SYNTHESIS OF SOME NEW SULFONAMIDE DERIVATIVES OF 7-CHLOROQUINOLINE-5,8-DIONE AND PYRIDOCARBAZOLEDIONES

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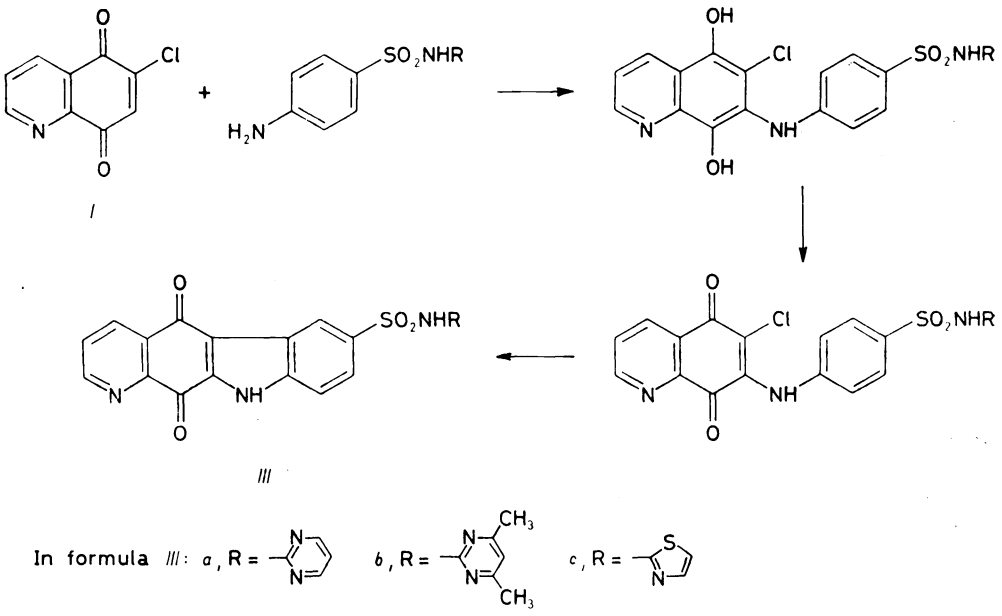
Interaction of 6-chloroquinoline-5,8-dione hydrochloride (*I*) or 6,7-dichloroquinoline-5,8-dione (*II*) with sulfa drug in ethanol containing diethylaniline afforded 7-substituted sulfonamide-10*H*-pyrido[3,2-*b*]carbazole-5,11-dione (*III*), and sulfonamide derivatives of 7-chloroquinoline-5,8-diones (*IV*). Moreover the reaction of *II* with arylamine in pyridine afforded substituted 6*H*-pyrido[2,3-*b*]carbazole-5,11-dione (*V*). The structure of the compounds was determined by elemental and spectral analysis, and by chemical reaction.

The well known antitumor and antibiotic streptonigrin contains the quinoline-5,8-dione system[1]. Substituted diaminoquinolinoquinones are effective in inhibiting aerobic glycolysis of tuberculoses[2]. Amino derivatives of 2-chloro-1,4-naphthoquinone[3] have been found to be quite potent as inhibitors of acid production by bacteria in the oral cavity. Moreover amine derivatives (amino, methylamino, acylamino) of 6-chloroquinoline-5,8-dione are used as fungicides[4]. These studies led us to synthesis of the title compounds of biological interest.

It was reported that 6-chloroquinoline-5,8-quinone reacts with amines in ethanolic solution at room temperature for 28 h to give 7-amino-6-chloroquinoline-5,8-dione. 6-Chloroquinoline-5,8-dione hydrochloride (*I*) also interacted with excess arylamines in ethanol and gave 10*H*-pyrido[2,3-*b*]carbazole-5,11-dione[5]. In the present work, interaction of *I* with sulfa drugs such as sulfadiazine, sulfadimidine, and sulfathiazole in ethanol and in presence of diethylaniline gave highly coloured products (brown to violet) of high melting points characterized as 7-substituted sulfonamide 10*H*-pyrido[3,2-*b*]carbazole-5,11-dione (*IIIa*–*IIIc*).

