

ANTIFUNGAL PROPERTIES OF SOME N,N-DIALKYLOXAMIDES

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ABSTRACT

N,N-Dialkyloxamides show potent antifungal activity against Pityrosporum ovale when used as solutions in polar solvents. The antifungal activity deteriorates rapidly due to decomposition of the oxamides in solution

INTRODUCTION

N,N-Dialkyloxamides have been evaluated as potential antibacterial agents¹⁻³ and as possible virucides^{4,5}, but not as antifungal agents. It has been shown that N-substituted-4-hydroxy-5-oxo-3-pyrroline-3-carboxylates are readily converted into the corresponding oxamides by the action of heat and protic solvents⁶, which may provide some explanation for the modest but inconsistent activity of these heterocycles against Pityrosporum ovale⁷. The object of the present work is to determine if there is any relationship between the length of the alkyl chain and the antifungal activity.

DISCUSSION

A series of N,N-dialkyl oxamides were prepared, all of which showed poor water solubility so it was necessary to solubilise them in a mixture of protic solvents. Table 1 shows that all the

TABLE 1.

Antifungal Testing Results for Oxamides M.I.C. $\mu\text{g}/\text{cm}^3$

Fresh Solutions

Chain length	C ₃	C ₄	C ₇	C ₈	C ₁₀	C ₁₂	C ₁₇	Pyri-thione
Organism								
P. ovale	7.8	7.8	7.8	7.8	46.8	7.8	7.8	16
A. niger	93.7	93.7	46.7	125	93.7	125	125	24
P. notatum	125	125	62.5	46.9	62.5	62.5	62.5	8

Solutions after storage at 25° for 7 days

Chain length	C ₃	C ₄	C ₇	C ₈	C ₁₀	C ₁₂	C ₁₇	
Organism								
P. ovale	125	125	78.1	62.5	62.5	46.9	-	

Solutions after storage at 25° for 14 days

Chain length	C ₃	C ₄	C ₇	C ₈	C ₁₀	C ₁₂	C ₁₇	
Organism								
P. ovale	125	125	125	125	125	125	-	

- = inactive at 125 $\mu\text{g}/\text{cm}^3$.

compounds tested had potent activity against P. ovale, with the exception of the N,N-didecyl analogue, the activity being greater in these tests than that of the reference fungicide, 1-hydroxypyridine-2-thione (Pyrithione). The oxamides showed modest activity against Aspergillus niger and Penicillium notatum, there was little evidence that the activity was dependent on the length of the alkyl chain. Since maximal potency was shown against P. ovale it was decided to concentrate further work on this organism. This decision was supported by the widely held view that P. ovale and the related yeast, P. orbiculare are implicated in the common scalp condition of dandruff.

Table 1. also shows that solutions of oxamides undergo considerable loss of activity on storage, this is most marked in the case of the lower molecular weight analogues. There is evidence that N,N-dialkyl oxamides undergo protonation in strongly polar solvents with subsequent decomposition to the oxalic acid salts of the corresponding amines⁹. The liberation of oxalic acid salts would raise some questions as to the safety of these compounds as medicinal or dermatological agents.

EXPERIMENTAL

N,N-Dialkylloxamides prepared from primary aliphatic amines (0.05 mole) and diethyl oxalate (0.025 mole) in absolute ethanol (75 cm³) by the method of Rice⁸.

The details of the products appear in Table 2.

N,N-Diheptadecyloxamide: prepared from heptadecylamine (0.05 mole) and diethyl oxalate (0.025 mole) as white crystals from butan-1-ol, mp. 123-125°. Found. C, 76.63; H, 12.94; N, 5.00. C₃₆H₇₂N₂O₂ requires, C,

TABLE 2.

N,N-Dialkyloxamides

Chain length	mp °C	Lit. mp °C	Yield g.	Percentage yield	Reference
C ₃	162-163	163	4.0	80	9
C ₄	155-156	153-154	5.0	89	8
C ₇	132-134	132-133	4.0	49	8
C ₈	123-124	124-125	6.0	50	8
C ₁₀	122-123	122-123	3.0	30	8
C ₁₂	124-125	123-124	1.5	15	8

76.53; H, 12.85; N, 4.96%. Yield 2.0 g. (13.6%)
(nujol mull) 3400, 1730 - 1665, 1530, 1230 - 1150 cm⁻¹.

Microbiological medium: Malt Extract Agar 6%;

Desiccated ox bile 2%; Tween 40 1%; glyceryl mono-oleate 0.25 % and distilled water to 100%.

The microbiological assays were carried out in petri dishes containing 20 cm³ of medium with concentrations of the oxamides ranging from 500 to 7.8 ug/cm³. The oxamides were solubilised by Rees method¹⁰ using a carrier solvent:

Carrier solvent: Absolute ethanol 50%; dimethyl sulphoxide 20%; Tween 40 10%; dimethylformamide 6% and water to 100%

The test compounds were dissolved in the carrier solvent so as to prepare a solution containing 1000 ug/cm³. Serial dilutions were then prepared in double strength medium. A second series of plates were made

containing Pyrithione as the reference fungicide. Incubation temperatures were 37° for P. ovale and 25° for A. niger and P. notatum, in all cases the incubation time was 48 hours. Total absence of colonies was taken as evidence of complete inhibition of growth. Assays were carried out in duplicate with frsh solution of the oxamides and with solutions 7 and 14 days old which had been stored at 25°. Controls were prepared containing 10, 5, 2.5, 1.25, 0.625, 0.31 and 0.15 cm³ of the carrier solvent in 20 cm³ of medium. These were inoculated with the test organisms. Similar controls were set up with solutions which had been stored at 25° for 7 and 14 days. All the controls supported growth of the test organisms.

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