SYNTHESIS OF 2-METHYL-3-(5-PHENYL OR 1,5-DIPHENYL--2-PYRAZOLIN-3-YL)-1,8-NAPHTHYRIDINES

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3-Cinnamoyl-2-methyl-1,8-naphthyridines *II* have been synthesized utilizing Claisen–Schmidt condensation of 3-acetyl-2-methyl-1,8-naphthyridine *I* with aromatic aldehydes. The cinnamoyl naphthyridines react with hydrazine hydrate and phenylhydrazine to create the corresponding pyrazolinyl 1,8-naphthyridine derivatives (*III* and *IV*). The structures *II*—*IV* have been confirmed by their elemental analyses and spectral data. Some of the compounds have been screened for their fungicidal activity.

From literature, it is evident that both 1,8-naphthyridines[1-4] and pyrazolines[5-8] are well known for their varied biological activities. Therefore, it was considered interesting to bring these two biologically active moieties within a molecular framework and to study their additive effects on biological properties. As a step in this direction and in the continuation of our work on 1,8-naphthyridines[9-14], synthesis and fungicidal evaluation of the compounds depicted in the title were carried out and the results are presented in this communication.

The synthesis is depicted on Scheme 1. 3-Acetyl-2-methyl-1,8-naphthyridine (*I*) has been obtained by the condensation of 2-aminonicotinaldehyde with acetylacetone in ethanol with piperidine as a catalyst[15]. Claisen–Schmidt condensation of *I* with aromatic aldehydes resulted in the formation of 3-cinnamoyl-2-methyl-1,8-naphthyridines *IIa*—*j* with good yields. Structures of these compounds have been established by elemental analyses and spectral data (see Table I). The IR spectra of *II* displayed a band at 1 660 (unsaturated C=O) and an intensive band at 1 600 cm^{-1} (C=N). The mass spectra of *II* exhibited strong molecular ion peaks consistent with their elemental analyses.

The 3-(5-phenyl-2-pyrazolin-3-yl)-methyl-1,8-naphthyridines *IIIa*—*j* were prepared by the reaction of *II* with hydrazine hydrate in ethanol in the presence of few drops of glacial acetic acid. Formation of *II* takes place probably via 1,2-addition of hydrazine hydrate to the carbonyl group of *II*, followed by dehydrative cyclization

* Part X in the series Substituted 1,8-Naphthyridines; Part IX: Collect. Czech. Chem. Commun. *53*, 1539 (1988).

TABLE I

Analytical data of compounds *II*, *III* and *IV*

Compound (yield, %)	Ar	M.p.[a] °C	Formula (mol. wt.)	Calculated/found		
				% C	% H	% N
IIa (76)	C_6H_5	117	$C_{18}H_{14}N_2O$ (274·3)	78·83 78·77	5·10 5·03	10·21 10·15
IIb (80)	*o*-CH_3O—C_6H_4	120	$C_{19}H_{16}N_2O_2$ (304·3)	75·00 75·11	5·26 5·30	9·21 9·25
IIc (86)	*p*-CH_3O—C_6H_4	145	$C_{19}H_{16}N_2O_2$ (304·3)	75·00 75·09	5·26 5·20	9·21 9·17
IId (85)	*p*-CH_3—C_6H_4	158	$C_{19}H_{16}N_2O$ (288·3)	79·16 79·10	5·55 5·48	9·72 9·66
IIe (82)	*o*-Cl—C_6H_4	120	$C_{18}H_{13}ClN_2O$ (308·8)	70·12 70·00	4·22 4·18	9·09 9·02
IIf (88)	*p*-Cl—C_6H_4	101	$C_{18}H_{13}ClN_2O$ (308·8)	70·12 70·01	4·22 4·17	9·09 9·01
IIg (76)	*o*-OH—C_6H_4	140	$C_{18}H_{14}N_2O_2$ (290·3)	74·48 74·39	4·82 4·89	9·65 9·60
IIh (75)	3-CH_3O-4-OH—C_6H_3	162	$C_{19}H_{16}N_2O_3$ (320·3)	71·25 71·15	5·00 5·07	8·75 8·70
IIi (80)	*p*-$N(CH_3)_2$—C_6H_4	210	$C_{20}H_{19}N_3O$ (317·4)	75·70 75·80	5·99 5·91	13·24 13·15
IIj (70)	*m*-NO_2—C_6H_4	160	$C_{18}H_{13}N_3O_3$ (319·3)	67·71 67·78	4·07 4·00	13·16 13·09
IIIa (67)	C_6H_5	172	$C_{18}H_{16}N_4$ (288·3)	75·00 75·10	5·55 5·48	19·44 19·38
IIIb (72)	*o*-CH_3O—C_6H_4	189	$C_{19}H_{18}N_4O$ (318·4)	71·69 71·60	5·66 5·70	17·61 17·55
IIIc (80)	*p*-CH_3O—C_6H_4	160	$C_{19}H_{18}N_4O$ (318·4)	71·69 71·58	5·66 5·70	17·61 17·56
IIId (78)	*p*-CH_3—C_6H_4	190	$C_{19}H_{18}N_4$ (302·4)	75·49 75·58	5·96 5·89	18·54 18·64
IIIe (80)	*o*-Cl—C_6H_4	145	$C_{18}H_{15}ClN_4$ (322·8)	67·08 67·00	4·66 4·60	17·39 17·30
IIIf (84)	*p*-Cl—C_6H_4	220	$C_{18}H_{15}ClN_4$ (322·8)	67·08 67·00	4·66 4·61	17·39 17·30
IIIg (72)	*o*-OH—C_6H_4	205	$C_{18}H_{16}N_4O$ (304·3)	71·05 71·20	5·26 5·20	18·42 18·35

