

Synthesis of Some Dihydropyridino Pyrazoles and Oxadiazole 5-Thiones and Their Antimicrobial Activity

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Hydrazides of substituted 1,4-dihydropyridines have been synthesised by condensing substituted dihydropyridine dicarboxylic acid ester with hydrazine hydrate. The hydrazides on condensing with β -diketones and CS_2/KOH give pyrazoles and oxadiazole 5-thiones respectively. The synthesised compounds were screened for antimicrobial activity.

INTRODUCTION

Antiinflammatory activity is associated with several compounds possessing pyrazole ring system^{1,2}. A dramatic increase in the antiinflammatory activity of cortisone and other steroids incorporating pyrazole nucleus in the molecule has also been reported³. The biological activities of 1,3,4-oxadiazoles such as tuberculosic⁴, anticonvulsant⁵, antimitotic⁶, analgesic, antiinflammatory, diuretic and antimetic properties are known. These observations prompted us to synthesise some pyrazoles and oxadiazole-5-thiones incorporating substituted dihydropyridino moiety. The 1,4-dihydro-4-phenyl-2,6-dimethyl-3,5-diacid hydrazides (I) on condensing with β -diketones give pyrazoles 1–24 (Table-1). The acid hydrazides on condensing with CS_2/KOH give oxadiazole-5-thiones 1–18 (Table-2). The steps involved in the synthesis are shown in Scheme-I. All compounds were screened for their antimicrobial activity against *Alternaria brassicicola*, *Fusarium udam*, *Staphylococcus* gram (+ve) and *Lactobacillus* gram (–ve).

EXPERIMENTAL

All melting points were taken in open capillary in a liquid paraffin bath and are uncorrected. Purity of all compounds was checked by TLC. IR spectra were recorded in nujol mulls on a Perkin-Elmer IR 1420 spectrophotometer while PMR spectra on FT-80A Spectrometer in CDCl_3 using TMS as an internal standard.

3,5-Bis(3',5'-dimethyl pyrazol-1'-yl carbonyl)-2,6-dimethyl-4-phenyl-1,4-dihydropyridine (01): A mixture of hydrazide (I) (0.01 mol), acetyl acetone (0.01 mol) and few drops of HCl is refluxed in ethanol (25 mL) for 4 h. The reaction

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TABLE-1
 CHARACTERISATION DATA OF PYRAZOLES (1-24)

