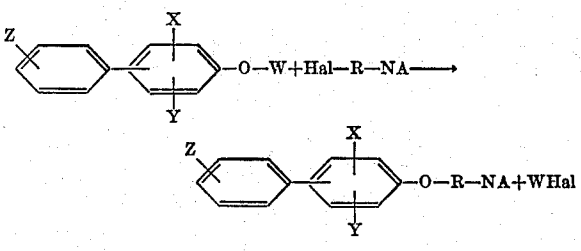
The ethers of this invention are characterized by the following formula



in which R is an alkylene group having from 2 to 6 carbon atoms inclusive, NA represents an amino group which is attached to the alkylene group through the nitrogen atom and includes the dialkylamino, the morpholinyl, the pyrrolidinyl, the N-methyl piperazinyl and the piperidinyl groups, X, Y and Z are either hydrogen or halogen but at least one must be halogen. The invention also includes the acid addition salts of the foregoing ethers with nontoxic acids, either organic or inorganic. For example, the hydrochloride, sulfate, oxalate, tartrate and other similar salts may be formed. In addition the quaterary salts of these ethers may be formed by the conventional method of quaternization with an alkyl halide.

The novel method of this invention is useful in exerting a strong fungistatic effect, e.g., against *Trichophyton mentagrophytes* and *Candida albicans*.

In general, the compounds employed in the method of this invention are prepared by forming an alkali metal or alkaline earth metal derivative of a halogenated hydroxy aryl compound, and reacting the resulting derivative of the aryl compound with an aminoalkyl halide to produce the alkamine ether of the halogen substituted hydroxy aryl compound. Reflux conditions are usually employed. The reaction is structurally illustrated as follows:



wherein Hal stands for halogen, W is from the group consisting of alkali metal and alkaline earth metal, and the other symbols are as previously indicated. When the basic compound is obtained, it can be converted to the salt by treating with a suitable salt-forming agent such as a hydrohalic acid. In like manner the quaternary salts may be obtained by treating the base with an alkyl halide under the usual conditions.

This application is a continuation-in-part of our copending U.S. Serial No. 508,324, filed May 13, 1955, as a continuation-in-part of our copending U.S. Serial No. 424,742, which was filed on April 21, 1954, as a continuation-in-part of our then copending U.S. Serial No. 187,666, which was filed on September 29, 1950. All the foregoing applications have now been abandoned.

The following example is presented in order to describe the chemicals more clearly but it should be understood that the example is not intended to be a limitation on the invention in any way.

EXAMPLE I

2-chloro-4-phenylphenyl γ-4-morpholinylpropyl ether

2-chloro-4-phenylphenol (11.5 g., 0.05 mole) and 2.8 g. (0.05 mole) of potassium hydroxide in 150 ml. of absolute alcohol (12A) are refluxed until the solution becomes clear. Then 8.1 g. (0.05 mole) of γ-4-morpholinylpropyl chloride are added and the product is heated under reflux for about 24 hours. The mixture is cooled and filtered to remove the precipitated salt, and the filtrate is concentrated under vacuum to remove most of the alcohol. Water is added, with sufficient hydrochloric acid to make slightly acidic, and the aqueous solution extracted with ether to remove impurities. The acidic solution is made basic by the addition of 40% sodium hydroxide and the base extracted by ether. The ethereal solution is dried and concentrated to obtain the solid base 2 - chloro-4-phenylphenyl γ-4-morpholinylpropyl ether. After recrystallization from petroleum ether, the base melts at 56–57° C. Its hydrochloride melts at 196–198° C. and is only sparingly soluble in water. In place of the γ-morpholinopropyl chloride one may employ other alkylene groups such as ethyl and butyl, and other amino groups such as piperidino, diethylamino, dimethylamino and dipropylamino.

The following γ-4-morpholinylpropyl ethers and their salts are prepared by the methods set forth in the preceding example and are all found to have physiological activity similar to the compounds already disclosed.

4-β-(4'-chlorophenyl)ethyl-phenyl, M.P. 79–80° C.
2 - chloro - 6 - phenylphenyl, hydrochloride, M.P. 187–188° C.
4 - chloro - 2 - phenylphenyl, hydrochloride, M.P. 186–187° C.
2-bromo-4-phenylphenyl, B.P. 208° C./0.9 mm., hydrochloride, M.P. 199–201° C.
4-(4'-chlorophenyl)phenyl, M.P. 93–94° C.
2,6-dichloro-4-phenylphenyl, hydrochloride, M.P. 206–208° C.
2 - bromo - 4 - (4' - bromophenyl)-phenyl, hydrobromide, M.P. 206–207° C.
2,6-dibromo-4-(4'-bromophenyl)-phenyl, hydrobromide, M.P. 219–220° C.
4'-bromophenylphenyl, hydrochloride, M.P. 251–253° C.
2,6-dibromo-4-phenylphenyl γ-4-morpholinylpropyl ether hydrobromide, M.P. 196–198° C.
2,4-dichloro-6-phenylphenyl β-4-morpholinylethyl ether hydrochloride, M.P. 189–190° C.