TABLE I
(*Continued*)

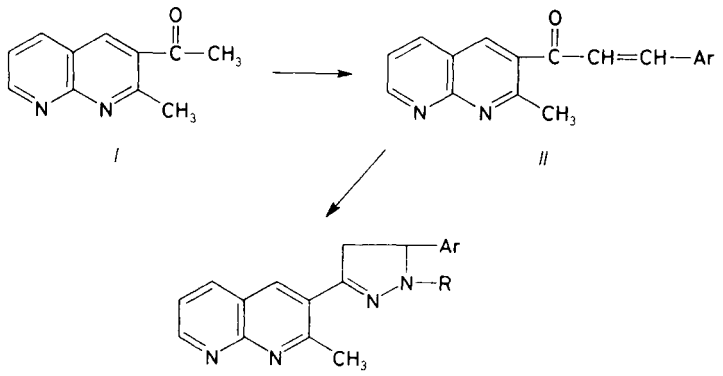
Compound (yield, %)	Ar	M.p.[a] °C	Formula (mol. wt.)	Calculated/found		
				% C	% H	% N
IIIh (70)	3-CH_3O-4-OH—C_6H_3	189	$C_{19}H_{18}N_4O_2$ (334·4)	68·26 68·10	5·39 5·32	16·77 16·82
IIIi (75)	*p*-$N(CH_3)_2$—C_6H_4	223	$C_{20}H_{21}N_5$ (331·4)	72·51 72·60	6·34 6·39	21·15 21·20
IIIj (62)	*m*-NO_2—C_6H_4	272	$C_{18}H_{15}N_5O_2$ (333·3)	64·86 64·80	4·50 4·45	21·02 21·09
IVa (72)	C_6H_5	195	$C_{24}H_{20}N_4$ (364·4)	79·12 79·00	5·49 5·43	15·38 15·30
IVb (76)	*o*-CH_3O—C_6H_4	192	$C_{25}H_{22}N_4O$ (394·5)	76·14 76·26	5·58 5·52	14·21 14·15
IVc (84)	*p*-CH_3O—C_6H_4	220	$C_{25}H_{22}N_4O$ (394·5)	76·14 76·25	5·58 5·53	14·21 14·14
IVd (82)	*p*-CH_3—C_6H_4	179	$C_{25}H_{22}N_4$ (378·5)	79·37 79·25	5·82 5·76	14·81 14·74
IVe (81)	*o*-Cl—C_6H_4	185	$C_{24}H_{19}ClN_4$ (398·9)	72·36 72·45	4·77 4·82	14·07 14·00
IVf (86)	*p*-Cl—C_6H_4	160	$C_{24}H_{19}ClN_4$ (398·9)	72·36 72·28	4·77 4·71	14·07 14·00
IVg (75)	*o*-OH—C_6H_4	195	$C_{24}H_{20}N_4O$ (380·4)	75·79 75·63	5·26 5·20	14·74 14·65
IVh (72)	3-CH_CO-4-OH—C_6H_C	225	$C_{25}H_{22}N_4O_2$ (410·5)	73·17 73·00	5·36 5·30	13·66 13·58
IVi (74)	*p*-$N(CH_3)_2$—C_6H_4	240	$C_{26}H_{25}N_5$ (407·5)	76·66 76·55	6·14 6·10	17·20 17·28
IVj (64)	*m*-NO_2—C_6H_4	190	$C_{24}H_{19}N_5O_2$ (409·4)	70·42 70·31	4·65 4·59	17·11 17·18

[a] Crystallized from ethanol.

and rearrangement. Their structures were confirmed by elemental analyses, IR, mass and ^1H NMR spectroscopies.

The reaction of *II* with phenylhydrazine in glacial acetic acid led to the formation of the 3-(1,5-diphenyl-2-pyrazolin-3-yl)-2-methyl-1,8-naphthyridines (*IVa–j*). Structures of these compounds were established by their elemental analyses and spectral

data. The IR spectra of *IV* revealed the absence of the C=O function and the mass spectrum of *IVa* showed the molecular ion at *m/z* 398.



