Antifungal Activity of 5-, 7-, and 5,7-Substituted 2-Methyl-8-Quinolinolns

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2-Methyl-8-quinolinol and sixteen 5-, 7-, and 5,7-substituted derivatives with fluoro, chloro, bromo, iodo, nitro, and amino substituents were tested for in vitro antifungal activity against five fungi, Aspergillus niger, A. oryzae, Trichoderma viride, Myrothecium verrucaria, and Trichophyton mentagrophytes. The 5,7-dichloro and 5,7-dibromo derivatives were the most fungitoxic of the compounds tested. With the exception of these two compounds and 5-iodo-2-methyl-8-quinolinol, the 2-methyl analogues were less active than the corresponding 8-quinolinolns.

As part of a program to elucidate the mechanisms of fungitoxicity of 8-quinolinol and its derivatives with respect to structure-activity relationships and cell penetration of their copper (II) chelates (6, 7, 9, 12), secondary mechanisms of action due to substituents (8, 10, 11), and relationship of stability of metal complexes to antifungal action (13), it was of interest to examine 2-methyl-8-quinolinol and its derivatives in parallel studies.

Upon searching the literature, a relatively small number of reports were found which contained antifungal data relating to the 2-methyl-8-quinolinolns. It was shown that 5,7-dichloro-2-methyl-8-quinolinol was inferior to 5-chloro-7-iodo-8-quinolinol as an antymycotic in Achorian quinckeana-infected guinea pigs (15). 5-Chloro-, 5,7-dichloro-, and 5,7-dibromo-2-methyl-8-quinolinolns were suggested for use in antiseptic soaps (E. W. Elliott and R. S. Shumard, U.S. Patent 2,695,881, 1954). Candida albicans was inhibited in vitro by 5,7-dichloro-2-methyl-8-quinolinol, but the agent was inactive in rabbits infected with the pathogen (18). 5,7-Dichloro-2-methyl-8-quinolinol was reported to be very effective in vitro against many animal systemic pathogenic fungi as well as against fungal plant pathogens. This compound was effective and well tolerated in curing mycotic dermatoses (17). The fungistatic effect of 2-methyl-8-quinolinol was found to be nil against Trichophyton gypseum, Epidermophyton floccosum, and Microsporum audouini in vitro (20), but, on the other hand, this compound was found to be highly toxic to the plant pathogen Monilinia fructicola by the spore drop germination test (4). Others have found that both 2-methyl-8-quinolinol and its 5,7-dichloro derivative were inhibitory to T. gypseum, Trichophyton rubrum, and E. floccosum in vitro, although they were not as active as some 8-quinolinolns (1). 5,7-Dibromo-2-methyl-8-quinolinol was found to have comparatively poor in vitro antifungal activity against seven fungi as compared with other 8-quinolinolns (21). In another study, 2-methyl-8-quinolinol and its 5,7-dichloro, 5,7-dibromo, and 5,7-diiodo analogues were tested in vitro against C. albicans, Saccharomyces cerevisiae, Aspergillus niger, and several Trichophyton spp. The inhibitory activity of unsubstituted 2-methyl-8-quinolinol was poor, and, although substitution with halogen enhanced the antifungal activity of these compounds with the dichloro derivative being the most active, none of these compounds was as active as the corresponding 8-quinolinol (2). More recently, in vitro tests against C. albicans indicated that 5,7-dichloro-2-methyl-8-quinolinol was both the most fungistatic and the most fungicidal of a series of 8-quinolinolns tested (16).

It is apparent that no systematic study of the antifungal activity of the 5-, 7-, and 5,7-substituted 2-methyl-8-quinolinolns has been conducted. This is due, in part, to the fact that many of the monosubstituted derivatives of 2-methyl-8-quinolinol were not previously prepared, and, of those derivatives that were studied, the fungitoxic results did not reveal any derivatives that were really superior to the 8-quinolinolns in fungitoxic action.

The present work is concerned with a systematic examination, in vitro, of the antifungal activity of seventeen 5-, 7-, and 5,7-substituted 2-methyl-8-quinolinolns, in which the substituents are fluoro, chloro, bromo, iodo, nitro, and amino groups.
MATERIALS AND METHODS

Compounds. Of the compounds studied (Table 1), only 2-methyl-8-quinolinol was commercially available. The monosubstituted compounds (H. Gershon and M. W. McNeil, J. Heterocycl. Chem., in press), 5,7-dichloro-2-methyl-8-quinolinol (5), 5,7-dibromo-2-methyl-8-quinolinol (14), 5,7-diodo-2-methyl-8-quinolinol (3), and 5,7-dinitro-2-methyl-8-quinolinol (19) were prepared by methods given in the indicated references.

