SYNTHESIS AND SOME REACTIONS OF CINNOLINE DERIVATIVES

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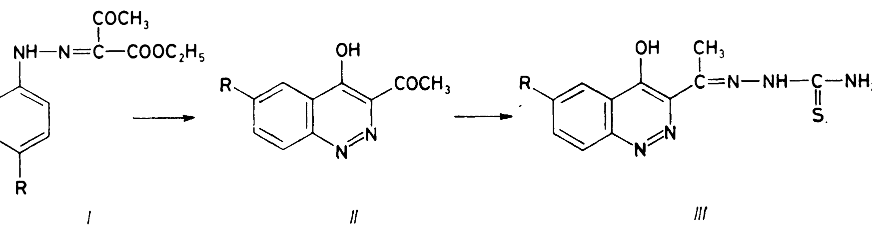
Received July 30, 1990
Accepted January 29, 1991

Biological activities of pyridazine systems[1] receive increasing interest since they were found in nature[2]. Recently another naturally occurring 1,2-diazine derivative nigellicine[3] has been described[4]. Gewald et al.[5] reported that the intermolecular Friedel–Crafts reaction of arylhydrazono derivatives yielded cinnoline. According to this method the 3-acetyl-4-hydroxycinnolines *IIa*–*IId* were synthesized to be starting material for preparation of different heterocyclic compounds with pyridazine system. Condensation of *II* with thiosemicarbazide in boiling acetic acid gives the corresponding thiosemicarbazones *III* (Scheme 1). Compounds *III* interacted with



In formulae *I*–*III*: *a*, R = H ; *b*, R = CH_3 ; *c*, R = OCH_3 ; *d*, R = Br

SCHEME 1

some α-haloketones and/or α-haloesters giving the thiazolyl derivatives *IV*–*VII*. By substitution of the latter reactants with diethyl malonate the pyrimidine thione derivative *VIII* was produced (Scheme 2). Compounds *II* with hydrazine or phenyl hydrazine yielded substituted pyrazolocinnolines *IX*. Fusion of *II* with malononitrile and ethyl cyanoacetate gave pyridocinnoline *X* and pyranocinnoline *XI*, respectively (Scheme 3). Alternative preparation of *IId* from *IIa* was elaborated (Scheme 4); bromination of *IIa* by N-bromosuccinimide (NBS) leads, however, to the bromoacetyl derivative *XII*.

TABLE I

Physical and spectral data of compounds *II* and *III*

Compound	M.p. °C	Yield %	Molecular formula (M.w.)	Calculated/Found % C	% H	% N	% S	Spectral data
IIa	155–156	65	$C_{10}H_8N_2O_2$ (188·2)	63·82 64·00	4·25 4·38	14·89 14·52	— —	IR: 3 150 (OH); 1 700 (C=O) ^{1}H NMR[a]: 2·5 s, 3 H (CH_3); 7·4 m, 4 H (Ar-H); 14·0 s, 1 H (OH)
IIb	195	70	$C_{11}H_{10}N_2O_2$ (202·2)	65·34 65·40	4·95 5·15	13·86 14·10	— —	IR: 3 150 (OH); 1 690 (C=O)
IIc	174–175	75	$C_{11}H_{10}N_2O_3$ (218·2)	60·55 60·67	4·58 4·32	12·84 13·08	— —	IR: 3 150 (OH); 1 690 (C=O). ^{1}H NMR[a]: 2·4 s, 3 H (CH_3); 3·8 s, 3 H (OCH_3); 7·3 m, 3 H (Ar-H); 13·5 s, 1 H (OH)
IId	220	62	$C_{10}H_7BrN_2O_2$ (267·1)	44·94 45·12	2·62 2·98	10·84 10·12	— —	IR: 3 150 (OH); 1 700 (C=O). ^{1}H NMR[a]: 2·5 s, 3 H (CH_3); 7·5 m, 3 H (Ar-H); 13·7 s, 1 H (OH)
IIIa	256–257	70	$C_{11}H_{11}N_5OS$ (261·3)	50·57 50·72	4·21 4·00	26·81 27·05	12·26 12·38	IR: 3 410, 3 260 (NH_2, NH); 3 260 (OH). ^{1}H NMR[b]: 2·2 s, 3 H (CH_3); 7·4 m, 4 H (Ar-H); 8·8 s, 2 H (NH_2); 9·4 s, 1 H (NH)
IIIb	262	72	$C_{12}H_{13}N_5OS$ (275·3)	52·36 52·56	4·72 4·98	25·45 25·12	11·63 11·54	IR: 3 410, 3 270 (NH_2, NH); 3 150 (OH)
IIIc	225	75	$C_{12}H_{13}N_5O_2S$ (291·3)	49·48 49·18	4·46 4·42	24·05 23·88	10·99 11·12	IR: 3 410, 3 270 (NH_2, NH); 3 150 (OH)
IIId	235	65	$C_{11}H_{10}BrN_5OS$ (340·2)	38·82 39·00	2·94 3·12	20·58 20·32	9·41 9·36	IR: 3 380, 3 270 (NH_2, NH); 3 150 (OH)

