SYNTHESIS AND APPLICATION OF SOME NEW FUROQUINOLINEDIONES AS BACTERICIDES

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Received April 18, 1990
Accepted August 4, 1990

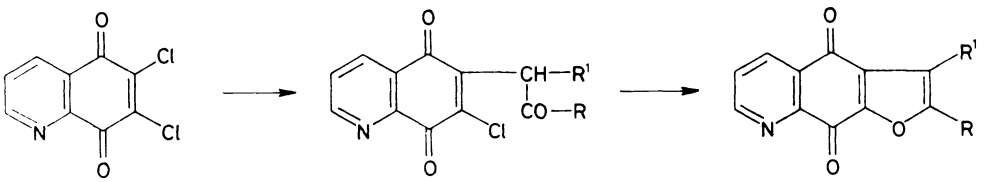
Furo[3,2-*g*]quinoline-4,9-diones were prepared through the reaction of active methylene compounds with 6,7-dichloroquinoline-5,8-dione, either by one step or two step method. Benzo[*b*]- and naphtho[1,2-*b* or 2,1-*b*]furo[3,2-*g*]quinolinediones were also prepared through the reaction of 6,7-dichloroquinoline-5,8-dione with phenols and naphthols in presence of pyridine. The structure of the synthesized compounds was determined by elemental and spectral analysis.

The discovery that several heterocyclic quinones posses attractive properties as dyes[1-4], catalysts[5], and drugs[6-8], led to a renewed attention to their synthesis from 6,7-dichloroquinoline-5,8-quinone. The first preparation of naphtho[2,3-*b*]-furan-4,9-dione from 2,3-dichloronaphthoquinone was carried out by condensing 2,3-dichloronaphthoquinone with an active methylene compound in ethanol and in presence of tributylamine[9]. On the other hand 6,7-dichloroquinoline-5,8-dione interacted with amines to give 6-amino-7-chloroquinoline diones[10-12].

It is therefore expected that 6,7-dichloroquinoline-5,8-quinone can react analogously with active methylene compounds such as acetylacetone, ethyl acetoacetate, ethyl cyanoacetate, or diethyl malonate to give 6-disubstituted methyl-7-chloroquinoline-5,8-dione (*I*), since the chlorine atom in position 6 is more liable to be substituted than that in position 7 (refs[10,12]). Cyclization of *I* could be affected by refluxing in ethanol and in presence of tributylamine to give *II*. In another route compounds *II* could be prepared by condensing equimolar amounts of 6,7-dichloroquinoline--5,8-dione and active methylene compound in ethanol and in presence of tributylamine in one step. Very probably the one step method proceeds via the same intermediate *I*.

The compounds obtained contained no halogen and the IR spectra showed absorptions characteristic of ν(C—O—C) of cyclic ethers (1 050–1 190 cm^{-1}), and carbonyl group (1 655 cm^{-1}). The ^1H NMR (TFA) spectrum of *IIc* revealed signals at δ 3·6, 4·45 (5 H, O—CH_2CH_3); 7·4–8·4 (3 H, pyridine nucleus).

The brazanquinone system (or benzo[*b*]naphtho[2,3-*d*]furan-6,11-diones) is usually prepared by heating at 100°C a mixture of 2,3-dichloronaphthoquinone and



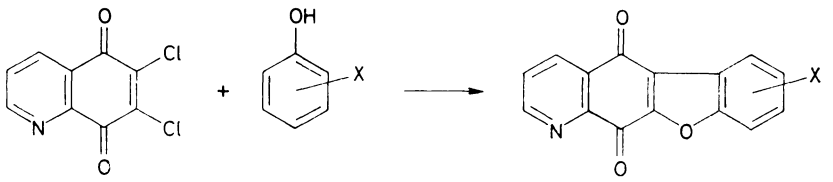
I *II*

In formulae *I* and *II*: *a*, R = CH_3; R^1 = $COCH_3$ *b*, R = CH_3; R^1 = $COOC_2H_5$ *c*, R = OC_2H_5; R^1 = CN
d, R = OC_2H_5; R^1 = $COOC_2H_5$

SCHEME 1

the phenol in pyridine[13,14]. Similarly the isolated products from the reaction of 6,7-dichloroquinoline-5,8-dione and phenols such as phenol, *p*-cresole, resorcinol, and α- or β-naphthols in pyridine gave benzo[*b*]furo[3,2-*g*]quinoline-5,13-dione *III*–*V*, respectively.