SCHEME 1

Some of the compounds were screened for their antifungal activity against *Drechslera rostrata* and *Fusarium oxysporum* utilizing the glass slide-humid chamber technique[16]; concentrations of 100, 150, 200, 250, and 300 ppm were used. These compounds exhibited good antifungal activity (Table II).

EXPERIMENTAL

Melting points were measured in open capillaries in a sulphuric acid bath and are uncorrected. IR spectra were recorded in Nujol on a Perkin–Elmer 283 spectrophotometer (ν_{max} in cm^{-1}). 90 MHz ^1H NMR spectra were recorded on a Varian-EM 390 instrument using tetramethylsilane as an internal standard. Chemical shifts are expressed in ppm. Mass spectra were scanned on a Varian MAT CH-7 spectrometer at 70 eV.

3-Cinnamoyl-2-methyl-1,8-naphthyridines (*IIa—j*)

To a solution of 3-acetyl-2-methyl-1,8-naphthyridines (*I*, 1 mmol) and appropriate aromatic aldehyde (1 mmol) in ethanol (25 ml), a solution of potassium hydroxide (10%, 10 ml) was added in portions, keeping the temperature of the reaction mixture below 20°C throughout the addition. The reaction flask was stoppered and kept for 24 h at room temperature. Then, the reaction mixture was poured onto crushed ice and acidified with dilute hydrochloric acid. The solid formed was filtered, washed and crystallized. (For the analytical data see Table I.) IR: 1 660, 1 600, 1 550, 1 490, 1 460, 1 410, 1 380, 1 230, 1 180, 1 090, 1 015, 970, 830, and 780 cm^{-1}. The mass spectra of *IIa* and *IIe* exhibited strong molecular ion peaks at *m/z* 274 and 308, respectively.

3-(5-Phenyl-2-pyrazolin-3-yl)-2-methyl-1,8-naphthyridines (*IIIa—j*)

A mixture of *II* (1 mmol) and hydrazine hydrate (2 mmol) in ethanol (20 ml) containing a few drops of glacial acetic acid was refluxed for 6 h and the reaction mixture concentrated, cooled

TABLE II

Fungicidal activity data of compounds *III* and *IV*

Concentration in ppm	% Spore germination inhibition		% Spore germination inhibition	
	D. rostrate	*F. oxysporum*	*D. rostrate*	*F. oxysporum*
	IIIa		*IVa*	
100	43·8	45·0	24·6	42·1
150	75·7	73·2	63·8	63·5
200	100·0	100·0	91·0	99·0
250	100·0	100·0	100·0	100·0
300	100·0	100·0	100·0	100·0
	IIIc		*IVc*	
100	11·3	8·7	35·7	42·5
150	32·5	22·5	71·0	85·2
200	54·0	48·2	100·0	100·0
250	74·7	55·8	100·0	100·0
300	91·1	73·2	100·0	100·0
	IIIe		*IVe*	
100	31·2	45·1	39·5	49·3
150	59·5	70·0	89·8	72·4
200	92·3	100·0	100·0	100·0
250	100·0	100·0	100·0	100·0
300	100·0	100·0	100·0	100·0
	IIIf		*IVf*	
100	21·3	32·5	14·4	21·4
150	49·1	69·1	29·0	39·5
200	85·4	92·0	49·7	67·5
250	100·0	100·0	66·7	83·1
300	100·0	100·0	83·1	100·0
	IIIg		*IVg*	
100	35·4	41·0	31·0	29·7
150	69·5	78·7	59·7	49·2
200	83·5	100·0	100·0	83·0
250	100·0	100·0	100·0	100·0
300	100·0	100·0	100·0	100·0

and poured into ice cold water. The solid formed was filtered, washed with water and crystallized. (The analytical data are given in Table I.) IR: 3 340 (NH) and 1 600(C=N); ^{1}H NMR of *IIIa* in trifluoroacetic acid (δ, ppm): 2·3 s, 3 H (CH_3); 3·2—3·7 ABX pattern, 3 H (pyrazoline —CH—CH_2—); 4·1 s, 1 H (NH); 8·8 m, 1 H (H-7); 8·4 m, 1 H (H-5); 7·8 m, 1 H (H-4) and 7·0—7·5 m, 6 H (H-6 and Ar—H). Mass spectrum of *IIIe*: *m/z* 322.

3-(1,5-Diphenyl-2-pyrazolin-3-yl)-2-methyl-1,8-naphthyridines (*IVa—j*)

A mixture of *II* (1 mmol) and phenylhydrazine (1 mmol) in glacial acetic acid (20 ml) was heated under reflux for 4 h. The reaction mixture was cooled and poured onto crushed ice. The precipitate thus obtained was filtered, washed thoroughly with water and crystallized. (For analytical data see Table I.)

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