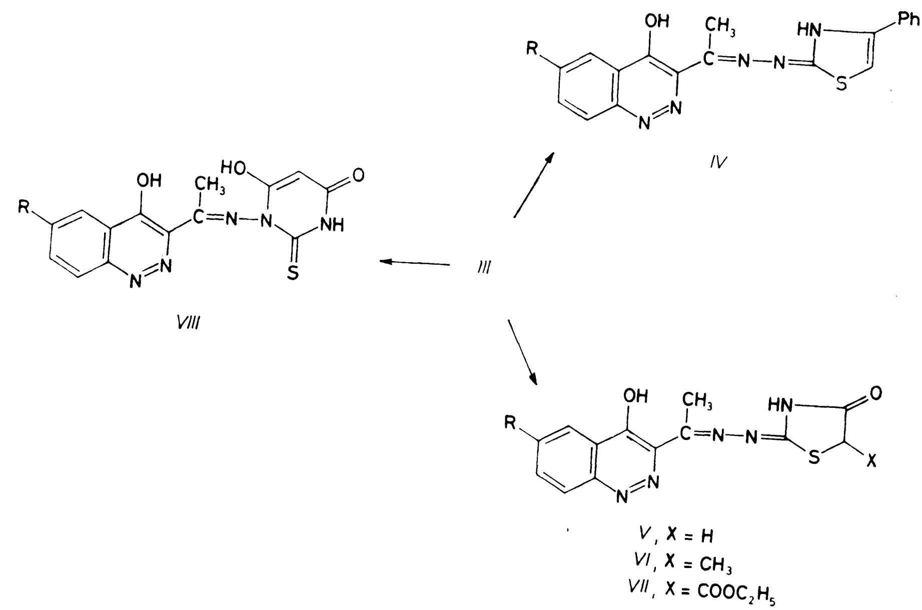
[a] In $CDCl_3$; [b] in $(CD_3)_2SO$.

TABLE II
Physical constants and spectral data of compounds *IV*–*VII*

Compound	M.p. °C	Yield %	Molecular formula (M.w.)	Calculated/Found % C	% H	% N	% S	% Br	Spectral data
IVa	213	87	$C_{19}H_{15}N_5OS$ (361·4)	63·15 62·87	4·15 4·00	19·39 19·52	8·86 9·00	 —	IR: 3 110 (OH); 1 670 (C=N); 1 600 (C=N)
IVb	205–207	85	$C_{20}H_{17}N_5OS$ (375·5)	64·00 63·82	4·53 4·72	18·66 18·42	8·53 8·72	— —	IR: 3 120 (OH); 1 670 (C=N); 1 600 (C=N)
IVc	172–174	85	$C_{20}H_{17}N_5O_2S$ (391·5)	61·38 61·52	4·34 4·22	17·90 18·10	8·18 8·00	— —	IR: 3 120 (OH); 1 670 (C=N); 1 590 (C=N)
IVd	215–217	78	$C_{19}H_{14}BrN_5OS$ (440·3)	51·81 52·00	3·18 3·34	15·90 16·02	7·27 7·34	18·18 18·30	IR: 3 120 (OH); 1 670 (C=N); 1 580 (C=N). ^{1}H NMR[a]: 2·4 s, 3 H (CH_3C=N); 7·4 m, 9 H (Ar-H, CH thiazole); 13·3 s, 1 H (OH)
Va	265–267	75	$C_{13}H_{11}N_5O_2S$ (301·3)	51·82 52·08	3·65 3·95	23·25 23·00	10·63 10·54	—	IR: 3 250–3 100 (NH, OH); 1 700 (C=O). ^{1}H NMR[b]: 2,4 s, 3 H (CH_3); 4·0 s, 2 H (CH_2); 7·6–7·0 m, 4 H (Ar-H); 12·2 s, 1 H (OH)