Compd. No.	R	R'	R''	Yield %	m.p.* (°C)	Molecular Formula	N% Found (Calcd.)
1	C ₆ H ₅	CH ₃	CH ₃	70	190	C ₂₅ H ₂₇ N ₃ O ₂	16.01 (16.31)
2	C ₆ H ₅	C ₆ H ₅	2-OH-5-Cl C ₆ H ₃	78	168	C ₄₅ H ₃₃ N ₅ O ₄ Cl ₂	8.70 (8.90)
3	C ₆ H ₅	3-Cl C ₆ H ₄	2-OH-5-CH ₃ C ₆ H ₃	76	159	C ₄₆ H ₃₅ N ₅ O ₄ Cl ₂	8.71 (8.83)
4	2-Cl C ₆ H ₄	CH ₃	CH ₃	69	155	C ₂₅ H ₂₆ N ₅ O ₂ Cl	14.80 (15.10)
5	2-Cl C ₆ H ₄	C ₆ H ₅	2-OH-5-Cl C ₆ H ₃	73	138	C ₄₅ H ₃₂ N ₅ O ₄ Cl ₃	8.42 (8.61)
6	2-Cl C ₆ H ₄	3-Cl C ₆ H ₄	2-OH-5-CH ₃ C ₆ H ₃	78	142	C ₄₆ H ₃₄ N ₅ O ₄ Cl ₃	8.20 (8.46)
7	4-Cl C ₆ H ₄	CH ₃	CH ₃	72	185	C ₂₅ H ₂₆ N ₅ O ₂ Cl	14.80 (15.10)
8	4-Cl C ₆ H ₄	C ₆ H ₅	2-OH-5-Cl C ₆ H ₃	71	146	C ₄₅ H ₃₂ N ₅ O ₄ Cl ₃	8.41 (8.61)
9	4-Cl C ₆ H ₄	3-Cl C ₆ H ₄	2-OH-5-CH ₃ C ₆ H ₃	77	171	C ₄₆ H ₃₄ N ₅ O ₄ Cl ₃	8.21 (8.46)
10	4-OCH ₃ C ₆ H ₄	CH ₃	CH ₃	71	175	C ₂₆ H ₂₉ N ₅ O ₃	15.05 (15.25)
11	4-OCH ₃ C ₆ H ₄	C ₆ H ₅	2-OH-5-Cl C ₆ H ₃	70	178	C ₄₆ H ₃₅ N ₅ O ₅ Cl ₂	8.62 (8.83)
12	4-OCH ₃ C ₆ H ₄	3-Cl C ₆ H ₄	2-OH-5-CH ₃ C ₆ H ₃	68	171	C ₄₇ H ₃₇ N ₅ O ₅ Cl ₂	8.21 (8.51)
13	3-Cl C ₆ H ₄	CH ₃	CH ₃	73	180	C ₂₅ H ₂₆ N ₅ O ₂ Cl	14.84 (15.10)
14	3-Cl C ₆ H ₄	C ₆ H ₅	2-OH-5-CH ₃ C ₆ H ₃	76	178	C ₄₅ H ₃₂ N ₅ O ₄ Cl ₃	8.21 (8.61)
15	3-Cl C ₆ H ₄	3-Cl C ₆ H ₄	2-OH-5-CH ₃ C ₆ H ₃	72	165	C ₄₆ H ₃₄ N ₅ O ₄ Cl ₃	8.16 (8.46)
16	4-CH ₃ C ₆ H ₄	CH ₃	CH ₃	77	161	C ₂₆ H ₂₉ N ₅ O ₂	8.80 (8.80)
17	4-CH ₃ C ₆ H ₄	C ₆ H ₅	2-OH-5-CH ₃ C ₆ H ₃	78	169	C ₄₆ H ₃₅ N ₅ O ₄ Cl ₂	8.40 (8.61)
18	4-CH ₃ C ₆ H ₄	3-Cl C ₆ H ₄	2-OH-5-CH ₃ C ₆ H ₃	79	173	C ₄₇ H ₃₇ N ₅ O ₄ Cl ₂	8.40 (8.68)
19	4-NO ₂ C ₆ H ₄	CH ₃	CH ₃	73	174	C ₂₅ H ₂₆ N ₆ O ₄	14.37 (14.76)
20	4-NO ₂ C ₆ H ₄	C ₆ H ₅	2-OH-5-CH ₃ C ₆ H ₃	74	179	C ₄₅ H ₃₂ N ₆ O ₆ Cl ₂	8.20 (8.50)
21	4-NO ₂ C ₆ H ₄	3-Cl C ₆ H ₄	2-OH-5-CH ₃ C ₆ H ₃	73	162	C ₄₆ H ₃₄ N ₆ O ₆ Cl ₂	8.15 (8.36)
22	2-CH ₃ C ₆ H ₄	CH ₃	CH ₃	75	167	C ₂₆ H ₂₉ N ₅ O ₂	15.62 (15.80)
23	2-CH ₃ C ₆ H ₄	C ₆ H ₅	2-OH-5-Cl C ₆ H ₃	76	158	C ₄₆ H ₃₅ N ₅ O ₄ Cl ₂	9.52 (9.61)
24	2-CH ₃ C ₆ H ₄	3-Cl C ₆ H ₄	2-OH-5-CH ₃ C ₆ H ₃	78	160	C ₄₇ H ₃₇ N ₅ O ₄ Cl ₂	8.51 (8.68)

*All compounds were crystallised from ethyl alcohol.

1605 cm^{-1} ($\text{C}=\text{C}$); PMR: δ 2.23 (s, 6H, $-\text{CH}_3$), 5.75 (s, 1H $-\text{CH}$ pyridyl), 7.1–7.5 (m, 5H, aromatic proton), 8.5–9.5 (s, 1H, $-\text{NH}$ pyridyl) and 14.4 (s, 1H $-\text{NH}$ oxadiazole).