In this case pyridine is supposed to act only as a basic reagent that facilitates the removal of hydrogen chloride. These products, *IIIa*–*IIIe*, contained no halogen and the IR spectra revealed absorptions at 1 050–1 190 cm^{-1} (ν(C—O—C) of cyclic ether), 1 650 cm^{-1} (ν(C=O) of quinone) and disappearance of characteristic bands of C—Cl. The ^{1}H NMR (TFA) spectrum of *IIIa* revealed signals at δ 7·3 to 8·82 m (7 H, phenylene and pyridine nuclei). The reaction can be represented by Scheme 2.



IIIa, X = H
IIIb, X = 7-OCH_3
IIIc, X = 6-OH

SCHEME 2

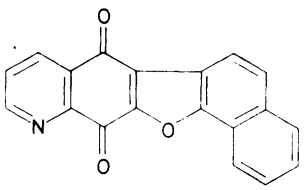
The ultraviolet-visible absorption spectra of ethanolic solutions, showed three absorption bands in UV region located at 230–240, 255–260, and 300–320 nm. They possessed a single broad band in the visible region at 418–450 nm which can be ascribed to intramolecular charge transfer of electrons on the heterooxygen atom of furan nucleus to the quinone ring. It is also remarkable that charge transfer band

of the products obtained from the reaction of quinone and α- or β-naphthol located at 438, 450 nm respectively are close to each other, the difference is ~12 nm. This strengthens the postulation that compounds *IV*, *V* are of angular type (i.e. antagonistic action of naphthyl ring on charge transfer does not differ largely).

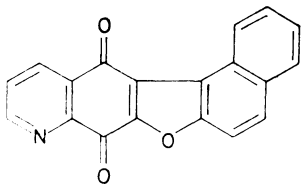
TABLE I
Analytical data of compounds *I*—*V*

Compound Colour	M.p., °C Yield, %	Formula (M.w.)	Calculated/Found			
			% C	% H	% Cl	% N
Ia	120	$C_{14}H_{10}ClNO_4$	57·63	3·43	12·19	4·80
Dark brown	60	(291·5)	57·82	3·32	11·96	4·55
Ib	144—146	$C_{15}H_{12}ClNO_5$	55·99	3·73	11·04	4·35
Brown red	42	(321·5)	56·19	3·89	10·91	4·15
Ic	180	$C_{14}H_9ClNO_4$	55·17	2·95	11·66	9·19
Violet brown	70	(304·5)	55·39	2·71	11·41	8·99
Id	169—171	$C_{16}H_{14}ClNO_6$	54·62	3·98	10·10	3·98
Reddish violet	79	(351·5)	54·89	3·87	9·82	3·75
IIa	215	$C_{14}H_9NO_4$	65·88	3·53	—	5·49
Violet brown	43	(255·4)	65·01	3·70	—	5·29
IIb	170	$C_{15}H_{11}NO_5$	63·16	3·86	—	4·91
Dark brown	28	(285·4)	63·40	3·98	—	4·69
IIc	195—197	$C_{14}H_8N_2O_4$	62·69	2·98	—	5·22
Brown	65	(268·4)	62·93	2·80	—	5·05
IId	224—226	$C_{16}H_{13}NO_6$	60·95	4·13	—	4·44
Dark brown	68	(315·3)	61·20	4·31	—	4·12
IIIa	310 (sub. 300)	$C_{15}H_7NO_3$	72·29	2·81	—	5·62
Dark brown	70	(249·2)	72·51	2·65	—	5·40
IIIb	>350	$C_{16}H_9NO_4$	68·82	3·22	—	5·02
Dark brown	65	(279·3)	68·99	3·34	—	4·92
IIIc	>350	$C_{15}H_7NO_4$	67·92	2·64	—	5·28
Violet brown	60	(265·3)	68·23	2·80	—	5·12
IV	320	$C_{19}H_9NO_3$	76·25	3·01	—	4·68
Yellow brown	78	(299·4)	76·54	3·30	—	4·36
V	300 (dec.)	$C_{19}H_9NO_3$	76·25	3·01	—	4·68
Brisk brown	73	(299·4)	76·54	3·25	—	4·29