Other compounds used in this invention are as follows:

2-chloro-4-phenylphenyl γ-diethylaminopropyl ether, B.P. 185–186° C./0.9 mm.
3-chloro-2(6)-phenylphenyl γ-4-morpholinylpropyl ether, B.P. 181° C./1.1 mm.
2-chloro-4-phenylphenyl Δ-morpholinobutyl ether hydrochloride, M.P. 190–191° C.

2-chloro-4-phenylphenyl Δ-piperidinobutyl ether hydrochloride, M.P. 174–175° C.

2-chloro-4-phenylphenyl Δ-(4-methyl-1-piperazinyl) butyl ether dihydrochloride, M.P. 247–250° C.

2-chloro-4-phenylphenyl Δ-(1-pyrrolidinyl) butyl ether hydrochloride, M.P. 179–180° C.

2-bromo-4-phenylphenyl ε-morpholinopentyl ether hydrochloride, M.P. 175–176° C.

2-bromo-4-phenylphenyl ε-piperidinopentyl ether hydrochloride, M.P. 184–186° C.

2 - bromo - 4 - phenylphenyl ε-(4-methyl-1-piperazinyl) pentyl ether dihydrochloride, M.P. 250–252° C.

2-bromo-4-phenylphenyl Δ-morpholinohexyl ether hydrochloride, M.P. 151–153° C.

2-bromo-4-phenylphenyl Δ-piperidinohexyl ether hydrochloride, M.P. 165–167° C.

2-bromo-4-phenylphenyl Δ-(1-pyrrolidinyl) hexyl ether hydrochloride, M.P. 138–140° C.

2-chloro-4-phenylphenyl β-dimethylaminoethyl ether

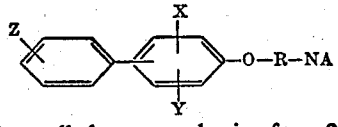
2-chloro-4-phenylphenyl γ-diethylaminopropyl ether, B.P. 185–186° C./0.9 mm.

2-bromo-4-phenylphenyl β-1-piperidinylethyl ether

Others may practice this invention in any of the numerous ways which will be suggested to one skilled in the art and all such practice is intended to be covered by this invention, provided, however, that it falls within the scope of the appended claims.

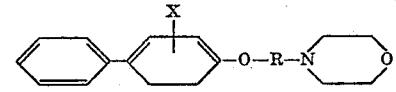
We claim:

1. A method of combatting the growth of a fungus which comprises applying to a growing fungus a fungicidal amount of a chemical compound selected from the group consisting of ethers, the acid addition salts of said ethers, and the quaternary ammonium salts of said ethers, said ethers having the formula



wherein R is an alkylene group having from 2 to 6 carbon atoms inclusive, NA is from the group consisting of dialkylamino, morpholinyl, pyrrolidinyl, N-methylpiperazinyl and piperidinyl, and X, Y and Z are from the group consisting of hydrogen chlorine and bromine with the further proviso that at least one of X, Y and Z must be selected from the group consisting of chlorine and bromine.

2. A method of combatting the growth of a fungus which comprises applying to a growing fungus a fungicidal amount of an acid addition salt of an ether having the formula



wherein R is an alkylene group having from 2 to 6 carbon atoms inclusive and X is selected from the group consisting of chlorine and bromine.

3. The method of claim 2 wherein the salt is an acid addition salt of 2-chloro-4-phenylphenyl γ-4-morpholinylpropyl ether.

4. The method of claim 2 wherein the salt is an acid addition salt of 2-chloro-6-phenylphenyl γ-4-morpholinylpropyl ether.

5. The method of claim 2 wherein the salt is an acid addition salt of 4-chloro-2-phenylphenyl γ-4-morpholinylpropyl ether.

6. The method of claim 2 wherein the salt is an acid addition salt of 2-chloro-4-phenylphenyl γ-diethylaminopropyl ether.

7. The method of claim 2 wherein the salt is an acid addition salt of 2-bromo-4-phenylphenyl γ-morpholinylpropyl ether.

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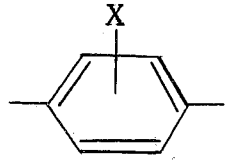
CERTIFICATE OF CORRECTION

Patent No. 2,935,439 May 3, 1960

Howard B. Wright et al.

It is hereby certified that error appears in the printed specification of the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 4, lines 12 to 15, the center portion of the formula should appear as shown below instead of as in the patent:



Signed and sealed this 18th day of October 1960.

(SEAL)
Attest:

KARL H. AXLINE
Attesting Officer

ROBERT C. WATSON
Commissioner of Patents