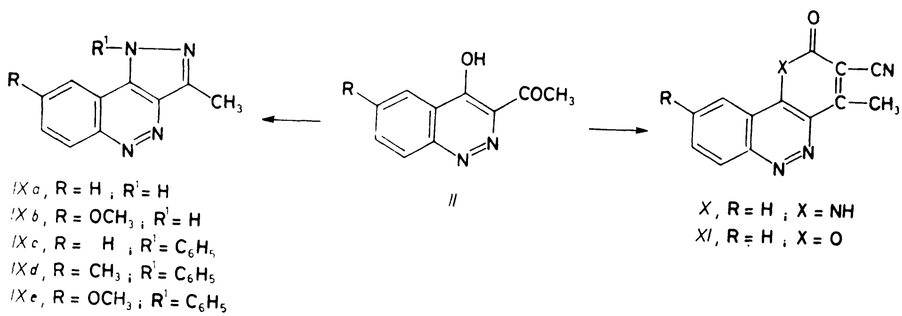
Vc	237–240	65	$C_{14}H_{13}N_5O_3S$	50·75	3·92	21·14	9·66		IR: 3 450–3 300 (OH, NH); 1 680–1 650
			(331·4)	51·03	4·18	20·88	9·42	—	(C=O).
									^{1}H NMR[c]: 2·9 s, 3 H (CH_3C=N); 3·9 s, 3 H (OCH_3); 4·3 s, 2 H (CH_2); 7·8–7·0 m, 3 H (Ar-H); 10·0 s, 1 H (OH)
Vd	>300	70	$C_{13}H_{10}BrN_5O_2S$	41·05	2·63	18·42	8·42	21·05	IR: 3 340–3 200 (NH, OH); 1 700
			(380·2)	40·82	2·94	18·66	8·12	20·80	(C=O)
VIa	250	72	$C_{14}H_{13}N_5O_2S$	53·33	4·12	22·22	10·15	—	IR: 3 500 (NH, OH); 1 700 (C=O)
			(315·4)	53·56	3·95	22·00	10·34	—	
VIb	>300	65	$C_{15}H_{15}N_5O_2S$	54·71	4·55	21·27	9·72	—	IR: 3 500–3 300 (NH, OH); 1 680–1 650
			(329·4)	55·00	4·32	21·58	9·62	—	(C=O)
VIIa	272–275	65	$C_{16}H_{15}N_5O_4S$	51·47	4·02	18·76	8·57	—	IR: 3 500–3 300 (NH, OH); 1 680–1 650
			(373·4)	51·69	3·84	19·00	8·32	—	(C=O).
									^{1}H NMR[b]: 1·1 t, 3 H (CH_3 ester); 3·6 s, 3 H (CH_3); 3·7 s, 1 H (CH thiazole); 4·0 q, 2 H (CH_2 ester); 7·2–6·9 m, 4 H (Ar-H)

[a] In $CDCl_3$; [b] in $(CD_3)_2SO$; [c] in CF_3CO_2H.

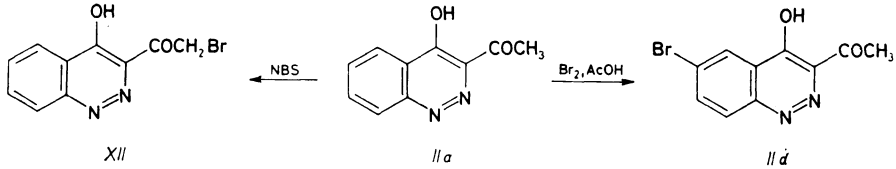


In formulae *III*-*VII*: *a*, R = H; *b*, R = CH_3; *c*, R = OCH_3; *d*, R = Br

SCHEME 2



SCHEME 3



SCHEME 4

EXPERIMENTAL

Melting points are not corrected. All reagents were purified before use. IR spectra were determined on a Perkin–Elmer Spectrometer using KBr disc technique and are given in cm^{-1}. ^{1}H NMR were obtained on 90 MHz Varian spectrometer in δ ppm relative to TMS. Elemental analyses were performed using Perkin–Elmer 240 C microanalyzer.

