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Synthesis of Some Diimidazolin-5-One Carboxamide Derivatives of 1,4-Dihydropyridine as Possible Antifungals and Insecticidals

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Diimidazolin-5-one carboxamide derivatives of 1,4-dihydropyridine were prepared in three steps: 1,4-dihydro-2,6-dimethyl-4-(aryl-substituted/2-furyl) pyridine-3,5-dicarboxylic acid dimethyl ester (I) were prepared by condensing methylacetoacetate, aromatic aldehydes and ammonia in the presence of ethanol. (I) on treatment with hydrazine hydrate gave 1,4-dihydro-2,6-dimethyl-4-(aryl-substituted/2-furyl) pyridine-3,5-dihydrazide (II). (II) on treatment with 4-benzylidene-2-phenyloxazol-5-one/4-furalidene-2- phenyloxazol-5-one in the presence of anhydrous pyridine gave 1,4-dihydro-2,6-dimethyl-4-(aryl-substituted/2-furyl) pyridine-3,5-di- [N-(4-(benzylidene substituted/furalidene)-2-phenyl imidazolin-5-one) carboxamide] (III).

Key Words: Synthesis, Diimidazolin-5-one Carboxamide, 1,4-Dihydropyridine, Antifungals, Insecticidals.

INTRODUCTION

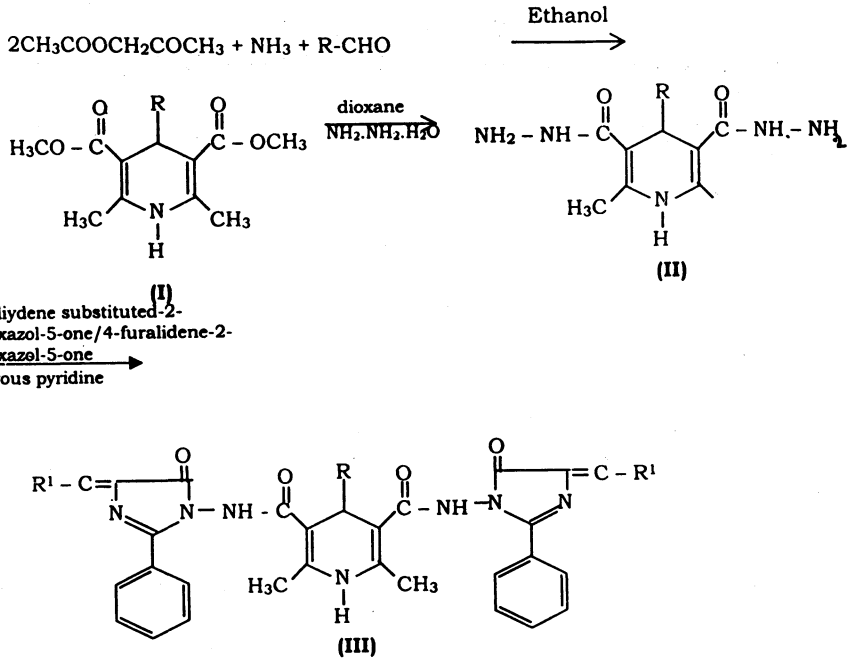
1,4-Dihydropyridine was first obtained more than a century ago by Hantzsch[1]. N-Substituted-4-aryl-1,4-dihydropyridines are versatile intermediates in the synthesis of pharmacologically active products[2]. The dimers of 4-aryl-1,4-dihydropyridines are of interest as novel potential inhibitors of HIV-1 protease and have anticancer activity[3]. The 1,4-dihydropyridines are oxygen transferring coenzymes of utmost importance in biological system. They have been reported to possess weak analgesic, curare like properties[4], antitumour[5] and coronary dilating activities[6]. The above works revealed that 1,4-dihydropyridines were active drugs with prolonged antihypertensive activity.

Since we did not find any reports regarding 1,4-dihydropyridines as antifungals and insecticides, and encouraged by the fact that furazolidone containing an oxazolone system is effective against a wide range of enteric infections and nitrofurantoin with imidazolone system has a broad spectrum of antimicrobial activity[7], here we report the synthesis of some new 1,4-dihydropyridine derivatives having imidazolin-5-one moieties at 3 and 5 positions.

Methylacetoacetate on treatment with different aromatic aldehydes in the presence of ammonia and ethanol gave 1,4-dihydro-2,6-dimethyl-4-(aryl-substi-

tuted/2-furyl) pyridine-3,5-dicarboxylic acid dimethyl ester **(I).** **(I)** on treatment with hydrazine hydrate in the presence of dioxane gave 1,4-dihydro 2,6-dimethyl-4-(aryl substituted/2-furyl) pyridine-3,5-dihydrazide **(II).** **(II)** on treatment with 4-benzylidene-2-phenyloxazol-5-one/4-furalidene2-phenyloxazol-5-one in the presence of anhydrous pyridine gave 1,4-dihydro-2,6-dimethyl-4-(aryl-substituted/2-furyl) pyridine-3,5-di[N-(4-(benzylidene substituted/furalidene)-2-phenyl imidazolin-5-one) carboxamide] **(III).** All the compounds were screened for antifungal and insecticidal activities.

Scheme-1



EXPERIMENTAL

Melting points were determined in open capillaries in a liquid paraffin bath and are uncorrected. Purity of the compounds was checked by TLC. IR spectra (KBr) were recorded on FTIR-Shimadzu 8400/8900 spectrophotometer. The structure of the compounds were established on the basis of elemental analysis and IR spectral data.

