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Addition of Benzonitrile Oxide to 3,4,5-Trimethoxybenzalanilines and Evaluation of Products as Antifungal Agents

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1,2,4-Oxadiazolines were prepared by the addition of benzonitrile oxide to 3,4,5-trimethoxybenzalanilines. The cycloadducts were identified and confirmed on the basis of elemental analysis and spectral studies. The products were tested *in vitro* for their antifungal activity against *Alternaria tenuis*, *Ustilago tritici*, *Sphaeceloma maydis*, *Puccinia recondita* and *Alternaria triticina*.

INTRODUCTION

Addition of benzonitrile oxides to benzalanilines and cinnamalanilines results in the formation of 1,2,4-oxadiazolines[1–3], which have been reported to possess antifungal activity[4]. It has also been reported that the presence of methoxy group in the phenyl ring incrases the antifungal activity of the parent compound[5]. So it is of interest to synthesize 1,2,4-oxadiazolines having three methoxy groups in the C–phenyl ring and to study their antifungal activity. This paper describes the synthesis of 1,2,4-oxadiazolines from 3,4,5-trimethoxybenzalanilines by addition of benzonitrile oxide and antifungal activity of the oxadiazolines.

EXPERIMENTAL

General procedure for preparation of 1,2,4-Oxadiazolines

3,4,5-Trimethoxybenzalaniline or its N-phenyl derivatives (0.01 mole) was dissolved in ether (100 mL) in a beaker (250 mL) and was cooled in an ice-bath to 0°C. Benzhydroxamoyl chloride (1.1 g, 0.01 mole) in ether (20 mL) was added to the above solution with constant shaking and the contents were kept at 0°C for some time. Triethylamine (1.2 mL) in ether (20 mL) was then added dropwise with continuous shaking. After complete addition of triethylamine, the reaction mixture was allowed to stand at 0°C for 2 h. The ether layer was separated out and the residue was washed thrice with dry ether. The combined ether layer and the washings on evaporation of the solvent yielded crude solid which on recrystallisation from benzene-petroleum ether mixture gave shining crystals of the respective 1,2,4-oxadiazolines in excellent yield.

In vitro Testing of Antifungal Activity

Each compound (20 mg) was dissolved initially in ethanol (0.5 mL). The final

volume was made up to 10 mL by adding distilled water. The resultant solution of 2000 ppm concentration was serially diluted to 1000, 500, 250, 100, 50 and 25 ppm concentrations. The spore suspension of the test fungus was mixed separately with the solution/suspension of the compound in cavities of the slides. These slides were kept in petri plates lined with moist filter paper and incubated for 20 h at 24 ± 1°C. To compare the activity of the compounds dithane M-45 and bavistin 50 Wp were used as a check. Percentage spore germination inhibition was calculated by the following formula:

% Spore germination inhibition =

$$\frac{\text{Spore germination in control} - \text{Spore germination in treatment}}{\text{Spore germination in control}} \times 100$$

ED_{50} and ED_{95} values (effective dose at which 50% and 95% spore germination inhibition was caused respectively) were calculated by log probability method.

RESULTS AND DISCUSSION

Reaction of benzonitrile oxide generated *in situ* by the action of triethylamine on hydroxamoyl chloride with 3,4,5-trimethoxybenzalaniline[6] yields a mixture of products which is separated into two components by fractional crystallisation from benzene-petroleum ether. Major product has been found to be the cycloadduct and the minor has been identified on the dimer of nitrile oxide on the basis of m.p. and m.m.p. determination.

The cycloadduct is identified as a 1,2,4-oxadiazoline derivative (I) on the basis of elemental analysis and spectral studies. The infrared spectrum of the adduct I shows bands at 1680 cm^{-1} indicating the presence of —C=N— linkage. The PMR spectrum in $CDCl_3$ shows 9 methoxy protons at 6.0 τ as a singlet and 12 aromatic protons between 2.4 to 2.8 τ as multiplet and one (CH) proton at 1.5 τ as a singlet.

Addition of benzonitrile oxide to 3,4,5-trimethoxybenzal-*p*-toluidine, 3,4,5-trimethoxybenzal-*p*-anisidine, 3,4,5-trimethoxybenzal-*p*-phentidine and 3,4,5-trimethoxybenzal-*p*-chloroaniline also results in the formation of 1,2,4-oxadiazolines (II to V). The oxadiazolines along with their characteristics are recorded in Table-1.

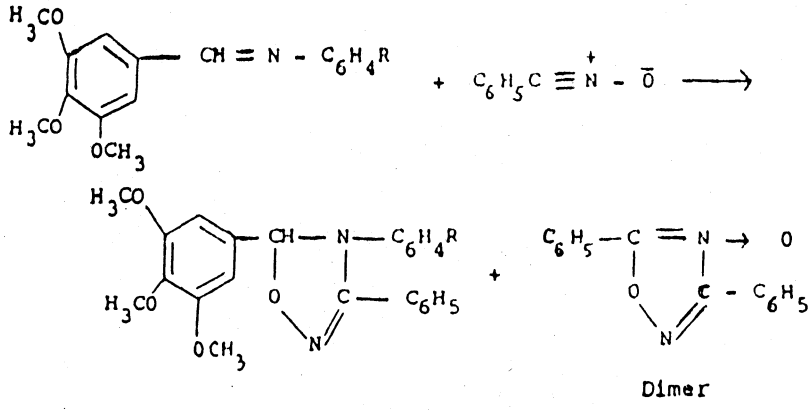
TABLE-1
CHARACTERISTICS OF 1,2,4-OXADIAZOLINES

Compound No.	R	m.p.* °C	Yield %	Molecular formula†
I	H	190	60	$C_{23}H_{22}N_2O_4$
II	*p*-CH_3	70	65	$C_{24}H_{24}N_2O_4$
III	*p*-OCH_3	90	67	$C_{24}H_{24}N_2O_5$
IV	*p*-OC_2H_5	92	62	$C_{25}H_{26}N_2O_6$
V	*p*-Cl	100	70	$C_{23}H_{21}N_2O_4Cl$

*All the melting points are uncorrected.
†All the compounds gave satisfactory elemental analysis.

Antifungal activity

1,2,4-Oxadiazolines have been tested *in vitro* for their antifungal activity against *Alternaria tenuis*, *Ustilago tritici*, *Sphaeceloma maydis*, *Puccinia recondita* and *Alternaria triticina* by spore germination inhibition method[7]. The compound I has been found to be effective in controlling *Puccinia recondita*. Three 1,2,4-oxadiazoline derivatives (II, III, IV) have ED_{95} values less than 1000 ppm for *Ustilago tritici*. Compound II has ED_{50} value of 800 ppm against *Alternaria tenuis*. None of the compounds has been found to be effective against *Sphaeceloma maydis* and *Alternaria triticina*.



I. R = H; II R = *p*-CH_3; III. R = *p*-OCH_3; IV. R = *p*-OC_2H_5; V. R = *p*-Cl

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