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Reaction of Thioglycollic Acid with 3,4,5-Trimethoxy benzalanilines

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Addition of thioglycollic acid to 3,4,5-trimethoxybenzalanilines has resulted in the formation of 4-thiazolidinones (I–V). These compounds were characterized on the basis of elemental analysis and spectral studies. The synthesized compounds were tested *invitro* against *Alternaria tenuis, Ustilago tritici, Sphaeceloma maydis, Puccinia recondita* and *Alternaria triticina.* Two of these compounds have been found to possess antifungal activity.

INTRODUCTION

4-Thiazolidinones[1] have been reported to possess antifungal activity[2–5]. It has also been reported that the presence of certain groups/atoms, *viz.*, methoxy[6], hydroxy[7], thio[8] and chloro[9] in the phenyl nucleus increases the activity of the parent compound. In view of it, in the present work we describe the preparation of 4-thiazolidinones having three methoxy groups in the C-phenyl ring and to study the effect of these groups on the antifungal activity of the 4-thiazolidinones.

EXPERIMENTAL

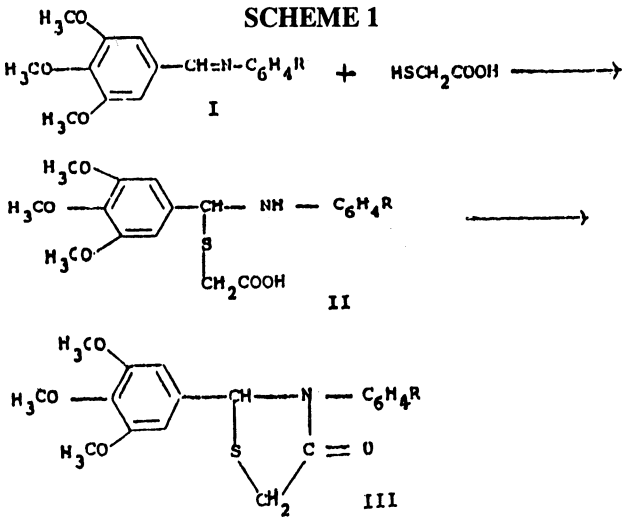
Preparation of 4-thiazolidinones: 3,4,5-Trimethoxybenzalaniline (2.71 g, 0.01 mole) was dissolved in dry benzene (20 mL) in a conical flask (100 mL). Thioglycollic acid (0.9 g, 0.01 mole) was added to the above solution in small instalments and with vigorous shaking. The mixture was heated for a few minutes and allowed to stand at room temperature for 24 h, when the whole mass was converted into a thick syrup which was passed through silica column to obtain fine yellow crystals of 2-(3,4,5-trimethoxyphenyl)-3-phenyl-4-thiazolidinone(IIIa), m.p. 68°C (yield 50%).

4-Thiazolidinones(IIIb to IIIe) were prepared by the addition of thiogllycolic acid to 3,4,5-trimethoxy-benzal-4-toluidine(Ib), 3,4,5-trimethoxybenzal-4-anisidine(Ic), 3,4,5-trimethoxybenzal-4-phenitidine(Id) and 3,4,5-trimethoxybenzal-4-chloroaniline (Ie) respectively by following the above procedure.

In vitro testing of antifungal activity

Each compound (20 mg) was dissolved in ethanol (0.5 mL) and the final volume was made to 10 mL by adding sterilized distilled water. The resultant

SCHEME 1



IIIa (R = H); IIIb (R = *p*-CH_3); IIIc (R = *p*-OCH_3); IIId (R = *p*-OC_2H_5); IIIe (R = *p*-Cl).

solution of 2000 ppm was diluted serially to get the desired concentrations of the compounds. Test samples of each compound after mixing with spore suspension in cavity slides were incubated at 25 ± 1°C for 18 h. The germination of spores was recorded and per cent spore germination was calculated by using the formula

% spore germination inhibition

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

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

RESULTS AND DISCUSSION

Addition of thiogllycolic acid to 3,4,5-trimethoxybenzalaniline and its N-phenyl derivatives results in the formation of thick syrups which on passing through silica column give the respective solid products. The products have been characterized as 4-thiazolidinones on the basis of elemental analysis, IR and PMR studies.

Infrared spectra of these compounds indicate bands at *ca.*1700 cm^{-1} showing the presence of —N—C=O group. PMR spectrum of IIIa in $CDCl_3$ indicates a

singlet at 6.0 τ due to nine methoxy protons, a multiplet between 2.4–2.7 τ due to six aromatic protons, a singlet at 7.1 τ due to two methylene protons and one proton of the C–2 of the 4-thiazolidinone ring is indicated at 2.2 τ.

It seems that thioglycollic acid initially adds to carbon–nitrogen double bond of the Schiff bases (I) to give thioethers (II) which cyclize due to interaction between >NH and —COOH groups to give 4-thiazolidinones (III) as shown in the Scheme 1.

4-Thiazolidinones prepared by the addition of thioglycollic acid to 3,4,5-trimethoxybenzalanilines along with their characteristics are recorded in Table-1.

TABLE-1
CHARACTERISTICS OF 4-THIAZOLIDINONES

Compound No.	R	Yield %	m.p* (°C)	Molecular Formula†
IIIa	H	55	68	$C_{18}H_{19}NSO_4$
IIIb	*p*-CH_3	50	105	$C_{19}H_{21}NSO_4$
IIIc	*p*-OCH_3	60	65	$C_{19}H_{21}NSO_5$
IIId	*p*-OC_2H_5	55	87	$C_{20}H_{23}NSO_5$
IIIe	*p*-Cl	50	82	$C_{18}H_{18}NSO_4Cl$

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

Antifungal activity

The synthesized 4-thiazolidinones (IIIa–IIIe) 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. The results are recorded in terms of ED_{50} values. None of the compounds has been found to have ED_{50} values less than 1000 ppm against *A. tenuis*, *P. recondita* and *A. triticina*. 4-Thiazolidinone IIIb has been found to be the most effective against *S. maydis* (ED_{50} 910 ppm) whereas *U. tritici is* best controlled by 4-thiazolidinone IIIe (ED_{50} 610 ppm).

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