SYNTHESIS OF SOME NEW INDOLIZINO[2,3-*g*]QUINOLINE--5,12-DIONE DERIVATIVES

Amal S. YANNI

Chemistry Department, Faculty of Science, Assiut University, Egypt

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Interaction of 6,7-dichloroquinoline-5,8-dione (*I*) with active methylene compounds and pyridine (or substituted pyridine) afforded indolizino[2,3-*g*]quinoline-5,12-diones (*III*, *IV*). When quinoline or isoquinoline was used instead of pyridine in the above reaction benzo[5,6]- or benzo[7,8]-indolizino[2,3-*g*]quinoline-5,12-diones (*V*, *VI*) were obtained. Their structure has been ascertained through elemental and spectral analysis.

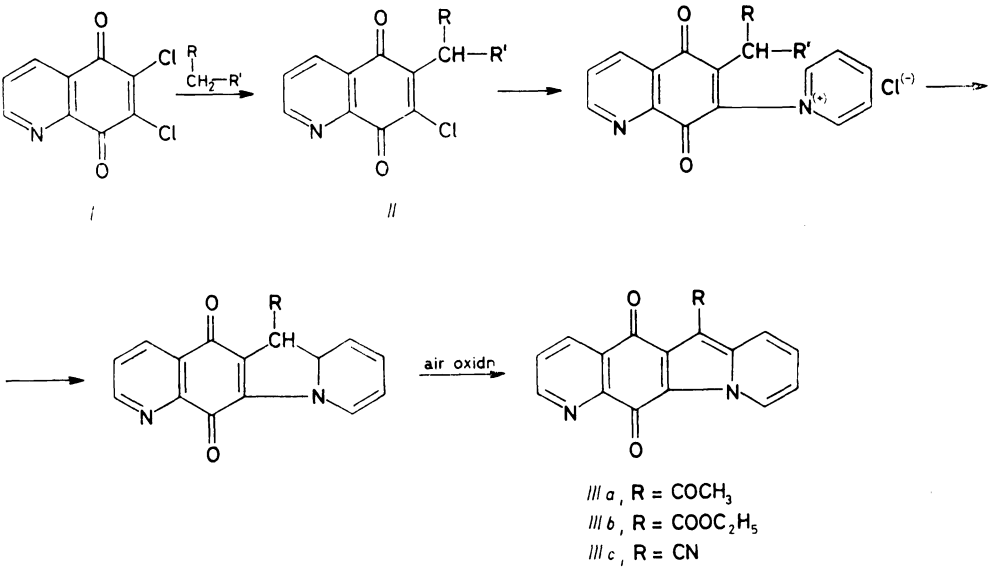
Pyrrocolines (indolizines) have been reported to be pharmacologically active[1] against convulsions, motor and respiratory paralysis. These pyrrocoline ring systems are of interest as they serve as starting material in the synthesis of corresponding mesodimethyl derivatives which are related to carcinogenic hydrocarbons. Moreover the antitumor drug hydroxycamptothecine contains indolizino[1,2-*b*]quinoline nucleus[2,3]. These studies prompted us to synthesize the title compounds which may be of certain biological interest in combination with the biologically active quinoline--5,8-dione system[4].

A number of substituted pyrrocoline quinones has been synthesized through condensation of chloranil either with active methylene compounds in pyridine[5] or with β-ketoalkylpyridinium iodides and pyridine in ethanol[6]. Luckenbaugh[7] and Suryanaryana et al.[8–10] reported the synthesis of first naphthindolizinediones while investigating the reaction of 2,3-dichloro-1,4-naphthoquinone with active methylene compounds and pyridine either in absolute ethanol[11] or in excess pyridine[10].