Biological screening of compounds *I*—*III* showed that 6,7-dichloroquinoline-5,8--quinone has no bactericidal activity but slight activity against *Staphylococcus aureus*. 6-Disubstituted methyl-7-chloroquinolinedione *I*, or 2,3-disubstituted furo[3,2-*g*]quinolinediones *II* induced no remarkable activity, while benzo[*b*]furo[3,2-*g*]quinolinedione *IIIa* induced strong bactericidal activity towards *Staphylococcus aureus*, *E. coli*, *Proteus vulgaris*, and *Pseudomonas aeruginosa*. Methoxy



IV



V

substitution in *IIIb* does not interfere with this potency, while 6-hydroxybenzo[*b*]-furo[3,2-*g*]quinolinedione (*IIIc*) has sharply decreased activity. On the other hand, naphthofuroquinolinediones *IV*, *V* do not have this activity.

TABLE II

Effect of compounds *I*—*V* on some Gram positive and Gram negative bacterial species using disc plate method

Compound	Bacterial species				
	Staphylococcus aureus	*Anthracoid*	*Escherichia coli*	*Proteus vulgaris*	*Pseudomonas aeruginosa*
Ia	++	—	—	—	—
IIa	++	—	—	—	—
Ib	++	—	—	—	—
IIb	—	—	—	—	—
Ic	+	—	—	—	—
IIc	+	—	+	—	—
IIIa	++++	+	++++	++++	++
IIIb	++	—	+	—	—
IIIc	++++	++	++++	++++	++++
IV	—	—	—	—	—
V	—	—	—	—	—

EXPERIMENTAL

Melting points are uncorrected. IR spectra in KBr were recorded on a Unicam SP 1200 spectrophotometer. UV-visible absorption spectra were recorded on a Pye Unicam SP 8000 Ultraviolet recording spectrophotometer using 1 cm matched silica cells. NMR spectra in TFA were measured on a Varian (90 MHz) instrument.

6-Disubstituted Methyl-7-chloroquinoline-5,8-diones (*Ia—Id*)

The preparation of the intermediates was carried by adding 6,7-dichloroquinoline-5,8-dione (0·005 mol) to a boiling solution of the active methylene compound (acetylacetone, ethyl acetoacetate or diethyl malonate, 0·005 mol) in absolute ethanol in which sodium (0·005 mol) was previously dissolved and refluxed for 4 h. The separated products were collected and crystallized from aqueous ethanol (see Table I).

2,3-Disubstituted Furo[3,2-*g*]quinoline-4,9-diones (*IIa—IId*)

To a solution of *I* (0·005 mol) in ethanol, 0·025 mol of tributylamine was added. The mixture was refluxed for about 8—10 h, cooled and acidified with acetic acid. The separated products were filtered off, and crystallized from methanol (see Table I). Compounds *II* were also obtained by refluxing equimolar amounts of 6,7-dichloroquinoline-5,8-dione and active methylene compounds in ethanol and in presence of tributylamine in one step.

Benzo[*b*] and Naphtho[1,2-*b* or 2,1-*b*]furo[3,2-*g*]quinolinediones (*IIIa—IIIe*)

A mixture of 6,7-dichloroquinoline-5,8-dione (0·005 mol), and phenol (0·005 mol) was refluxed in pyridine (8—10 h) until the reaction mixture attained a permanent colour and a dark solid precipitated. The reaction mixture was cooled and filtered. The precipitates were washed with boiling water and crystallized from acetic acid (see Table I).

Antibacterial Activity of Compounds *I—V*

The bactericidal activities of compounds *I—V* were determined by the usual disc assay method against *Staphylococcus aureus, Anthracoid, Escherichia coli, Proteus vulgaris,* and *Pseudomonas aeruginosa* at concentrations 5 micrograms 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 (for results see Table II).

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