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Synthesis of Some New Triazino-Thiadiazolos and Thiadiazolo-Quinazoles as Antifungal Agents

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Some new 2-aryloxymethyl-5 substituted 1,3,4-thiadiazolo[3,2-a]-1,3,5-triazine-7-thiaones (IIIa-e) and 2-aryloxymethyl-1,3,4-thiadiazolo[2,3-b] quinazolin-4-ones (Va-e) have been prepared. These compounds have been screened for their antifungal activity against two fungi viz. *Aspergillus niger* and *Helminthosporium oryzae* at 1000, 100 and 10 ppm concentration. A possible structure activity relationship has been discussed.

INTRODUCTION

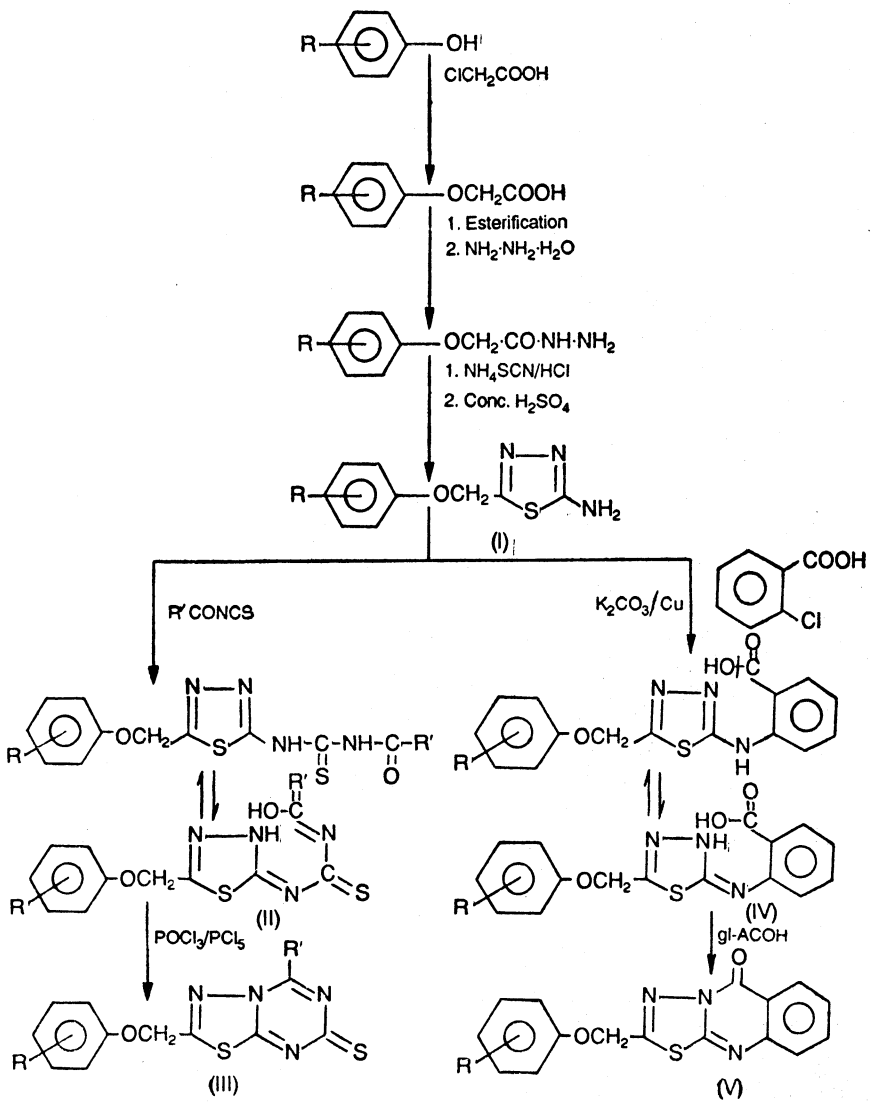
The structure (III) incorporates a thiourea structure (—N—CS—N—), thiosemicarbazone (>C=N—N—CS—N<) and a triazine ring. Thiosemicarbazone and thiourea are well known for their use as fungicides, herbicides and bactericides. Likewise sym-triazine derivatives are also known to have biological activities.

Quinazolone derivatives have prodigious range of activities e.g. CNS depresant[4], hypnotic[5], anticonvulsant[6] and pesticidal[7]. The activity is probably due to the presence of structural features of pyrimidine and a >C=O group in nitrogen heterocycles[8].

These observations coupled with the fact that planarity and compactness of a molecule might augment its other biological activities as it often does with the herbicidal activity[9,10], the biolabile *s*-triazine[11], quinazolone[12] and thiadiazole[12] nuclei were fused to yield the title thiadiazolo-*s*-triazines (IIIx-c) and thiadiazoloquinazolones (Va-e) which were evaluated for their fungicidal activity.

