HETEROCYCLIC QUINONES: SYNTHESIS OF SOME NEW HETEROCYCLIC QUINONES FROM 6-CHLOROQUINOLINE--5,8-DIONE HYDROCHLORIDE

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Received July 27, 1990
Accepted January 20, 1991

Interaction of 6-chloroquinoline-5,8-dione hydrochloride with amides and/or thioamides in ethylene glycol afforded oxazolo[5,4-*g*]quinoline-4,9-dione (*III*) and thiazolo[5,4-*g*]quinoline--4,9-dione (*V*). Using semicarbazide and/or thiosemicarbazide in the above reaction, oxadiazino-, and thiadiazino[6,5-*g*]quinoline-5,10-diones (*VI*, *VII*), respectively, were obtained. Their bactericidal activities have been determined.

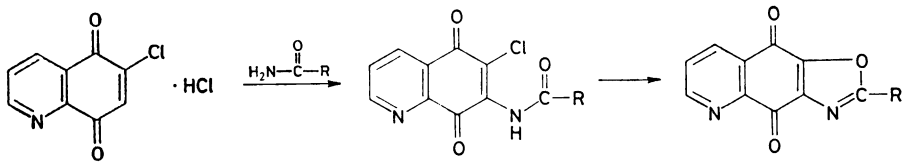
It has been reported that derivatives of quinoline-5,8-quinone possess chemotherapeutic activity[1-6]. Recently, it has been reported[7,8], that interaction of 2,3-dichloro-1,4-naphthoquinone with amides and thioamides in highly polar solvents leads to the formation of naphthoxazole and naphthothiazolediones. This has prompted us to extend this reaction to 6-chloroquinoline-5,8-quinone hydrochloride[9].

Refluxing of a mixture of equimolecular amounts of 6-chloroquinoline-5,8-dione hydrochloride (*I*) and acid amide such as formamide, acetamide, oxamide, urea, benzamide, and nicotinamide in ethylene glycol for 10–15 h resulted in red to reddish brown colour of reaction mixture and brown solids were separated after prolonged reflux.

These products show high melting points and low solubility in majority of organic solvents; they contain no halogene and their IR spectra show absorption bands at 1 040–1 150 cm^{-1} (ν C—O—C of cyclic ether), 1 640–1 680 cm^{-1} (ν C=O of quinone), and 1 590–1 600 cm^{-1} (ν C—N), and no absorptions due to ν NH or C—Cl. The NMR spectra (TFA) of compounds *IIIb*, *IIIe* and *IIIf* reveal signals at δ 4·05 (s, 3 H, CH_3), δ 7·3–8·2 (m, 3 H, pyridine nucleus); δ 7·15–8·1 (m, 8 H, pyridine and phenyl nuclei); δ 7·3–8·1 (m, 7 H, two pyridine nuclei), respectively. Mass spectrum of compound *IIIa* gave $[M^+]$ peak at m/z 200. Therefore we can characterize these products as 2-substituted oxazolo[5,4-*g*]quinoline-4,9-diones (*IIIa–f*). The reaction was enhanced by addition of catalytic amounts of bicarbonate, but did not proceed in non-polar solvents such as benzene or weak polar solvents such as chloroform or dioxane. However, the above reaction was suggested to proceed via

the intermediate 7-acylamino-6-chloroquinoline-5,8-dione (*II*) (ref.[10]) formed by nucleophilic addition to quinone salt *I*.

Involvement of the intermediate *II* was ascertained by means of its formation after the reaction in ethanol–glycol mixture and short time reflux (15 min). Transformation of *II* to the cyclic product *III* was achieved by prolonged reflux either in ethylene glycol or ethanol–bicarbonate resulting in a loss of hydrogen chloride molecule. The reaction can be represented by Scheme 1.



