SYNTHESIS OF 2-(4-ARYL-2-PYRAZOLIN-3-YL)-1,8-NAPHTHYRIDINES BY 1,3-DIPOLAR CYCLOADDITION*

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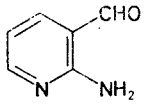
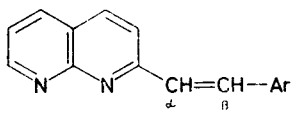
2-(4-Aryl-2-pyrazolin-3-yl)-1,8-naphthyridines *III* have been prepared by the cycloaddition of diazomethane to 2-styryl-1,8-naphthyridines *II*. The structures of the compounds have been confirmed by elemental analyses and spectral data. All these compounds have been screened for fungicidal activity.

The biological importance of 1,8-naphthyridines[1-4] as well as pyrazolines[5-7] prompted us to construct molecules possessing both the ring systems. With this aim in view and in continuation of our earlier work on the synthesis and biological activity of substituted 1,8-naphthyridines[8-12], we report the synthesis and fungicidal activity of the hitherto unreported 2-(4-aryl-2-pyrazolin-3-yl)-1,8-naphthyridines.

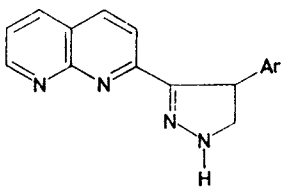
The starting compounds, 2-styryl-1,8-naphthyridines (*II*) were obtained by condensation of 2-aminonicotinaldehyde (*I*) with benzalacetones in ethanol containing a catalytic amount of potassium hydroxide[8]. Cycloaddition of diazomethane to



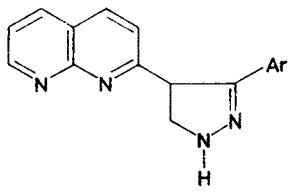
I



II



III



IV

* Part XIV in the series Substituted 1,8-Naphthyridines; Part XIII: Indian Drugs, in press.

styryl naphthyridines *II* in dry ether furnished 2-(4-aryl-2-pyrazolin-3-yl)-1,8-naphthyridines *IIIa–IIIj* in reasonable yields. The initially formed 1-pyrazolines evidently underwent prototropic rearrangement to give *III*. The absence of the isomeric 2-(3-aryl-2-pyrazolin-4-yl)-1,8-naphthyridines *IV* may be ascribed to the polarisation of the ethylenic double bond in *II* towards the naphthyridine moiety by the ring C=N rendering the β-carbon positively charged[13]. The pyrazolines obtained are stable and have very long half-life as indicated by invariable melting points measured from time to time. This is the first report of cycloaddition of diazomethane to the 1,8-naphthyridine derivative.

The structures of these compounds were in conformity with their elemental analyses (Table I) and spectral data.

TABLE I
Analytical data of compounds *III*

Compound (yield, %)	Ar	M.p. °C	Formula (M.w.)	Calculated/Found		
				% C	% H	% N
IIIa	phenyl	125	$C_{17}H_{14}N_4$	74·45	5·11	20·44
(55)			(274·4)	74·34	5·07	20·38
IIIb	*p*-methylphenyl	112	$C_{18}H_{16}N_4$	75·00	5·55	19·44
(70)			(288·4)	75·15	5·60	19·51
IIIc	*p*-methoxyphenyl	141	$C_{18}H_{16}N_4O$	71·12	5·26	18·42
(67)			(304·4)	71·01	5·21	18·48
IIId	*o*-chlorophenyl	125	$C_{17}H_{13}ClN_4$	66·23	4·22	18·18
(52)			(308·4)	66·35	4·26	18·11
IIIe	*p*-chlorophenyl	136	$C_{17}H_{13}ClN_4$	66·23	4·22	18·18
(60)			(308·4)	66·33	4·27	18·13
IIIf	*p*-(N,N-dimethyl-	126	$C_{19}H_{19}N_5$	71·92	5·99	22·08
(50)	amino)phenyl		(317·4)	71·83	5·93	22·17
IIIg	2,4-dichlorophenyl	176	$C_{17}H_{12}Cl_2N_4$	59·65	3·51	16·37
(55)			(343·2)	59·75	3·58	16·30
IIIh	2,6-dichlorophenyl	231	$C_{17}H_{12}Cl_2N_4$	59·65	3·51	16·37
(50)			(343·2)	59·74	3·57	16·31
IIIi	2-methoxy-3,5-di-	130	$C_{18}H_{14}Cl_2N_4O$	58·06	3·76	15·05
(48)	chlorophenyl		(373·2)	58·20	3·71	15·12
IIIj	2-thienyl	106	$C_{15}H_{12}N_4S$	64·28	4·29	20·00
(50)			(280·3)	64·17	4·25	20·08