Antimicrobial Activity

From the activity data it is observed that compound nos. 9, 12, 18, 7, 10, 13 and 13 from Table-1 and Table-2 respectively were screened for their antifungal activity against *Alternaria brassicicola* and *Fusarium udam* while for antibacterial activity against *Lactobacillus* and *E. coli* by paper disc method⁸, at 250 ppm and 500 ppm concentration in dimethyl sulfoxide. Standard Zapkes medium was used. Filter paper discs of 5 mm size were used, and the diameters of zones of inhibition formed around each disc after incubating for a period of 48 h at 30°C were recorded. Results were compared with reference to fungicides (carben-diazium) and bactericide (streptomycine). The compounds 9 and 21 (Table-1) and 7, 10, and 13 (Table-2) were showing good results when compared with standards because 9 is having more percentage of Cl atoms while 21 is having nitro-group as well as Cl compounds. 7, 10 and 13 are having thione group in it.

TABLE-2
CHARACTERISATION DATA OF OXADIAZOLE 5-THIONFS (1–18)

Compd. No	R	Yield %	m.p.* (°C)	Molecular formula	% N	
					Found	(Calcd.)
1	C ₆ H ₅	68	150	C ₁₇ H ₁₅ N ₅ O ₂ S ₂	18.00	(18.18)
2	3-NO ₂ C ₆ H ₄	70	173	C ₁₇ H ₁₄ N ₆ O ₄ S ₂	19.21	(19.53)
3	4-NO ₂ C ₆ H ₄	72	148	C ₁₇ H ₁₄ N ₆ O ₄ S ₂	19.23	(19.53)
4	2-Cl C ₆ H ₄	75	167	C ₁₇ H ₁₄ N ₅ O ₂ S ₂ Cl	16.42	(16.68)
5	3-Cl C ₆ H ₄	73	158	C ₁₇ H ₁₄ N ₅ O ₂ S ₂ Cl	16.51	(16.68)
6	4-Cl C ₆ H ₄	76	172	C ₁₇ H ₁₄ N ₅ O ₂ S ₂ Cl	16.33	(16.68)
7	3-Br C ₆ H ₄	69	178	C ₁₇ H ₁₄ N ₅ O ₂ S ₂ Br	14.80	(15.08)
8	2-OCH ₃ C ₆ H ₄	71	135	C ₁₈ H ₁₇ N ₅ O ₃ S ₂	16.60	(16.86)
9	3-OCH ₃ C ₆ H ₄	77	145	C ₁₈ H ₁₇ N ₅ O ₃ S ₂	16.66	(16.86)
10	4-OCH ₃ C ₆ H ₄	79	153	C ₁₈ H ₁₇ N ₅ O ₃ S ₂	16.62	(16.86)
11	2-CH ₃ C ₆ H ₄	80	161	C ₁₈ H ₁₇ N ₅ O ₂ S ₂	17.23	(17.54)
12	3-CH ₃ C ₆ H ₄	72	173	C ₁₈ H ₁₇ N ₅ O ₂ S ₂	17.21	(17.54)
13	4-CH ₃ C ₆ H ₄	75	139	C ₁₈ H ₁₇ N ₅ O ₂ S ₂	17.21	(17.54)
14	2-OH C ₆ H ₄	76	102	C ₁₇ H ₁₅ N ₅ O ₃ S ₂	17.34	(17.45)
15	4-OH C ₆ H ₄	73	198	C ₁₇ H ₁₅ N ₅ O ₃ S ₂	17.31	(17.45)
16	2-Furyl	71	170	C ₁₅ H ₁₃ N ₅ O ₃ S ₂	18.52	(18.66)
17	3-Pyridyl	76	205	C ₁₆ H ₁₄ N ₆ O ₂ S ₂	21.61	(21.81)
18	2-Thienyl	77	168	C ₁₅ H ₁₃ N ₅ O ₃ S ₃	17.68	(17.90)

*All compounds were crystallised from ethyl alcohol.

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