1,3-Diacyl Derivatives of Imidazolidine and Hexahydropyrimidine: II. Antimycotic Activity[1]

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ABSTRACT

Series of 1,3-diacylated derivatives of imidazolidine and hexahydropyrimidine have been screened for antimycotic activity. Optimum activity was found for the 1,3-dihexanoyl derivatives in the imidazolidine series, with the higher and lower derivatives being much less active. In the hexahydropyrimidine series the 1,3-dipentanoyl, -dihexanoyl, -diheptanoyl and -dioctanoyl derivatives all exhibited a high degree of inhibition against all four of the test organisms. The latter were *Trichophyton rubrum, T violaceum, Microsporum gypseum* and *Aspergillus flavus.*

INTRODUCTION

Many N-substituted fatty amides have been shown to possess antimycotic activity (1,2). A variety of substituted imidazolidines and hexahydropyrimidines have also been reported to have antimycotic activity (3,4). The availability of a series of 1,3-diacylated imidazolidines and analogous hexahydropyrimidines from other research (5) gave a unique opportunity to investigate the antimycotic activity of compounds having the amide function incorporated in one of these two heterocyclic rings in the same molecule.

EXPERIMENTAL PROCEDURES

The preparation of the 1,3-diacylated imidazolidines and hexahydropyrimidines used in this study is reported elsewhere (5). The microorganisms used were obtained from stock cultures. Difco Dehydrated Mycological Agar at pH 7.0 was used to test the inhibition of the test organisms by the compounds being screened. Suspensions of the test organisms were prepared by transferring a loop of spores into sterile saline. Hardened agar plates were inoculated by placing three drops of the suspension onto the agar. The microorganisms were spread over the surface of the plates with sterile glass rods. These plates were employed in the activity estimation against microbial growth. Filter paper discs 6.5 mm in diamter, made from Whatman Number 1 filter paper were used to evaluate the liquid compounds, samples 13, 14, 15, 16, 17, 18, 19 and 23 of Table I. Stainless steel cylinders 5 mm i.d. were used for the remainder of the samples which were solids. The paper discs wetted until they were completely saturated with the test compound or stainless steel cylinders containing the test solid compound were placed on the surface of the agar plates inoculated with the test organisms. To eliminate any errors which could result from an insufficient number of tests, a minimum of three experiments, at different times, employing duplicate plates were made for each compound under test. All plates were incubated at the optimum growing temperature for each organism and readings were taken after 24, 48, 72 and 120 hr periods.

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RESULTS AND DISCUSSION

The 12 imidazolidines and 11 hexahydropyrimidines named in Table I were screened for activity against the following organisms: *Trichophyton rubrum, T violaceum, Microsporum gypseum* and *Aspergillus flavus.* The data reveal that 9 of the imidazolidines and 10 of the hexahydropyrimidines displated significant inhibition against at least one of the test organisms. In examining the data in Table I it should be borne in mind that compounds rated xx (organism failed to grow on saturated disc or solid) are not necessarily inferior to those rated + (the zone of inhibition was less than 0.5 cm) or ++ (the zone of inhibition was greater than 0.5 cm) as the failure to inhibit the growth of an organism beyond the point of actual application to the plate may result from inability to diffuse through the culture medium rather than from low antimycotic activity.

Maximum activity in the 1,3-diacylated imidazolidine series was achieved at the C_6 level with 1,3-dihexanoylimidazolidine strongly inhibiting the growth of all four test organisms. The compounds above and below the dihexanoyl in this series were much less effective on an overall basis in inhibiting the growth of these organisms.

TABLE I

Antimycotic Activity of 1,3-Diacyl Derivatives of Imidazolidine and Hexahydropyrimidine

Sample No.	Compound	Antimicrobial Activity,[a] Microorganism[b] A	B	C	D
1	1,3-Diacetylimidazolidine	–	–	–	–
2	1,3-Dibutyrylimidazolidine	xx	++	x	+
3	1,3-Dipentanoylimidazolidine	–	–	–	–
4	1,3-Dihexanoylimidazolidine	++	++	++	++
5	1,3-Diheptanoylimidazolidine	–	xx	x	–
6	1,3-Dioctanoylimidazolidine	–	+	–	–
7	1,3-Dinonanoylimidazolidine	++	x	x	+
8	1,3-Didecanoylimidazolidine	xx	x	x	x
9	1,3-Dipalmitoylimidazolidine	–	–	xx	–
10	1,3-Distearoylimidazolidine	xx	x	x	xx
11	1,3-Dioleoylimidazolidine	xx	–	x	xx
12	1,3-Dipalmitoyl-4-methylimidazolidine	–	–	–	–
13	1,3-Diacetylhexahydropyrimidine	++	–	–	–
14	1,3-Dibutyrylhexahydropyrimidine	++	–	–	–
15	1,3-Dipentanoylhexahydropyrimidine	++	++	++	++
16	1,3-Dihexanoylhexahydropyrimidine	++	++	++	++
17	1,3-Diheptanoylhexahydropyrimidine	++	++	+	++
18	1,3-Dioctanoylhexahydropyrimidine	++	++	+	++
19	1,3-Dinonanoylhexahydropyrimidine	+	xx	x	xx
20	1,3-Didecanoylhexahydropyrimidine	xx	x	x	x
21	1,3-Dipalmitoylhexahydropyrimidine	x	x	x	xx
22	1,3-Distearoylhexahydropyrimidine	–	–	–	–
23	1,3-Dioleoylhexahydropyrimidine	–	–	–	+

[a]++ = The zone of inhibition was at least 0.5 cm beyond disc or cylinder area at 120 hr. + = The zone of inhibition was less than 0.5 cm beyond disc or cylinder area at 120 hr. xx = Organism failed to grow on disc or cylinder area at 120 hr. x = Slight growth on the saturated disc or cylinder area at 120 hr. – = No inhibition detectable.

[b]A, *T. rubrum;* B, *M. gypseum;* C, *A. flavus;* D, *T. violaceum.*

The 1,3-diacylated hexahydropyrimidines were in general more effective than were the members of the imidazolidine series, and four of these compounds, the dipentanoyl, dihexanoyl, diheptanoyl and dioctanoyl derivatives strongly inhibited the growth of all four test organisms.

It may be noted that all of the imidazolidines screened for antimycotic activity in this study were solids and all of the very active hexahydropyrimidines were liquids (5). Thus, there may have been differences in the ability of the compounds tested to dissolve in the agar and diffuse. However, such differences do not appear to account for the fact that the test results indicate a more general antimycotic activity in the hexahydropyrimidine series than in the imidazolidine series. At the C_9 and C_{10} levels, for example, the compounds in both series exhibit some inhibition toward all four organisms. The zones of inhibition against both *T rubrum* and *T violaceum* were greater for 1,3-dinonanoylimidazolidine than for the hexahydropyrimidine analogue. At the C_7 and C_8 levels, on the other hand, where solubility would be expected to be greater, the imidazolidines showed no detectable inhibition against the same two organisms, whereas the hexahydropyrimidine analogues exhibited strong inhibition to growth of these organisms.

The tests carried out in this study were screening tests against a limited number of organisms. The effective inhibition of all of the organisms used by five of the compounds indicates that a more thorough investigation is warranted and suggests that some of these compounds may have potential utility as biostatic additives in commercial products.

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