I *II* *III*

In formulae *II* and *III*: *a*, R = H ; *b*, R = CH_3 ; *c*, R = $CONH_2$; *d*, R = NH_2 ; *e*, R = C_6H_5 ; *f*, R = 3-C_5H_5N

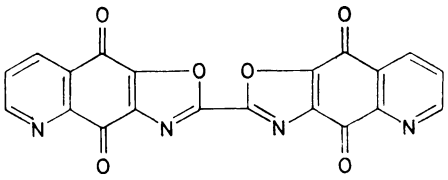
SCHEME 1

Only 2-methyloxazolo[4,5-*g*]quinoline-4,9-dione has been previously prepared[11,12] by a two step method, through interaction of 6,7-dichloroquinoline-5,8-dione with ammonia in alcoholic solution to form 6-acylamino-7-chloroquinoline, followed by treatment with one equivalent of boiling acetic anhydride and a small amount of concentrated sulfuric acid.

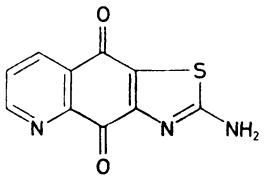
On the other hand, when 2 moles of quinone *I* and one mole of oxamide were used in the above reaction and under the same conditions, 2,2'-bis(oxazolo[5,4-*g*]quinoline)-4,4',9,9'-tetrone (*IV*) was isolated. Its IR spectra showed disappearance of absorptions of νNH_2 (3 200, 3 320 cm^{-1}) and $\nu C{=}O$ of amides (1 700 cm^{-1}) of compound *IIIc*.

Thiourea also interacted with quinone *I* in ethylene glycol or in ethanol and bicarbonate as a catalyst to give 2-aminothiazolo[5,4-*g*]quinoline-4,9-dione (*V*) whose IR spectra showed absorption characteristic of νNH_2 (3 310, 3 400 cm^{-1}), $\nu C{=}O$ of quinone (1 680 cm^{-1}) and ν C—S—C cyclic thioether (1 030–1 120). Mass spectrum of *V* gave *m/z* peak at 232.

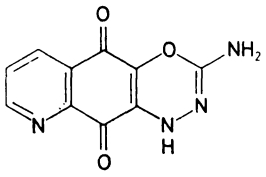
Moreover, interaction of *I* with semicarbazide and /or thiosemicarbazide in ethylene glycol gave compounds containing no halogen and were identified by analysis as oxadiazino- and thiadiazino[6,5-*g*]quinoline-5,10-dione *VI* and *VII*, respectively. Their IR spectra showed absorption characteristic of νNH_2 (3 280, 3 400 cm^{-1}), ν C—O—C cyclic ether (1 090–1 120 cm^{-1}) for compound *VI*; νNH_2 (3 240, 3 360 cm^{-1}), ν C—S—C cyclic (1 040–1 130 cm^{-1}) for *VII*.



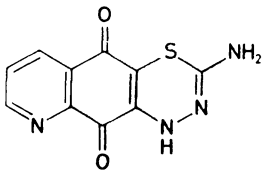
IV



V



VI



VII

Biological testing of these compounds against some gram positive and gram negative bacteria species showed that all 2-substituted oxazolo[5,4-*g*]quinolines *III* have a remarkable bactericidal activity against *Bacillus cereus*. Thiazolo[5,4-*g*]quinoline *V* is more effective than the corresponding oxazolo[5,4-*g*]quinoline *IIId* and also exhibits a remarkable activity against *Micrococcus roseus*. Moreover, six-member oxadiazino- and thiadiazino[6,5-*g*]quinolines *VI*, *VII* are more potent than five--member oxazolo[5,4-*g*]quinoline *IIId*. Oxadiazinoquinoline *VI* exhibited strong bactericidal activity against *Micrococcus roseus*. Thiazolo[5,4-*g*]quinoline *V* and thiadiazino[6,5-*g*]quinoline *VII* had the same potency (see Table I). On the other hand, all these compounds reflected no activity against *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Serratia sp.*

TABLE I

Effect of compounds *III*— *VII* on some gram-positive and gram-negative bacterial species using agar-plate method (disc diameter 5 mm) expressed as diameter of inhibition zone in mm

Organism	*IIIa*	*IIIb*	*IIIc*	*IIId*	*IIIe*	*IIIf*	*IV*	*V*	*VI*	*VII*
Bacillus cereus	—	12	8	8	9	8	9	14	12	14
Micrococcus roseus	—	—	—	—	—	—		15	12	—
Escherichia coli	—	8 p.i.[a]	—	—	—	—	—	—	—	—

[a] Partial inhibition.