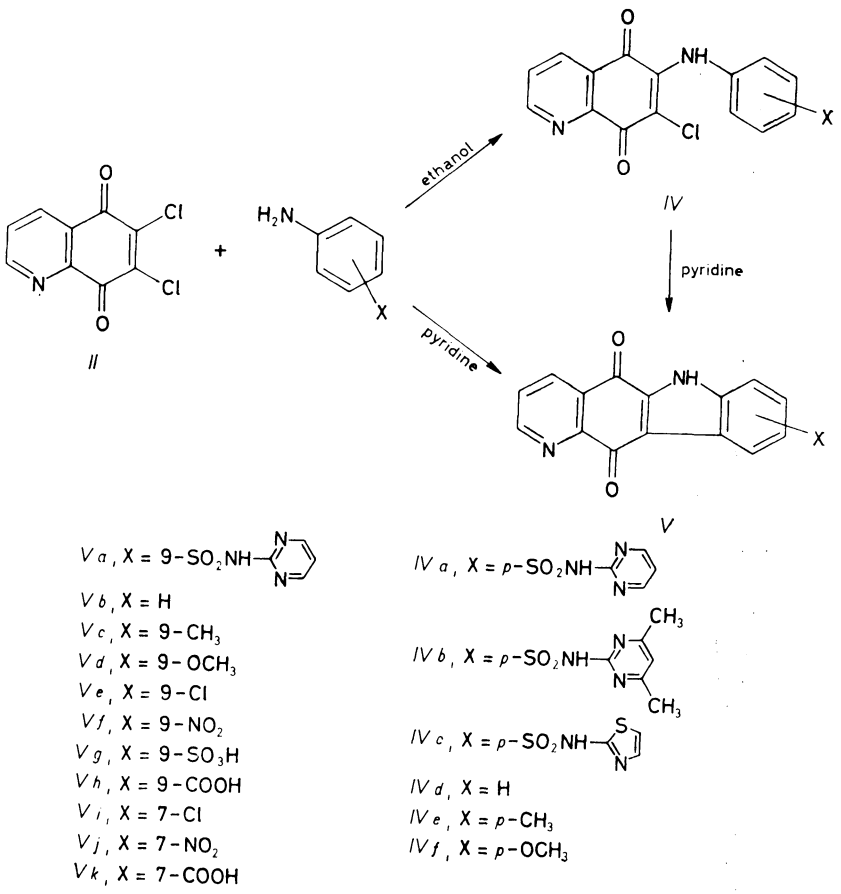
Their IR spectra exhibited well defined bands at 1 645 cm^{-1} (ν(C=O) of quinone), 3 400 cm^{-1} (ν(NH)), and at 1 330 cm^{-1}, 1 140 cm^{-1} (ν(—SO_2—)) but no bands due to C—Cl and N^+.HCl. It was suggested that the reaction proceeds through initial formation of 6-chloroquinoline-5,8-dione free base under the basic condition followed by 1,4-nucleophilic addition of sulfa drug giving 7-arylamino-6-chloroquinoline-5,8-dione intermediate which cyclised under the action of excess diethylaniline to give *IIIa*–*IIIc* (see Scheme 1).