The synthon 2-amino-5-aryloxymethyl-1,3,4-thiadiazoles (I) were prepared according to the method of Maffii *et al*[14]. This on reaction with aroyl/aryl isothiocyanate in acetone furnished the corresponding aroyl/acylthioureas which on refluxing with $POCl_3/PCl_5$ gave the desired compounds (IIIa-e). Similarly, the treatment of (I) with 2-chlorobenzoic acid in the presence of K_2CO_3 and Cu in ethanol furnished the compounds (IVa-e) which on heating with gl. acetic acid furnished the titled compounds (Va-e) (Scheme I).

SCHEME I



In II and III		In IV and V
a, R = 2,4-diCH$_3$	R′ = CH$_3$	a, R = 3,4-diCH$_3$
b, R = 2,4-diCH$_3$	R′ = C$_6$H$_5$	b, R = 2-Cl
c, R = 2,4-diCl	R′ = 2,4-diCl-C$_6$H$_3$-OCH$_2$-	c, R = 4-CH$_3$
d, R = 4-Cl	R′ = 2.4-diCl-C$_6$H$_3$-OCH$_2$-	d, R = 2,4-diCl
e, R = 4-Cl	R′ = CH$_3$	e, R = 2-CH$_3$

The structures of these products were established by elemental and spectral (IR and PMR) analysis.

EXPERIMENTAL

All the melting points were taken in open capillaries and are uncorrected. IR spectra were recorded on Perkin-Elmer-157 spectrophotometer, phase KBr and PMR on Perkin-Elmer R-32 spectrometer in DMSO-d_6 and TMS as internal reference. Elemental analyses (C, H, N) were satisfactory.

1-Benzoyl-3-[5-(2,4-dimethylphenoxymethyl)-1,3,4-thiadiazol-2-yl] thiourea (IIIb)

2-Amino-5-(2,4-dimethyl-chlorophenoxymethyl)-1,3,4-thiadiazole (0.01 mol) and benzoyl isothiocyanate [prepared by refluxing ammonium thiocyanate (0.01 mol) and benzoyl chloride (0.01 mol) in acetone (100 ml)]; in acetone, were refluxed for 3 hrs. Five crystals separated out which were filtered and recrystallised from ethanol, M.pt. 151°C, yield 69%. Anal. Calcd. $C_{19}H_{18}O_2S_2N_4$: C 57,3; H 4.5; N 14.1; Found : C 57.0; H 4.3; N 13.8%; IR (KBr) cm^{-1}; 3420 (—OH), 3200 (—NH), 1540 (C=N), 1070 (C=S), 1030, 1240 (C—O—C); PMR : 2.3 (S, 6H,—CH_3), 4.5 (S, 2H, —OCH_2), 7.3—8.2 (M, 8H, aromatic protons), 9.9 (S, 1H, —NH). Other compounds are prepared similarly (Table 1).

(2,4-Dimethylphenoxymethyl)-5-Phenyl-1,3,4-Thiadiazolo-[3,2-a]-1,3 5-Triazin-7-Thione (IIIb)

A mixture of IIb (0.01 mol), PCl_5 (0.11 mol) and $POCl_3$ (1.5 ml) was refluxed for 2 hrs and crushed ice added to it. The solid thus obtained was crystallised from methanol to give IIIb, M.pt. 138°C, yield 65%. Anal. Calc. $C_{19}H_{16}ON_4S_2$: C 60.0; H 4.2; N 14.7; Found : C 59.8; H 4.0; N 14.5%; IR (KBr) cm^{-1}; 1590 (C=N); 11.20 (C=S), 1030 and 1250 (C-O-C); PMR : 2.2 (s, 6H, CH_3), 4.5 (s, 2H, -OCH_3) and 6.6-7.0 (m, 8H, aromatic protons). Other such compounds are similarly prepared (Table 1).