TABLE II

Physical and analytical data of compounds *II*—*VII*

Compound R	M.p. °C	Yield %	Formula (M.w.)	Calculated/Found			IR spectra, cm^{-1}
				% C	% H	% N	
IIb	>350	40	$C_{11}H_7ClN_2O_3$[a] (250·5)	52·69 52·95	2·79 3·00	11·18 11·55	3 400 (ν NH), 1 720 (ν C=O of amide), 1 650 (ν C=O of quinone), 1 580 (ν C=N)
IIIa H	>350 (ignites)	52	$C_{10}H_4N_2O_3$ (200)	60·0 60·22	2·00 2·15	14·00 13·95	1 645 (ν C=O of quinone), 1 600 (ν C=N), 1 070—1 120 (ν C—O—C-cyclic)
IIIb CH_3	>350	38	$C_{11}H_6N_2O_3$ (214)	61·68 61·90	2·06 2·99	13·08 12·89	2 900 (ν CH Ar.) 1 650 (ν C=O of quinone), 1 600 (ν C=N), 1 050—1 150 (ν C=O cyclic)
IIIc $CONH_2$	>350 (250 darkens)	47	$C_{11}H_5N_3O_4$ (243)	54·32 54·60	2·06 216	17·28 17·50	3 200, 3 320 (ν NH_2), 1 700 (ν C=O of amide), 1 650 (ν C=O of quinone), 1 610 (ν C=N), 1 060—1 120 (ν C—O—C cyclic)
IIId NH_2	>350	65	$C_{10}H_5N_3O_3$ (215)	55·81 55·99	2·34 2·45	19·53 19·30	3 370, 3 260 (ν NH_2), 1 660 (ν C=O of quinone), 1 600 (C=N), 1 040—1 120 (ν C—O—C cyclic)

IIIe C_5H_6	>350	32	$C_{15}H_8N_2O_3$ (264)	68·18 68·40	3·03 3·20	10·60 10·39	1 640 (ν C=O of quinone), 1 600 (ν C=N), 1 050–1 130, (ν C—O—C cyclic)
IIIf 3-C_5H_5N	290 (ignites)	30	$C_{15}H_8N_3O_3$ (278)	64·75 64·95	2·88 2·99	15·11 14·88	1 670 (ν C=O of quinone), 1 590–1 620 (ν C=N), 1 040–1 120 (ν C—O—C cyclic)
IV	>350	50	$C_{20}H_6N_4O_6$ (398)	60·30 60·55	1·51 1·78	14·07 13·87	1 680 (ν C=O of quinone), 1 580–1 610 (ν C=N), 1 040–1 120 (ν C—O—C cyclic)
V	>350	70	$C_{10}H_5N_3O_2S$[b] (231)	51·95 52·15	2·16 2·30	18·18 18·32	3 400, 3 310 (ν NH_2), 1 660 (ν C=O of quinone), 1 600 (ν C=N), 1 030–1 120 (ν C—S—C cyclic)
VI	>350	65	$C_{10}H_6N_4O_3$ (230·2)	52·17 52·42	2·60 2·47	24·35 24·15	3 400, 3 280 (ν NH_2), 1 660 (ν C=O of quinone), 1 600 (ν C=N), 1 030–1 120 (ν C—O—C cyclic)
VII	>350	68	$C_{10}H_6N_4O_2S$[c] (246)	48·78 48·97	2·44 2·20	22·76 22·56	3 380, 3 240 (ν NH_2), 1 660 (ν C=O of quinone), 1 600 (ν C=N), 1 040–1 130 (ν C—S—C cyclic)

[a] Calculated 14·17% Cl; found 13·85% Cl; [b] calculated 13·87% S; found 13·62% S; [c] calculated 13·02% S; found 12·85% S.