The IR spectra of *III* indicated the presence of NH grouping at 3 410 cm^{-1}. The ^1H NMR spectrum of *IIIb* in deuteriochloroform showed a three proton singlet at 2·25 due to methyl group. The multiplets in the region 4·90–5·20, 3·95–4·20 and

TABLE II

Fungicidal screening results of compounds *III* (expressed as % spore germination inhibition)

C_{III}, ppm	*D. rostrata*	*F. oxysporum*	*D. rostrata*	*F. oxysporum*
	IIIa		*IIIf*	
130	5·9	12·5	28·8	19·3
160	16·6	18·6	36·4	32·4
190	29·4	29·6	51·9	44·2
220	41·8	49·4	72·5	59·8
250	60·6	62·4	80·5	70·6
	IIIb		*IIIg*	
130	15·7	8·8	15·8	20·6
160	28·8	24·7	29·5	38·2
190	40·1	39·8	42·1	60·0
220	62·1	60·0	66·7	84·1
250	75·0	82·8	82·1	100·0
	IIIc		*IIIh*	
130	8·0	12·8	12·0	15·7
160	22·6	25·0	21·8	29·7
190	36·4	37·0	32·4	41·6
220	43·8	48·5	55·2	60·5
250	54·1	61·9	70·0	77·2
	IIId		*IIIi*	
130	8·7	17·4	24·4	20·5
160	22·1	34·1	43·8	38·5
190	39·5	65·4	67·0	69·6
220	60·6	71·0	88·6	100·0
250	72·8	100·0	100·0	100·0
	IIIe		*IIIj*	
130	10·4	18·9	33·5	46·8
160	23·5	26·4	53·7	75·2
190	36·8	34·7	85·4	91·3
220	59·4	51·4	97·8	100·0
250	74·6	72·7	100·0	100·0

3·60–3·85 could be attributed to the pyrazoline $CHCH_2$ protons (AMX pattern). The NH proton appeared as a broad singlet at 7·1 (exchangeable with D_2O). The C-3, C-4, C-5, C-6 and C-7 protons on naphthyridine framework appeared as multiplets centred at 8·1, 8·4, 9·0, 7·9 and 9·2, respectively. The remaining four aromatic protons appeared as a multiplet at 7·2–7·7. Mass spectral data of *III* (formation of styrene) also support the proposed structure. The mass spectra of *IIIa* and *IIIe* showed molecular ions at *m/z* 274 and 308 and other significant peaks appeared at *m/z* 104 and 138 ascribable to styrene and *p*-chlorostyrene, respectively.

All the compounds synthesized were screened for their fungicidal activity against *Drechslera rostrata* and *Fusarium oxysporum* using the glass slide-humid Chamber technique[14]; concentrations 130, 160, 190, 220, and 250 ppm were used. These compounds showed good fungicidal activity. The fungicidal screening results are summarised in Table II.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The compounds were routinely checked for their purity by TLC on silicagel G. The IR spectra in KBr were recorded on a Perkin–Elmer 283 spectrophotometer (ν_{max} in cm^{-1}). 100 MHz ^1H NMR spectra were recorded on a Varian XL-100 spectrometer using tetramethylsilane as an internal reference. Chemical shifts are expressed in ppm. Mass spectra were recorded on a Varian MAT CH-7 mass spectrometer at 70 eV.

2-(4-Aryl-2-pyrazolin-3-yl)-1,8-naphthyridines (*IIIa–IIIj*)

To a solution of *II* (1 mmol) in dry benzene (30 ml), was added slowly a solution of diazomethane (1 mmol) in dry ether (30 ml) and the mixture was stirred at room temperature for 3 h. The solvent was removed at ambient temperature and the gummy residue triturated with petroleum ether, filtered and crystallized from ethanol.

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