In the present work, refluxing a mixture of 6,7-dichloroquinoline-5,8-quinone (*I*), active methylene compounds such as acetylacetone, ethyl acetoacetate, ethyl cyanoacetate, and/or diethyl malonate, and pyridine either in absolute ethanol or in excess pyridine furnished highly coloured products (reddish brown to deep violet) with high melting points and low solubility in yield 50–60%. These products contained no halogen and were characterised as 6-substituted indolizino[2,3-*g*]quinoline-5,12--diones *IIIa–IIIc*. Their IR spectra showed absorption bands characteristic of ν(C=O) of quinones (1 650–1 670 cm^{-1}), ν(C=N) (1 580–1 620 cm^{-1}), ν(C—N) (1 240–1 300 cm^{-1}) and disappearance of absorption of ν(C—Cl) band. The ^{1}H NMR spectrum ($CDCl_3$ + drops of TFA) of compound *IIIa* revealed signals at

δ 2·9 (s, 3 H, $COCH_3$), 7·4–8·5 (m, 7 H, heterocyclic nucleus). Mass spectra of compound *IIIc* gave M + 1 peak at *m/z* 274. It was also found that products obtained from *I* and ethyl acetoacetate or diethyl malonate were the same as indicated by their melting points, elemental analysis and IR spectra. Moreover diethyl malonate does not form indolizino[2,3-*g*]quinoline-5,12-dione (*IIIb*) on using equivalent pyridine in boiling ethanol, however this compound was obtained by carrying out the reaction in boiling pyridine.

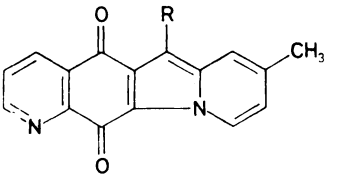
It was suggested that the reaction proceeds through initial formation of 6-disubstituted methyl-7-chloroquinoline-5,8-quinone *II* (refs[12,13]) which undergoes cyclisation under influence of pyridine and air oxidation to indolizino[2,3-*g*]quinoline-5,12-diones *IIIa*–*IIIc*. The involvement of such intermediate (*II*) was ascertained through its preparation by adding 6,7-dichloroquinoline-5,8-dione to a solution of the active methylene compound in absolute ethanol in which one equivalent of sodium was previously dissolved and then refluxing for about 1 h. Transformation of *II* to the cyclic product *III* was effected by refluxing in ethanol containing pyridine (Scheme 1).



SCHEME 1

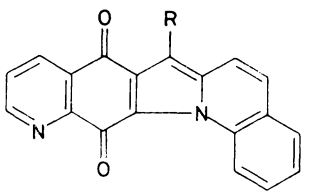
The radical R in Scheme 1 is one of the electron attracting groups of the active methylene compound. The other group generally the more electron attracting one is cleaved during the reaction. Besides pyridine, substituted pyridine such as 4-methylpyridine has been used successfully in this reaction, to give 6,8-disubstituted indolizi-

no[2,3-*g*]quinoline-5,12-diones *IVa*–*IVc*. The NMR (TFA) spectrum of compound *IVc* revealed signals at δ 2·65 (s, 3 H, CH_3), 7·5–8·5 (m, 6 H, hetrocyclic nucleus).

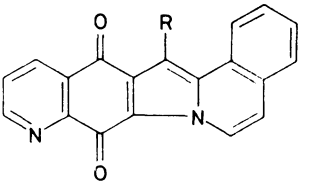


IV a, R = $COCH_3$
IV b, R = $COOC_2H_5$
IV c, R = CN

It has also been reported[14,15] that 2,3-dichloronaphthoquinone interacted with active methylene compounds and quinoline or isoquinoline in ethanol to give benzonaphthindolizinediones. Similarly, when quinoline or isoquinoline is used in place of pyridine in the condensation of *I* with active methylene compounds in ethanol as described above in the preceding reaction, benzo[5,6]- or benzo[7,8]indolizino-[2,3-*g*]quinoline-5,12-diones (*V*, *VI*) were obtained in yields 40–55%. IR spectra showed bands at 1 670 cm^{-1} (ν(C=O) of quinone), 1 240–1 300 cm^{-1} (ν(C—N)), and 1 600 cm^{-1} (ν(C=N)), 1 720 cm^{-1} (ν(C=O) of ester for compound *Vb*), 1 700 cm^{-1} (ν(C=O) of ketone for compound *Va*) 2 200 cm^{-1} (ν(C=N) for compound *Vc*). Mass spectra of compound *VIc* gave M + 1 peak at *m*/*z* 324.