The newly synthesized compounds show remarkable bactericidal activity against *Bacillus cereus*. Six-member oxadiazino and thiadiazino derivatives are more potent than oxazoloquinolinediones, except for the 2-methyl derivative. The replacement of oxygen by sulfur in the oxazole nucleus increased the bactericidal potency.

EXPERIMENTAL

Melting points are uncorrected. IR spectra in KBr were recorded on a Unicam SP 1200 spectrophotometer. NMR spectra in CF_3COOH were measured on a Varian Instrument (90 MHz). Mass spectra were measured on a Mass Spectrometer Varian MAT-311 at 70 eV.

2-Substituted Oxazolo[5,4-*g*]quinoline-4,9-diones (*IIIa*—*IIIf*)

A mixture of *I* (0·002 mol) and the acid amide (0·003 mol) was covered with 15 ml ethylene glycol and refluxed for about 10—15 h, when the reaction mixture attained brown to reddish brown colour and brown to reddish brown solids were formed. The reaction mixture was cooled, diluted with aqueous ethanol, and the precipitated products were collected and recrystallized from dimethylformamide. Yield, 35—65%. These compounds are intensively brown to reddish brown with high melting points and very low solubility in majority of organic solvents. The results are given in Table II.

Repeating the above reaction using acetamide in ethanol and in presence of sodium bicarbonate (0·002 mol) as a catalyst, resulted in oxazoloquinolinedione *IIIb*, yield, 35%.

6-Chloro-7-acetamidoquinoline-5,8-dione (*IIb*)

A mixture of *I* (0·002 mol) and acetamide (0·003 mol) was dissolved in ethanol–glycol mixture (20 ml), heated for about 15 min till red colour was attained, cooled, and diluted with water. The precipitated solid was collected and recrystallized from dimethylformamide to give fine crystals of *IIb*. M.p. >350°C (see Table II). On refluxing *IIb* in ethylene glycol for prolonged time, the compound cyclised to *IIIb*.

2,2′-Bis(oxazolo[5,4-*g*]quinoline)-4,4′,9,9′-tetrone (*IV*)

Obtained by refluxing *I* (0·002 mol) with oxamide (0·001 mol) under the above reaction conditions for 15 h. Deep brown fine crystals from dimethylformamide, m.p. > 350°C (see Table II).

2-Aminothiazolo[5,4-*g*]quinoline (*V*)

Obtained by refluxing *I* (0·002 mol) with thiourea (0·002 mol), either in ethylene glycol (15 ml) or in ethanol (25 ml) containing sodium bicarbonate (0·002 mol) as a catalyst for about 10 h. Reddish brown fine crystals from dimethylformamide, m.p. >350°C (see Table II).

Oxadiazino- and Thiadiazino[6,5-*g*]quinoline-5,10-(4*H*)-diones (*VI*, *VII*)

Obtained by refluxing *I* (0·002 mol) with semicarbazide or thiosemicarbazide (0·002 mol) in ethylene glycol (15 ml) or in ethanol (30 ml) containing sodium bicarbonate (0·002 mol) as a catalyst for about 10 h (see Table II). Crystallized from dimethylformamide: *VI*, orange brown fine crystals.

Determination of Antibacterial Activity

The antibacterial activity of compounds *III*, *IV*, *V*, *VI*, *VII* was determined by usual disc assay method[13] against *Bacillus cereus*, *Micrococcus roseus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Serratia sp.* at concentrations 5 μg per disc. The culture medium used was composed of normal nutrient agar containing 1 g yeast/l. 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.

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Translation revised by H.-M. Mašková.