The IR spectra of the compounds show characteristic bands at 1870–1800 cm^{-1} ν(—C=O of imidazoline), 1680–1600 cm^{-1} ν(—C=N of imidazolone), 3085–3025 cm^{-1} ν(—C—H of pyridine), 1050–900 cm^{-1} (pyridine ring breathing), 1650–1610 cm^{-1} ν(—C=C— str. of pyridine ring).

1,4-Dihydro-2,6-dimethyl-4-(arylsubstituted/2-furyl) pyridine-3,5-dicarboxylic acid dimethyl ester **(I):** To a solution of aromatic aldehyde (0.03 mol) in ethanol (50 mL), methylacetoacetate (0.06 mol) and liquid ammonia (2.5 mL) were added. The mixture was refluxed for 4 h and the solid obtained was collected and filtered. It was washed with cold ethanol and recrystallised from ethanol.

1,4-dihydro-2,6-dimethyl-4-(aryl-substituted/2-furyl) pyridine-3,5-dihydrazide **(II):** A mixture of 1,4-dihydro-2,6-dimethyl-4-(aryl-substituted/2-furyl) pyridine-3,5-dicarboxylic acid dimethyl ester (I) (0.01 mol) and hydrazine hydrate (0.02 mol) in dioxane (25 mL) were refluxed for 7 h over a sand bath. The mixture was concentrated by distillation under reduced pressure. The concentrated mixture is poured over crushed ice. The solid formed is recrystallised from ethanol.

1,4-Dlhydro-2,6-dimethyl-4-(arylsubstituted / 2-furyl) pyridine-3,5-di [N-(4-(benzylidene substituted/furalidene)-2-phenyl imidazolin-5-one) carboxamide] **(III):** A mixture of 1,4-dihydro-2,6-dimethyl-4-(aryl-substituted/-2-furyl)pyridine-3,5-dihydrazide (II) and 4-benzylidene substituted-2-phenyloxazol-5-one/4-furalidene-2-phenyloxazol-5-one[8] in the presence of anhydrous pyridine (25 mL) were refluxed for 8 h.

The excess pyridine was distilled off under reduced pressure and the concentrated mixture was poured over crushed ice and neutralised with conc. HCl. The precipitate formed was washed with water and recrystallised from glacial acetic acid. The yields, melting points and elemental analysis data are shown in Table-1.

TABLE-1
ANALYTICAL AND PHYSICAL DATA OF VARIOUS 1,4-DIHYDROPYRIDINES

S.No.	R or R^1	m.f. (m.w.)	m.p. (°C)	Yield (%)	% Analysis: Found (Calcd.)		
					C	N	H
1.	C_6H_5	$C_{47}H_{37}N_7O_4$ (763)	168	71	73.90 (73.91)	12.86 (12.84)	4.82 (4.84)
2.	4-OCH_3-C_6H_4	$C_{50}H_{43}N_7O_7$ (853)	155	66	70.24 (70.33)	11.57 (11.48)	5.06 (5.04)
3.	4-Cl-C_6H_4	$C_{47}H_{34}N_7O_4Cl_3$ (866.5)	173	84	65.17 (65.08)	11.22 (11.30)	4.01 (3.92)
4.	2-furyl	$C_{41}H_{31}N_7O_7$ (733)	163	54	67.12 (67.12)	13.30 (13.36)	4.19 (4.22)
5.	4-OH-3-OCH_3-C_6H_4	$C_{50}H_{43}N_7O_{10}$ (901)	181	59	66.47 (66.59)	10.94 (10.87)	4.69 (4.77)

Pharmacological Screening

Antifungal Activity: Antifungal activity is done *in-vitro*[9-10] by filter paper disc diffusion plate method[11].

The medium is prepared by mixing agar agar, dextrose, and potato slices in

distilled water. The test sample solutions of 4 and 2% were prepared in DMF. The filter paper discs of 6 mm diameter which were soaked in the percentage solutions were kept on the culture and mantained at 37°C for 72 h. A clear zone of growth of inhibition was found around the discs in some of the plates. The results are shown in Table-2.

TABLE-2
ANTIFUNGAL ACTIVITY RESULTS

S.No.	R or R^1	*Aspergillus niger*		*Aspergillus parasitica*		*Trichoderma viridae*		*Chrysosporium* sps.	
		4%	2%	4%	2%	4%	2%	4%	2%
1.	C_6H_5	+++	++	++	+	++	+	+++	++
2.	4-OCH_3-C_6H_4	+++	++	++	+	++	+	+++	++
3.	4-Cl-C_6H_4	–	–	+++	++	+++	++	++	+
4.	2-Furyl	+++	++	+++	++	+++	++	++	+
5.	4-OH-3-OCH_3-C_6H_4	++	+	+++	++	–	–	+++	+

(+) : inhibition zone occurs
(–) : inhibition zone absent.
+ : inhibition zone 10 mm and below
++ : inhibition zone above 10 mm.
+++ : inhibition zone above 15 mm
++++ : inhibition zone above 20 mm.

Insecticidal Activity: Insecticidal activity was done on cockroaches, by injecting test sample solution in the abdominal region. The 4% (w/v) solutions of test samples were prepared in acetone. The time of death was noted as K_D value (knockdown value). The results are shown in Table-3.

TABLE-3
INSECTICIDAL ACTIVITY RESULTS

S.No.	R or R^1	Time of death. (K_D in min)
1.	C_6H_5	25
2.	4-OCH_3-C_6H_4	18
3.	4-Cl-C_6H_4	16
4.	2-furyl	20
5.	4-OH-3-OCH_3-C_6H_4	15
6.	Standard cypermethrin 25% (EC)	5

RESULTS AND DISCUSSION

The compounds exhibited moderate to good antifungal and insecticidal activity.

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