3-Acetyl-4-hydroxycinnolines *IIa*—*IId*

A mixture of ethyl 2-arylhydrazono-3-oxobutanoate (0·01 mol), aluminium chloride (0·02 mol) and chlorobenzene (30 ml) was refluxed on water bath for one hour, then the reaction mixture was allowed to cool and poured into concentrated HCl (50 ml). The solid product was filtered off and recrystallized from benzene as yellow crystals. The physical constants and spectral data of compounds *IIa*—*IId* are presented in Table I.

Thiosemicarbazones of 3-Acetyl-4-hydroxycinnolines *IIIa*—*IIId*

A mixture of cinnoline *II* (0·01 mol), thiosemicarbazide (0·01 mol) and acetic acid (30 ml) was refluxed for two hours, then the reaction mixture was allowed to cool. The solid product was filtered off and recrystallized from ethanol to give orange crystals *IIIa*—*IIId*. The physical constants and spectral data are listed in Table I.

Reaction of Thiosemicarbazones *IIIa*—*IIId* with α-Haloketones and α-Haloesters

To a mixture of thiosemicarbazone *III* (0·01 mol) and α-haloketone or α-haloester (0·01 mol) in ethanol (30 ml), sodium acetate (2 g) was added. The mixture was refluxed for 4 h, then allowed to cool, the solid product was collected and recrystallized from acetic acid to yield yellow crystals of compounds *IV*—*VII*. The physical constants and spectral data of compounds *IV*—*VII* are given in Table II.

Reaction of Thiosemicarbazone *IIIa* with Diethyl Malonate

A mixture of compound *IIIa* (0·01 mol) and diethyl malonate (0·01 mol) was refluxed in alcoholic solution of sodium ethoxide for 5 h. The reaction mixture was allowed to cool and then acidified with acetic acid. The solid product was filtered off and recrystallized from ethanol to give yellow crystals of compound *VIII* in 67% yield, m.p. 195—7°C. For $C_{14}H_{11}N_5O_3S$ (329·3) calculated: 51·06% C, 3·34% H, 21·27% N, 9·72% S; found: 50·84% C, 3·56% H, 21·30% N, 9·65% S. IR spectrum: 3 180 (NH); 1 690—1 670 (2 C=O); 1 590 (C=N). ^{1}H NMR in $(CD_3)_2SO$: 2·1 s, 3 H (CH_3); 7·6 s, 1 H (CH of pyrimidine ring); 7·0—7·5 m, 4 H (Ar-H); 11·7 s, 2 H (2 OH).

3-Methyl-pyrazolo[4,5-*c*]cinnolines *IXa*, *IXb*

A mixture of cinnoline *II* (0·01 mol) and hydrazine hydrate (0·01 mol) in ethanol (30 ml) was refluxed for 5 h, then the reaction mixture was allowed to cool. The solid product was filtered off and recrystallized from ethanol as orange crystals of compound *IXa*, *IXb*. The physical constants and spectral data are reported in Table III.

3-Methyl-1-phenyl-pyrazolo[4,5-*c*]cinnolines *IXc*—*IXe*

A mixture of compound *II* (0·01 mol) and phenylhydrazine (0·01 mol) in acetic acid (30 ml) was

TABLE III
Physical constants and spectral data of compounds *IX*

Compound	M.p., °C	Yield %	Molecular formula (M.w.)	Calculated/Found			Spectral data
				% C	% H	% N	
IXa	198	85	$C_{10}H_8N_4$ (184·2)	65·21 65·38	4·34 4·12	30·43 30·65	IR: 3 170 (NH). ^{1}H NMR[a]: 2·3 s, 3 H (CH_3); 7·0–7·5 m, 4 H (Ar-H); 8·9 s, 1 H (NH)
IXb	205–207	80	$C_{11}H_{10}N_4O$ (214·2)	61·68 61·82	4·67 4·43	26·16 26·00	IR: 3 150 (NH). ^{1}H NMR[a]: 2·2 s, 3 H (CH_3—C=N); 3·8 s, 3 H (OCH_3); 7·0–7·4 m, 3 H (Ar-H); 10·4 s, 1 H (NH)
IXc	150	70	$C_{16}H_{12}N_4$ (260·3)	73·84 74·05	4·61 4·75	21·53 21·37	IR: 1 650 (C=N). ^{1}H NMR[a]: 2·35 s, 3 H (CH_3); 7·1–7·9 m, 9 H (Ar-H)
IXd	133–135	75	$C_{17}H_{14}N_4$ (274·3)	74·18 73·92	5·45 5·22	20·36 20·54	IR: 1 650 (C=N)
IXe	137–139	82	$C_{17}H_{14}N_4O$ (290·3)	70·10 69·85	5·15 5·00	19·24 19·52	IR: 1 650 (C=N). ^{1}H NMR[a]: 2·3 s, 3 H (CH_3—C=N); 3·8 s, 3 H (OCH_3); 6·9–8·0 m, 8 H (Ar-H)