Organisms. The five fungi employed in this test system included A. niger, A. oryzae, Trichoderma viride, Myrothecium verrucaria, and Trichophyton mentagrophytes.

All of the compounds were screened by published methods (9) in shake culture in Sabouraud dextrose broth (Difco) enriched with 0.05% yeast extract (Difco); spores of the five organisms were used as inocula. Minimal levels of fungistatic and fungicidal action of the compounds were recorded and are summarized in Table 1.

RESULTS

2-Methyl-8-quinolinol inhibited three fungi, T. viride, T. mentagrophytes, and M. verrucaria, and was also fungicidal with respect to M. verrucaria. Four organisms were inhibited by 5-fluoro-2-methyl-8-quinolinol. These included A. niger in addition to the three organisms for which it was also fungicidal. The latter three were the same organisms which were inhibited by the nonfluorinated parent compound. The 5-chloro-, 5-bromo-, and 5-iodo-2-methyl-8-quinolinols showed fungistatic activity against all five fungi and were fungicidal to T. mentagrophytes and M. verrucaria. The order of activity was I > Br > Cl. 5-Nitro-2-methyl-8-quinolinol also inhibited all five fungi and was fungicidal to the last three organisms of the set. The 5-amino analogue inhibited only T. mentagrophytes, for which it was also fungicidal. The antifungal activity of 7-fluoro-8-quinolinol paralleled that of the 5-fluoro analogue except that it was somewhat more fungitoxic. The 7-chloro- and 7-bromo-2-methyl-8-quinolinols were also slightly more active than the corresponding 5-halogeno compounds. The reverse was true for 7-iodo-2-methyl-8-quinolinol and its 5-iodo isomer. The fungitoxic activity of 2-methyl-5-nitro-8-quinolinol was markedly greater than that of the 7-nitro analogue, and 7-amino-2-methyl-8-quinolinol showed the same inactivity as the 5-amino isomer. Of the compounds studied in this series, 5,7-dichloro- and 5,7-dibromo-2-methyl-8-quinolinols were by far the most fungitoxic, with the dibromo compound being more active than the dichloro derivative for all organisms except A. oryzae. The diiodo derivative was fungicidal against T. mentagrophytes, and the dinitro compound was fungicidal against the same organism and also fungistatic against M. verrucaria.

Table 1. Minimal antifungal activity of substituted 2-methyl-8-quinolinols

<table>
<thead>
<tr>
<th>Position of substituent</th>
<th>Aspergillus niger</th>
<th>A. oryzae</th>
<th>Trichoderma viride</th>
<th>Trichophyton mentagrophytes</th>
<th>Myrothecium verrucaria</th>
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a Activity determined in Sabouraud dextrose broth after 6 days at 28°C, expressed as millimoles per liter.

b S = fungistatic; C = fungicidal.

c NA = not active below 100 μg/ml, the highest level tested.

d Tested as monohydrochloride.
DISCUSSION

As has been mentioned, 5,7-dichloro- and 5,7-dibromo-2-methyl-8-quinolinols are the most fungitoxic compounds of this series according to the results of the test system employed. It is also apparent from the data that monohalogenation enhances antifungal activity, and the order of activity in the 5-halogeno series is I > Br > Cl > F, whereas, in the 7-halogeno series, it is 7-I = Br > Cl > F. Addition of the second atom of halogen to the monochloro and monobromo compounds increased fungitoxicity 5- to 10-fold over the monohalogenated compounds. Since evidence has been reported which indicated that the increased activity of the halogenated 8-quinolinols over that of the parent compound was due to nonchelating secondary mechanisms of fungitoxication (8, 10, 11), it would be reasonable to extrapolate these concepts to the 2-methyl-8-quinolinol series.

The substituted 2-methyl-8-quinolinols and the analogous 8-quinolinols (12; Gershon et al., unpublished data) have been systematically studied by the same test methods (9), and it is of interest to compare the antifungal results obtained for each set of compounds. With the exceptions of the 5-iodo, 5,7-dichloro, 5,7-dibromo, and 5,7-dinitro compounds, the 8-quinolinol derivatives were more fungitoxic than the corresponding 2-methyl analogues.

Studies on the copper(II) chelates of these ligands and the relationship of stability of the complex to antifungal action will be reported elsewhere.

ACKNOWLEDGMENT

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LITERATURE CITED