V



VI

In formulae *V*, *VI*: *a*, R = $COCH_3$ *b*, R = $COOC_2H_5$ *c*, R = CN

The ^{1}H NMR spectrum (TFA) of compounds *Va*, *VIa* revealed signals at δ 3·15 (s, 3 H, $COCH_3$), 7·6–8·6 (m, 9 H, heterocyclic nucleus), and 3·0 (s, 3 H, $COCH_3$), 7·6–8·5 (m, 9 H, heterocyclic nucleus) respectively. UV absorption spectra of compounds *III*–*VI* in absolute ethanol were shown in Table II.

Antimicrobial activity was tested against some microorganisms and it was found that most of the compounds exhibited remarkable bactericidal activity against *Bacillus cereus*, *E. coli*, and *Candida albicans* (Table III).

TABLE I

Physical and analytical data of compounds *III*–*VI*

Compound	M.p., °C Yield, %	Formula M.w.	Calculated/Found % C	 % H	 % N	IR, $\tilde{\nu}$, cm^{-1}
IIIa	>350	$C_{17}H_{10}O_3N_2$	70·34	3·47	9·65	1 600 (C=O of ketone), 1 640 (C=O of quinone),
	52	290·3	70·50	3·65	9·80	1 580 (C=N), 1 310 (C—N)
IIIb	>350	$C_{18}H_{12}O_4N_2$	67·50	3·78	8·75	1 710 (C=O of ester), 1 675 (quinone), 1 620
	50	320·3	67·79	3·58	8·90	(C=N), 1 290–1 240 (C—N)
IIIc	>350	$C_{16}H_7O_2N_3$	70·33	2·58	15·38	1 660 (C=O of quinone), 1 640–1 620 (C=N),
	(210 dec.)	273·3	70·51	2·39	15·59	2 220 (C≡N), 1 310–1 240 (C—N)
	61					
IVa	270	$C_{18}H_{12}O_3N_2$	71·05	3·97	9·21	1 665 (C=O of ketone), 1 640 (C=O of quinone),
	50	304·3	71·29	3·72	9·00	1 620 (C=N), 1 300–1 240 (C—N)
IVb	>350	$C_{19}H_{14}O_4N_2$	68·26	4·22	8·38	1 720 (C=O of ester), 1 680 (C=O of quinone),
	55	334·3	67·50	4·05	8·18	1 630–1 580 (C=N), 1 290–1 240 (C—N)
IVc	235	$C_{17}H_9O_2N_3$	71·08	3·16	14·63	1 670 (C=O of quinone), 1 625–1 580 (C=N),
	65	287·3	71·20	3·20	14·42	2 200 (C≡N), 1 360–1 290 (C—N)
Va	>350	$C_{21}H_{12}O_3N_2$	74·14	3·55	8·23	1 675 (C=O of ketone), 1 650 (C=O of quinone),
	45	340·3	74·32	3·40	8·06	1 580 (C=N), 1 260 (C—N)
Vb	>350	$C_{22}H_{14}O_4N_2$	71·35	3·78	7·57	1 720 (C=O of ester), 1 640 (C=O of quinone),
	43	370·4	71·49	3·59	7·40	1 580 (C=N), 1 290–1 240 (C—N)
Vc	>350	$C_{20}H_9O_2N_3$	74·30	2·81	13·00	1 680 (C=O of quinone), 1 630–1 570 (C=N),
	55	323·3	74·49	2·60	12·80	2 200 (C≡N), 1 360–1 280 (C—N)
VIa	310	$C_{21}H_{12}O_3N_2$	74·12	3·53	8·23	1 680 (C=O of ketone), 1 660 (C=O of quinone),
	43	340·3	74·30	3·35	8·51	1 580 (C=N), 1 280–1 240 (C—N)
VIb	>350	$C_{22}H_{14}O_4N_2$	71·35	3·78	7·57	1 720 (C=O of ester), 1 660 (C=O of quinone),
	40	370·4	71·56	3·55	7·39	1 630 (C=N), 1 300–1 280 (C—N)
VIc	>350	$C_{20}H_9O_2N_3$	74·30	2·78	13·00	1 670 (C=O of quinone), 1 620–1 590 (C=N),
	50	323·3	74·50	2·55	12·88	2 210 (C≡N), 1 270 (C—N)

