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Synthesis and Antifungal Studies of Some New 2, 6 Bis (Substituted Oxadiazolyl) Pyridines

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Abstract: A series of Bis 2, 6 (substituted oxadiazolyl) pyridines have been synthesized from 2, 6 dipicolinic acid, starting from esterification it undergoes reaction with hydrazine hydrate and then cyclocondensation in presence of CS_2 and KOH in excess ethanol, resulting in formation of Bis 2,6[2-thiono(substituted oxadiazolyl)]pyridines pyridines (II). This on further reaction with substituted aldehydes in presence of glycine in excess methanol yields Bis 2,6[2-thiono(substituted methyl) -1,3,4 oxadiazol-5-yl] pyridines (III). Elemental analysis IR and H'NMR data confirmed the structure of newly synthesized compounds. All of them were screened for antifungal activity against *Alternaria alternata* and *Fusarium moniliforme*.

Key words: Oxadiazol · Pyridine · IR · H'NMR · Antifungal activity · food poisoning technique

INTRODUCTION

Oxadiazole derivatives are well known for their wide range of biological activity [1] namely anti-inflammatory [2], analgesic [3], antipyretic [3,4], anticonvulsant [4, 5], antifungal [6-8], antiparasitic [9], antibacterial [10-14], antimycobacterial [15] etc. whereas, pyridine derivatives have been reported to have fungicidal [16-17], insecticidal [18], herbicidal [19] and bactericidal properties [20]. So, union of above two moieties are supposed to give compounds of diverse biological activities.

The current work was carried out to develop potential fungicides and agrochemicals to be used commercially to prevent losses at the farm level as well as during storage.

MATERIALS AND METHODS

The present work was carried out in the Department of chemistry, Agra College, Agra, India. Further characterization of the synthesized compounds by NMR and IR spectroscopy were done at the Central Drug Research Institute (CDRI), Lucknow, India.

All melting points were taken in open capillaries and are uncorrected. The IR and H'NMR spectra are recorded and DMSO-d_6 was used as solvent. All the fungicidal activities are studied by food poisoning technique [21-22] and readings are taken as growth of fungus in vertical and horizontal diameters in centimeters at 28 ± 1°C in sterilized petriplates at 10, 100 and 1000 ppm concentrations of synthesized compounds.

Preparation of 2, 6 Bis - 2 - Thiono - 1, 3, 4 Oxadiazol - 5 - Yl - Pyridine (II): 2, 6 dipicolinic acid hydrazide (1mole) was dissolved in CS_2 (2 moles) and added KOH (2 moles) which was refluxed for 4 hours using ethanol as solvent on water bath, then content was poured in ice water containing conc. HCl. The precipitate thus formed was filtered, washed and dried and recrystallized from aqueous ethanol.

Mp. (250°C), M.F. $C_9H_5N_5O_2S_2$
(IR 3473 (N - H) pyridine, 1418 (C = C) aromatic, 1050 (C - O - C), 727 (C - S)
H'NMR - 7.65 (3H pyridine, 10.3 - SH)

Preparation of Bis 2, 6 [(3 - Substituted Methyl) - 2 - Thiono 1, 3, 4 - Oxadiazol - 5 YL] Pyridines: Compound above (0.01 m *i.e.* 2.67 gms), glycine (0.02 moles *i.e.* 1.5 gms) and 4-chlorobenzaldehyde (0.02 mole *i.e.* 2.8 gms) in excess methanol was refluxed for 4 hours, kept at room temperature for 2 hours and then filtered, washed and dried, recrystallized from aqueous C_2H_5OH. Similarly other compounds of this series were synthesized.

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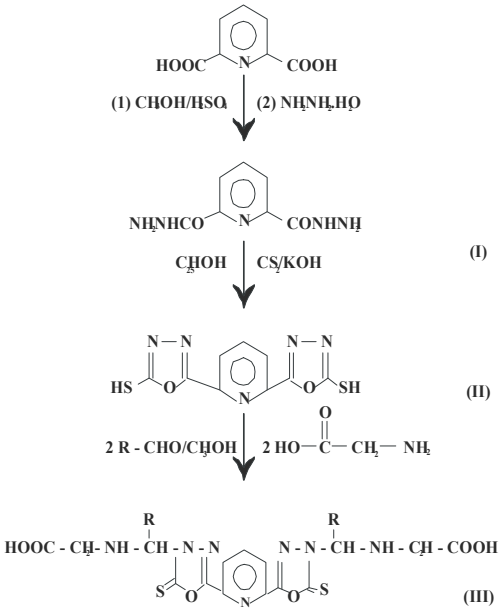
RESULTS AND DISCUSSION

In continuation of our earlier work on the synthesis of N-bridged azoles and their fungicidal activity [23, 24] we report in this paper the synthesis and fungicidal activity of substituted oxadiazolyl pyridine. Literature survey shows that substituted 1,3,4-oxadiazoles exhibit broad spectrum of antifungal [25], antibacterial [26] and other biological activities [27].

