SYNTHESIS OF 1-ARYLAZO-3-ACETYL-1*H*-CINNOLIN-4-ONE DERIVATIVES

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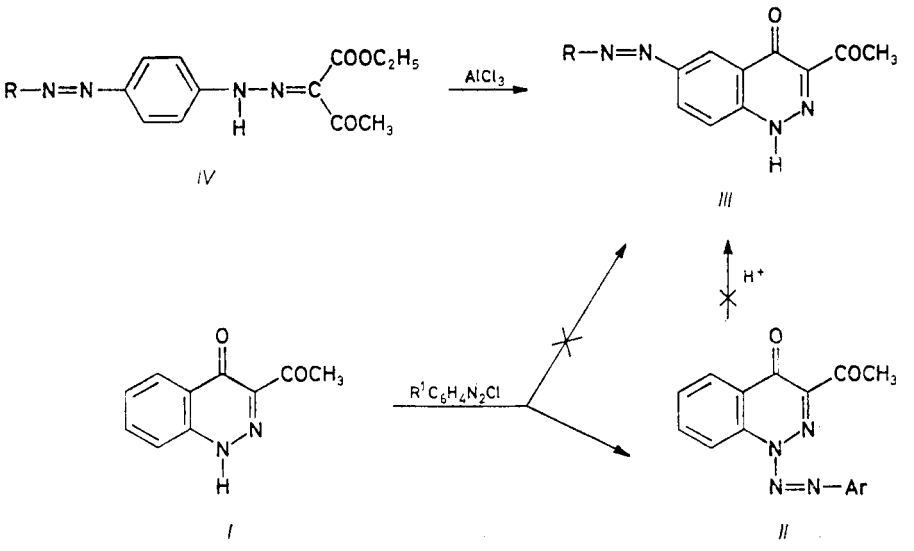
The biological activity of azocinnoline derivatives especially in the chemotherapy of *Trypanosomiasis* was already reported[1-3]. In 1971 for the first time pyridazine derivatives were found in nature[4] and quite recently another naturally occurring derivative (nigellicine)[5] has been described[6].

Considering the foregoing and in continuation of our previous work[7], 3-acetyl-1*H*-cinnolin-4-one (*I*) has been well exploited as a coupling component. Compound *I* has two potentially nucleophilic centres, i.e. position 1 and 6 and was expected to undergo azo-coupling reaction at either or both of these positions. In fact, reaction of *I* with aryldiazonium salts proceeds smoothly in aqueous ethanol in the presence

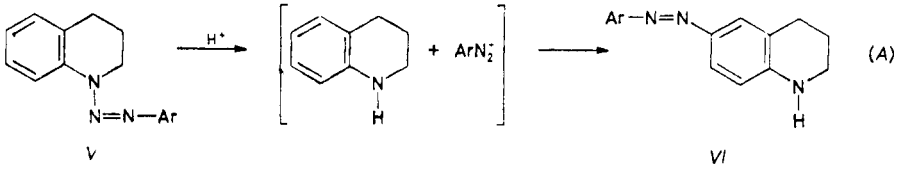


In formula *II*: *a*, R^1 = H *b*, R^1 = *p*-CH_3 *c*, R^1 = *p*-OCH_3 *d*, R^1 = *p*-NO_2 *e*, R^1 = *p*-Br *f*, R^1 = *o*-COOH *g*, R^1 = *p*-SO_3H

SCHEME 1

of sodium carbonate to give red coloured dyes identified as 1-arylazo-3-acetyl-1*H*--cinnolin-4-ones (*II*) (Scheme 1).

On the other hand, it was reported that the diazoimino derivatives of tetrahydroquinoline (*V*) are rearranged in dilute mineral acid to the isomeric 6-areneazotetrahydroquinoline[8] (*VI*) (Equation (*A*)). Attempts at rearrangement of *IIa* by boiling



V *VI*

dilute hydrochloric acid to give the isomeric 6-arylazo-3-acetyl-1*H*-cinnolin-4-one (*III*) were unsuccessful. Compound *III* (R = C_6H_5) was prepared by another route, by intramolecular cyclization of ethyl acetoacetate (4-phenylazo)phenylhydrazone (*IV*), which was prepared by coupling of diazotized 4-aminoazobenzene with ethyl acetoacetate by anhydrous $AlCl_3$ in chlorobenzene (Scheme 1).

TABLE I
UV spectra of compounds *I*—*III* (Scheme 1)

Compound	λ_{max}[a]	$\varepsilon_{max}\ 10^{-3}$,[a]	λ_{max}	$\varepsilon_{max}\ 10^{-3}$	λ_{max}	$\varepsilon_{max}\ 10^{-3}$
I	350	23·333	296 sh 286 sh	4·666 3·999	242	11·833
IIa	440	23·666	300 260	17·333 10·333	250	11·666
IIb	442	24·833	306	17·166	254	11·666
IIc	450	26·833	322	18·333	252	13·999
IId	434	16·999	304	8·833	248	6·499
IIe	442	23·666	306 260 sh	15·999 9·666	254	10·666
IIf	434	25·333	300	19·666	244	10·166
IIg	358	32·333	308 sh 298 sh	6·333 5·499	253	18·333
III	402	40·500	300 br	4·250	246	10·500

[a] λ_{max} in nm and ε_{max} in $mol^{-1}\ cm^2$.