TABLE II

UV spectra (nm) of compounds *III*—*VI*

Compound	λ_{max} (log ε)					
IIIa	245 (3·52),	282 (sh) (3·23),	325 (3·13),	335 (sh) (3·11),	355 (3·00),	472 (3·15)
IIIb	250 (3·0),	280 (sh) (2·79),	320 (2·56),	335 (sh) (2·54),	350 (2·51),	460 (2·24)
IIIc	245 (3·65),	280 (sh) (3·31),	320 (3·19),	330 (sh) (3·13),	350 (3·00),	454 (3·14)
IVa	248 (3·79),	—,	330 (3·36),	—,	355 (sh) (3·24),	500 (3·06)
IVb	250 (3·65),	270 (sh) (3·52),	330 (3·17),	—,	385 (sh) (3·07),	495 (3·02)
IVc	246 (3·40),	275 (sh) (3·23),	320 (3·10),	—,	380 (sh) (2·72),	472 (2·59)
Va	225 (3·89),	258 (3·86),	310 (3·51),	340 (3·40),	370 (sh) (3·24),	468 (3·38)
Vb	225 (3·65),	268 (3·53),	310 (3·24),	340 (3·06),	370 (sh) (2·87),	458 (3·0)
Vc	225 (3·9),	268 (3·56),	310 (3·38),	340 (3·02),	370 (sh) (2·93),	425 (2·98)
VIa	230 (4·00),	270 (3·94),	310 (3·64),	344 (3·43),	400 (sh) (3·20),	470 (3·44)
VIb	230 (4·48),	270 (4·50),	305 (4·18),	340 (4·02),	395 (sh) (3·83),	460 (3·92)
VIc	230 (3·6),	265 (4·65),	310 (3·25),	330 (sh) (3·03),	390 (sh) (2·95),	440 (sh) (2·68)

Eventhough 6-substituted indolizino[2,3-*g*]quinolinediones *III* posses the greatest potency, further substition (as in 6,8-disubstituted indolizinoquinoline dione *IV*) decreases this potency. Benzindolizinoquinolinediones *V*, *VI* exhibited the least activity. Also type of substituent R affects the antimicrobial activity, thus acetyl derivative is more potent than corresponding carboethoxy derivative, while cyano-derivatives posses the least potency. Some of these compounds showed moderate bactericidal activity against *Pseudomonas aeruginosa*, and *Klebsiella pneumonia*. All compounds have no effect on *Penicillium martensii* and *Trichocethium roseum*.

EXPERIMENTAL

Melting points are uncorrected, IR spectra in KBr were recorded on a Unicam SP 1200 Spectrophotometer, and electronic spectra on a Pye-Unicam SP 8000 Spectrophotometer using 1 cm matched silica cells. ^{1}H NMR spectra ($CDCl_3$ + TFA) were measured on the spectrometer Varian, at 90 MHz. Mass spectra were measured on a Mass Spectrometer Varian MAT-311 at 70 eV.