2-(2-Chlorophenoxymethyl)-5-(2-Carboxyphenyl Amino)-1,3,4-Thiadiazole (IVb)

A mixture of 2-amino-5-(2-chlorophenoxy methyl)-1,3,4-thiadiazoles (0.01 mol), 2-chlorobenzoic acid (0.01 mol), potassium carbonate (0.021 mol) and Cu powder (0.5 g) was refluxed in methanol for 8 hrs and solvent removed. The residue was dissolved in H_2O (100 ml). On acidification, with diluted HCl, white mass of the desired compound precipitates out, m. pt. 111°C, yield 52%. Anal. Calcd. $C_{26}H_{12}O_3N_3SCl$: C 53.1; H 3.3; N 11.6; Found : C 53.0; H 3.2; N 11.2%; IR (KBr) cm^{-1}; 3400 (-OH),

TABLE 1

PHYSICAL DATA OF COMPOUNDS IIa-e, IIIa-e, IVa-e and Va-e

Compound No.	M.pt. (°C)	Yield (%)	Molecular formula	Analysis (%) of N	
				Found	Calc.
IIa	169	64	$C_{14}H_{16}O_2N_4S_2$	16.5	16.6
IIb	151	69	$C_{19}H_{18}O_2S_2N_4$	13.8	14.0
IIc	187	63	$C_{18}H_{12}O_3N_4S_2Cl_4$	10.2	10.4
IId	138	62	$C_{18}H_{13}O_3N_4S_2Cl_3$	10.8	11.1
IIe	126	64	$C_{12}H_{11}O_2N_4S_2Cl$	16.2	16.3
IIIa	182	62	$C_{14}H_{14}ON_4S_2$	17.5	17.6
IIIb	138	65	$C_{19}H_{16}ON_4S_2$	14.5	14.7
IIIc	154	60	$C_{18}H_{10}O_2N_4S_2Cl_4$	10.6	10.7
IIId	149	60	$C_{18}H_{11}O_2N_4S_2Cl_3$	11.4	11.5
IIIe	139	61	$C_{12}H_9ON_4S_2Cl$	17.0	17.2
IVa	114	62	$C_{18}H_{17}O_3N_3S$	11.2	11.8
IVb	111	52	$C_{16}H_{12}O_3N_3SCl$	11.2	11.6
IVc	79	50	$C_{17}H_{15}O_3N_3S$	11.9	12.3
IVd	102	64	$C_{16}H_{11}O_3N_3SCl_2$	10.4	10.6
IVe	101	56	$C_{17}H_{15}O_3N_3S$	11.9	12.3
Va	167	66	$C_{18}H_{15}O_2N_3S$	12.2	12.4
Vb	157	48	$C_{16}H_{10}O_2N_3SCl$	12.1	12.2
Vc	83	61	$C_{17}H_{13}O_2N_3S$	12.5	13.0
Vd	178	64	$C_{16}H_9O_2N_3SCl_2$	10.6	11.1
Ve	104	63	$C_{17}H_{13}O_2N_3S$	12.7	13.0

3260 (-NH), 1710 (>C=O), 1670 (C=N), 1030 and 1230 (C-O-C); PMR 4.5 (s, 2H, $-OCH_2$) and 6.7-7.8) (m, 8H, aromatic protons). Other such compounds are similarly prepared (Table 1).

2-(2-Chlorophenoxymethyl)-1,3,4-Thiadiazolo[2,3-b]-Quinazol-4-one (Vb)

The requisite compound (IVb) (0.01 mol), was dissolved in gl. acetic acid (25 ml) and heated under reflux for 2 hrs. On cooling, the reaction

mixture was poured into crushed ice. The solid mass thus obtained was crystallised from methanol. M.pt. 157°C, yield 48%, Anal. Calcd. $C_{16}H_{10}O_2N_3SCl$ C 55.9; H 2.9; N 12.2; Found : C 55.7; H 2.7; N 12.1%; IR (KBr) cm^{-1}; 1710 (>C=O), 1670 (C=N), 1030, 1230 (C–O–C); PMR 4.6 (s, 2H, $-OCH_2$) and 6.7–7.4 (m, 8H, aromatic proton) Other such compounds are similarly prepared (Table 1).

Antifungal Activity

All the compounds have been screened for their antifungal activity by agar growth technique[15] against two fungi, namely *A. niger* and *H. oryzae.* The fungus was planted in three replicate, in agar growth media, mixed with test compounds. The diameter of the fungus colony was measured at 1000, 100 and 10 ppm concentration. Inhibition of the fungus growth was determined as the difference in growth between the control plate and those treated with the test compounds. The activity of the test compound was compared with commercial fungicide carbendazim.

RESULTS AND DISCUSSION

All the compounds, screened, showed moderate toxicity to both the fungal samples but their activity decreases considerably upon dilution. In general triazino-thiadiazoles are more active than corresponding acyl/aroyl thiourea and thiadiazol-quinazoles on both the species of fungi, but they are slightly more active against *H. orygae.*

The activity of triazinothiadiazoles (IIIc and IIId) and carboxyphenyl thiadiazole (IVd) have the activity (85 to 90%) quite comparable with commercial fungicide carbendazim. In general presence of chlorine atom increases fungitoxicity. Further screening of these compounds on wider range of fungi are under process.

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