SCHEME 1

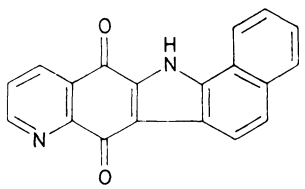
On the other hand interaction of 6,7-dichloroquinoline-5,8-quinone (*II*) with sulfa drugs under the above described conditions gave the new 6-substituted sulfonamide derivatives of 7-chloroquinoline-5,8-quinone *IVa*–*IVc* (Scheme 2). The structure of the isolated products was determined by elemental analysis and IR spectra. Further confirmation of the structure of *IV* was achieved by the reaction of *II* with aniline, *p*-toluidine, and *p*-anisidine in ethanol which gave 6-arylamino-7-chloroquinoline--5,8-quinones *IVd*–*IVf* as reported previously[6,7] in the literature. Cyclisation of *IVa* could be achieved by refluxing with pyridine to give *Va*. In another route the cyclised products *V* could be obtained by the reaction of *II* with aromatic amines in pyridine in one step. The isolated products were identified as 9-substituted 6*H*-pyrido[2,3-*b*]carbazole-5,11-diones (*V*). Elemental analyses of these compounds showed no halogen, the IR spectra exhibited well defined bands at 1 645 cm^{-1} (ν(C=O) of quinones) and at 3 400 cm^{-1} (ν(NH)), but no bands due to C—Cl. The ^{1}H NMR spectrum of compounds *Vb*, *Vc* revealed signals at δ 4·25 s, 1 H (NH); 7·5–8·8 m, 7 H (heterocyclic nucleus); 2·3 s, 3 H (CH_3); 4·25 s, 1 H (NH); 7·2 to 8·8 m, 6 H (heterocyclic nucleus), respectively.

The reaction was suggested to proceed through initial substitution of the halogen atom at the 6-position by the amino group[6,7], followed by dehydrohalogenation under the basic condition to give the cyclised product *V*.

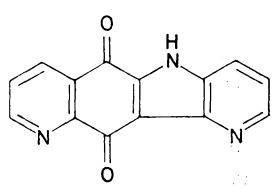


SCHEME 2

On using α-naphthylamine, 3-aminopyridine in the above reaction, the isolated products were identified as pyrido[2,3-*b*]benzo[*h*]carbazole-5,13-dione (*VI*), and dipyrido[3,2-*b*; 2,3-*f*]indole-6,11-dione (*VI*).



VI



VI

TABLE I

Analytical data of compounds *III*—*VI*

Compound	M.p., °C (Yield, %)	Formula (M.w.)	Calculated/Found				
			% C	% H	% Cl	% N	% S
IIIa	289—291	$C_{19}H_{11}N_5O_4S$	56·30	2·72	—	17·28	7·9
	(79)	(405·4)	56·49	2·49		17·02	7·64
IIIb	350	$C_{21}H_{15}N_5O_4S$	58·20	3·46	—	16·17	7·39
	(75)	(433·4)	58·45	2·20		15·95	7·12
IIIc	350	$C_{18}H_{10}N_4O_4S$	57·14	2·64	—	14·18	8·46
	(73)	(378·4)	57·35	2·45		13·98	8·20
IVa	300	$C_{19}H_{12}ClN_5O_4S$	51·64	2·72	8·84	15·85	7·25
	(75)	(441·5)	51·68	2·50	8·60	15·52	7·00
IVb	269—271	$C_{21}H_{16}ClN_5O_4S$	53·67	3·41	7·56	14·9	6·81
	(72)	(469·5)	53·89	3·28	7·24	14·72	6·55
IVc	290—292	$C_{18}H_{11}ClN_4O_4S$	52·11	2·65	8·56	13·51	7·72
	(70)	(414·5)	51·90	2·38	8·32	13·20	7·45
Va	249—251	$C_{19}H_{11}N_5O_4S$	56·30	2·77	—	17·28	7·90
	(55)	(405·4)	56·08	2·53		17·02	7·61
Vb	229—231	$C_{15}H_8N_2O_2$	72·58	3·22	—	11·30	—
	(73)	(248·2)	72·88	3·05		11·04	
Vc	350	$C_{16}H_{10}N_2O_2$	73·28	3·82	—	10·69	—
	(68)	(262·3)	73·50	3·57		10·70	
Vd	350	$C_{16}H_{10}N_2O_3$	69·10	3·60	—	10·07	—
	(66)	(278·3)	69·30	3·41		9·90	
Ve	350	$C_{15}H_7ClN_2O_2$	63·72	2·48	12·56	9·91	—
	(58)	(282·5)	63·98	2·62	12·22	9·61	
Vf	350	$C_{15}H_7N_3O_4$	61·43	2·39	—	14·33	—
	(78)	(293·2)	61·72	2·20		14·04	
Vg	350	$C_{15}H_8N_2O_5S$	54·88	2·44	—	8·53	9·76
	(57)	(328·4)	54·99	2·12		8·23	9·44
Vh	350	$C_{16}H_8N_2O_4$	65·75	2·74	—	9·58	—
	(62)	(292·2)	65·90	2·48		9·31	
Vi	350	$C_{15}H_7ClN_2O_2$	63·72	2·48	12·56	9·91	—
	(60)	(282·5)	63·55	2·19	12·30	9·69	
Vj	350	$C_{15}H_7N_3O_4$	61·43	2·39	—	14·33	—
	(78)	(293·2)	61·4	2·10		14·00	
Vk	350	$C_{16}H_8N_2O_4$	65·75	2·74	—	9·58	—
	(62)	(292·2)	65·94	2·52		9·28	
Vl	350	$C_{19}H_{10}N_2O_2$	76·51	3·35	—	9·29	—
	(68)	(298·3)	76·35	3·13		9·08	
VI	350	$C_{14}H_7N_3O_2$	67·47	2·81	—	16·54	—
	(70)	(249·2)	67·25	2·52		16·54	