EXPERIMENTAL

All melting points are uncorrected and were recorded on Fisher–Johns melting point apparatus. ^{1}H NMR were obtained on 90 MHz Varian spectrometer in δ ppm relative to TMS. Electronic spectra were recorded on a Shimadzu UV 200S spectrophotometer using 1 cm matched silica cells.

3-Acetyl-1*H*-cinnolin-4-one (*I*)

This compound was prepared by cyclization of ethyl 2-(phenylhydrazono)-3-oxobutanoate with $AlCl_3$ in chlorobenzene as cited in ref.[7].

1-Arylazo-3-acetyl-1*H*-cinnolin-4-ones (*IIa*—*IIg*)

General procedure. A solution of diazotized aryl amine (0·01 mol) was added gradually with stirring to a solution 3-acetyl-1*H*-cinnolin-4-one (0·01 mol) in aqueous sodium carbonate (200 ml,

TABLE II
Physical and analytical data of compounds *II*—*IV*

Compound	M.p. °C	Yield %	Formula M.w.	Calculated/Found		
				% C	% H	% N
IIa	125—127	95	$C_{16}H_{12}N_4O_2$	65·75	4·14	19·17
			292·30	66·05	4·30	18·95
IIb	132—135	93	$C_{17}H_{14}N_4O_2$	66·66	4·61	18·29
			306·32	66·42	4·25	17·98
IIc	130	90	$C_{17}H_{14}N_4O_3$	63·35	4·38	17·38
			322·32	63·50	4·30	17·27
IId	182—185	75	$C_{16}H_{11}N_5O_4$	56·98	3·29	20·76
			337·29	56·78	2·95	20·70
IIe	158—160	80	$C_{16}H_{11}N_4O_2Br$	51·77	2·99	15·09[a]
			371·19	51·67	3·15	14·94
IIf	195	78	$C_{17}H_{12}N_4O_4$	60·71	3·60	16·66
			336·30	60·87	3·65	16·64
IIg	160—162	69	$C_{16}H_{12}N_4O_5S$	51·61	3·25	15·05[b]
			372·35	51·82	3·37	15·25
III	220	75	$C_{16}H_{12}N_4O_2$	65·75	4·14	19·17
			292·30	65·70	4·10	19·25
IV	145—147	94	$C_{18}H_{18}N_4O_3$	63·90	5·36	16·56
			338·36	63·78	5·23	16·51

[a] Calculated: 21·53% Br, found: 21·66% Br. [b] Calculated: 8·61% S, found: 8·68% S.

2·5%) and ethanol (20 ml) at 0—5°C during 15 min. The resulting red precipitate was filtered off and recrystallized from ethanol. Compound *II* precipitated after acidification with acetic acid. The ^{1}H NMR spectrum of *IIa* in $CDCl_3$ exhibited signals at δ 2·55 s, 3 H (CH_3); δ 7·25 to 7·65 m, 9 H (CH-Ar), and the disappearance of the signal at δ 14 due to NH. Results are summarized in Tables I and II..

Ethyl 2-[(4-phenylazo)phenylhydrazono]-3-oxobutanoate (*IV*)

A solution of 4-aminoazobenzene (0·025 mol) in acetic acid (10 ml) and hydrochloric acid (20 ml, 50% (v/v)) was diazotized at 0—5°C by addition of sodium nitrite (0·025 mol) dissolved in water (10 ml). The resulting suspension was added with stirring to a cold solution of ethyl acetoacetate (0·025 mol) in aqeuous ethanol (40 ml, 50%) containing sodium acetate (10 g) during 15 min. The resulting solid was recrystallized from ethanol, giving orange red needles of m.p. 145—147°C. The ^{1}H NMR of *IV* in $CDCl_3$ showed signals at δ 1·25—1·40 t, 3 H (CH_3-ester); δ 2·50 s (CH_3—$COCH_3$), δ 4·15—4·40 q, 2 H (C_2H-ester); δ 7·30—7·90 m, 9 H (CH—Ar), and at δ 14·65 s, 1 H (NH).

6-Phenylazo-3-acetyl-1*H*-cinnolin-4-one (*III*)

A mixture of ethyl 2-[(4-phenylazo)phenylhydrazono]-3-oxobutanoate (*IV*) (0·01 mol), anhydrous aluminium chloride (0·02 mol) and chlorobenzene (30 ml) was refluxed on a water bath for 1 h. The resulting complex was cooled and decomposed by addition of concentrated hydrochloric acid (20 ml). The product was recrystallized from benzene, affording orange crystals of m.p. 220°C. The ^{1}H NMR spectrum of *III* in $CDCl_3$ exhibited signals at δ 2·65 s, 3 H ($COCH_3$); 7·45—8·05 m, 8 H (CH-Ar), and at δ 14·00 s, 1 H (NH).

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