[a] In $CDCl_3$.

refluxed for 4 h, then allowed to cool. The solid product was filtered off and recrystallized from ethanol to produce orange crystals of compound *IXc—IXe*. The physical constants and spectral data of compound *IXc—IXe* are listed in Table III.

3-Cyano-4-methyl-pyrido[3,2-*c*]cinnoline-2(1*H*)-one *X*

To a mixture of cinnoline *IIa* (0·01 mol) and malononitrile (0·01 mol) in ethanol (30 ml), several drops of piperidine were added and the mixture was refluxed for two hours, then the reaction mixture was allowed to cool. The solid product was filtered off and recrystallized from ethanol as yellowish white crystals in 65% yield, m.p. > 300°C. For $C_{13}H_8N_4O$ (236·2) calculated: 66·10% C, 3·88% H, 23·72% N; found: 65·84% C, 3·52% H, 23·80% N. IR spectrum: 3 310 (NH); 2 230 (C≡N); 1 700 (C=O). ^{1}H NMR in $CDCl_3$: 3·15 s, 3 H (CH_3); 6·7 s, 1 H (NH); 7·0 to 7·6 m, 4 H (Ar-H).

3-Cyano-4-methyl-pyrano[3,2-*c*]cinnoline *XI*

A mixture of cinnoline *IIa* (0·01 mol) and ethyl cyanoacetate (0·01 mol) was heated at 160 to 170°C for 5 h. The reaction mixture was allowed to cool, and the solid product was filtered off and recrystallized from ethanol to produce yellowish white crystals of compound *XI* in 70% yield, m.p. 267—70°C. For $C_{13}H_7N_3O_2$ (237·2) calculated: 65·82% C, 2·95% H, 17·22% N; found: 66·08% C, 3·18% H, 17·53% N. IR spectrum: 2 250 (C≡N); 1 760 (C=O). ^{1}H NMR in $(CD_3)_2SO$: 2·65 s, 3 H (CH_3); 7·0—7·8 m, 4 H (Ar-H).

Bromination of 3-Acetyl-4-hydroxycinnoline

A) *Using* $Br_2/AcOH$ *or* $Br_2/CHCl_3$: To a solution of cinnoline *IIa* (0·01 mol) in acetic acid or chloroform bromine (0·01 mol) was added dropwise with stirring. After the addition was finished, the solid product was filtered off and recrystallized from ethanol to give yellow needles of 3-acetyl-6-bromo-4-hydroxycinnoline *IId* in 80% yield, m.p. 220°C. For $C_{10}H_7BrN_2O_2$ (267·1) calculated: 44·94% C, 2·62% H, 29·96% Br, 10·48% N; found: 45·12% C, 2·98% H, 30·27% Br, 10·12% N.

B) *Using* NBS: A mixture of cinnoline *IIa* (0·01 mol) and NBS (0·01 mol) in CCl_4 (30 ml) was refluxed for 6 h, then the mixture was filtered to remove the formed succinimide and the filtrate was concentrated. The solid product was crystallised from petroleum ether to give *XII* as yellowish white crystals in 75% yield, m.p. 112°C. For $C_{10}H_7BrN_2O_2$ (267·1) calculated: 44·94% C, 2·62% H, 29·96% Br, 10·48% N; found: 44·75% C, 2·93% H, 30·18% Br, 10·56% N. IR spectrum: 3 250 (OH); 1 700 (C=O). ^{1}H NMR in $CDCl_3$: 2·6 s, 2 H (CH_2); 7·0—7·6 m, 4 H (Ar-H); 8·5 s, 1 H (OH).

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