Further studies are also being carried out in the Dept. of Bioscience and Biotechnology, Banasthali University, Banasthali, India, on the antifungal activity and systemic acquired response (SAR) with a view of using these compounds as chemical activators of SAR in disease resistance as well as using them for developing potential fungicides.

Bis 2, 6 [(3-substituted methyl) - 2 - thiono 1, 2, 4 - oxadiazol - 5yl] pyridines were prepared according to scheme (I)



Scheme (I)

Table 1: Physical analytical and spectroscopic data for compounds III (a - e)

S.No	Colour	M.P.	Yield	Molecular Formula	Elemental analysis C	H	N
III a	black	230°	22.6	$C_{23}H_{21}N_7O_8S_2$	47.01	3.57	16.69
					(40.02	1.56	10.68)
III b	crimson	202	59.47	$C_{27}H_{23}O_6N_7S_2$	47.01	3.57	16.69
					(43.02	2.56	14.02)
IIIc	yellow crystals	179	99.11	$C_{27}H_{21}O_6Cl_2N_7S_2$	48.07	3.11	14.54
					(45.05	2.07	13.03)
III d	yellow	231	98.53	$C_{27}H_{21}O_{10}N_9S_2$	46.61	3.02	18.11
					(44.08	2.09	16.08)
III e	pale yellow	220	99.06	$C_{27}H_{21}O_{10}N_9S_2$	46.61	3.02	18.11
					(44.00	2.08	16.01)
III f	Light brown	270	98.76	$C_{27}H_{19}N_9Cl_2S_2$	42.40	2.48	16.47
					(42.00	2.02	16.02)
III g	brown	222	174.00	$C_{29}H_{27}O_8N_7S_2$	52.33	4.06	14.73

(50.323.0512.72)

Table 2: Antifungal activity (IIIa - g)

S.No.	Alternaria alternata (V/H) Control	10ppm	100ppm	1000ppm	Fusarium moniliforme (V/H) Control	10ppm	100ppm	1000ppm
III a	2.0	1.7	1.4	1.2	2.6	1.6	1.5	1.3
	2.0	1.7	1.4	1.2	2.4	1.7	1.5	1.3
III b	1.2	0.9	0.5	0.4	3.3	3.0	2.2	1.6
	1.2	0.9	0.5	0.4	3.4	3.0	2.0	1.3
III c	4.0	3.2	1.5	0.9	4.5	3.6	2.0	1.3
	3.7	2.5	2.0	1.1	4.5	3.6	2.2	1.4
III d	3.1	1.1	1.0	0.9	3.5	2.5	2.8	2.2
	3.0	1.1	1.0	0.9	3.5	2.7	2.4	2.2
III e	2.1	2.0	1.8	1.5	3.9	3.8	3.7	3.4
	2.1	2.0	1.8	1.5	3.9	3.8	3.7	3.4
III f	3.1	2.9	2.8	2.0	3.9	3.8	3.7	3.5
	3.4	2.9	2.8	2.0	3.9	3.8	3.7	3.5
III g	3.3	2.0	1.9	0.7	5.0	3.9	2.9	2.8
	3.4	1.7	1.5	0.9	5.5	4.5	3.7	2.8

- III (a)=C_5H_5CHOIII (d)2 NO_2 - C_6H_4CHO
- III (b)=C_6H_5CHOIII (e)3 NO_2 - C_6H_4CHO
- III (c)=4 - Cl C_6H_4CHOIII (f)2 - Cl, 5 - $NO_2.C_6H_5CHO$
- II (g) 4 - CH_3O - C_6H_4CHO

IR, NMR Data for III b:

- 3120 = N - H stretching, 1941 = CH (CH_2 stretching), 1605, 1510
- 1401 → C = C (aromatic), 1030 → C - O - C, 1685 - C = N,
- 825 → C - Cl

H'NMR → 3.7 - 4.0 → (m, 4 H, CH_2), 7.7 - 8.7 (m - aromatic) 6.9 → N - H aromatic, 12.3 → S - H

III (g) IR:

- 3117 - N - H (stretching), 2171 → C - H stretching
- 1665 → C - N (stretching) 1400, 1498, 1593 → C = C (aromatic)
- 1078 → C - O - C, 928 → C - S, 1330 - C - H,
- 836 → para substituted
- NMR → 12.5 → (s, 1 H, COOH), 9.8 → (s, 1 H, NH)
- 73 - 7.6 → (m, 3 H, pyridine), 7.9 - 8.7 →
- m, 5 H, Aromatic, 3.4 - 3.7 → (m, 3 H, OCH_3)

Compound III c is most active against both fungal species, whereas others are moderate. Compound III g is most active against *Alternaria alternata.* Least active compound against *Alternaria* is III e, whereas III f and III e are least active against *Fusarium moniliforme.*

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