6-Substituted Indolizino[2,3-*g*]quinoline-5,12-diones (*IIIa*—*IIIc*)

A mixture of 6,7-dichloroquinoline-5,8-dione (*I*, 0·002 mol), active methylene compound such as acetylacetone, ethyl acetoacetate, diethyl malonate, and/or ethyl cyanoacetate (0·002 mol) pyridine (0·003 mol) in ethanol (30 ml) was refluxed for 10 h. The colour of the reaction mixture was changed to brownish red or violet red colour and dark solids which precipitated were filtered and recrystallised from acetic acid. Yield 50—60%. Physical and analytical data are given in Table I and II. The reaction of *I* with diethyl malonate proceeded only on refluxing with excess boiling pyridine and gave *IIIb*. On repeating the above reaction in boiling with excess pyridine *IIIa*—*IIIc* were obtained.

TABLE III

Effect of compounds *III*—*VI* on some Gram positive, Gram negative bacterial species and some fungi using disc plate method (disc diameter 5 mm), expressed as diameter of inhibition zone in mm

Organism	Compound									
	III	*IIIb*	*IVa*	*IVb*	*IVc*	*Va*	*Vb*	*Vc*	*VIa*	*VIb*
Bacillus cereus	20	17	17	15	13	15	14	13	15	11
E. coli	16	14	12	6	9[a]	10	8	9[a]	—	—
Pseudomonas aeruginosa	—	—	—	—	—	8[a]	—	6[a]	—	—
Klebsiella pneumonia	8	10	8	7	—	—	—	—	—	—
Serratia sp.	8[a]	—	—	—	—	8[a]	—	—	—	—
Candida albicans	12	15	12	12	—	8	6	8	—	—

[a] Partial inhibition.

6-(1-Ethoxycarbonyl-2-oxopropyl)-7-chloroquinoline-5,8-dione

6,7-Dichloroquinoline-5,8-dione (*I*, 0·0025 mol) was added to a boiling solution of ethyl acetoacetate (0·0025 mol) in absolute ethanol, in which sodium (0·0025 mol) was previously dissolved, and refluxed for about 1 h. The separated product was collected and crystallized from ethanol to give brownish red fine crystals of the title compound, m.p. 145°C. For $C_{15}H_{12}ClNO_5$ (312·7) calculated: 55·99% C, 3·73% H, 11·04% Cl, 4·35% N; found 56·20% C, 3·49% H, 10·90% Cl, 4·15% N. Refluxing of the product in pyridine or ethanol–pyridine mixture afforded indolizino[2,3-*g*]quinolinedione *IIIb*, m.p. > 350°C.

6,8-Disubstituted Indolizino[2,3-*g*]quinoline-5,12-diones (*IVa—IVc*)

A mixture of 6,7-dichloroquinoline-5,8-dione (*I*, 0·0025 mol), active methylene compound (acetylacetone, ethyl acetoacetate, and/or ethyl cyanoacetate 0·0025 mol) and 4-methylpyridine (0·005 mol) in absolute ethanol (30 ml) was refluxed for 10 h. The colour of reaction mixture changed to brownish red or violet. The precipitated dark solids were filtered and recrystallised from acetic acid. Yield 50—65%. The analytical results are given in Tables I and II.

Benzo[5,6]- and Benzo[7,8]indolizino[2,3-*g*]quinoline-5-12-diones (*Va— VIc*)

The same procedure was adopted, only quinoline and/or isoquinoline was used instead of pyridine and reaction mixture was refluxed for 14 h. Yields 40—55%. The products were crystallized from acetic acid. Physical and analytical data are given in Tables I and II.

Antimicrobial Activity of Compounds

Antimicrobial activity of compounds *III— VI* was determined by the usual disc assay method against *Bacillus cereus, Micrococcus roseus, E. coli, Pseudomonas aeruginosa, Klebsiella pneumonia, Serratia sp., Candida albicans, Penicillium martensii, Trichothecium roseum* at concentrations 5 microgram per disc. The culture medium used was of normal nutrient agar containing one gram yeast/litre. The bacterial suspension was prepared by adding one ml of sterile distilled water to a 24 h old culture of the test organism grown on nutrient agar slant (see Table III).

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