Biological testing of these compounds showed that sulfonamides *IIIa*–*IIIc* and *IVa*–*IVc* showed moderate to slight bactericidal activity against *Streptococci*, *Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus albus* and *Staphylococcus citrus*, remarkable activity towards *Sarcina luteus* and no activity against *Anthracoid* or *Micrococcus luteus*.

EXPERIMENTAL

Melting points are uncorrected. IR spectra in KBr were recorded on a Unicam SP 1200 spectrophotometer. NMR ($(CD_3)_2SO$) spectra were measured on a Varian spectrometer (90 M Hz)

7-Substituted Sulfonamide-10*H*-pyrido[3,2-*b*]carbazole-5,11-dione (*IIIa*–*IIIc*)

A mixture of equimolecular quantities of 6-chloroquinoline-5,8-dione hydrochloride (*I*), sulfadiazine, sulfadimidine, and/or sulfathiazole in ethanol and in presence of diethylaniline was refluxed for 18 h. The highly coloured products (reddish brown to violet brown) of high melting points, isolated on cooling, were crystallized from ethanol and were freely soluble in sodium hydroxide solution (see Table I). Yield 73–79%.

Sulfonamide Derivatives of 7-Chloroquinoline-5,8-dione (*IVa*–*IVf*)

A mixture of equimolecular quantities of 6,7-dichloroquinoline-5,8-dione (*II*), sulfadiazine, sulfadimidine, and/or sulfathiazole in ethanol containing diethylaniline was refluxed for ~18 h. The products isolated on cooling were recrystallized from ethanol (see Table I). Yield 70–75%.

Compound *II* (0·001 mol) was refluxed with aniline, *p*-toluidine and/or *p*-anisidine (0·001 mol) in ethanol for 3 h, products (*IVd*–*IVf*) were isolated. Their melting points were 208°C, 214 to 217°C, and 225°C, respectively in accordance with those reported in literature[6,7].

TABLE II

Effect of compounds *IIIa*–*IIIc*, *IVa*–*IVc* on some Gram positive and Gram negative bacterial species using disc plate method

Bacterial species	Compound					
	IIIa	*IIIb*	*IIIc*	*IVa*	*IVb*	*IVc*
Staphylococcus aureus	+	++	+	++	+	+
Staphylococcus albus	–	–	++	++	–	++
Staphylococcus citrus	+	–	++	+	–	–
Streptococci	++	+++	–	++	+	–
Escherichia coli	++	++	++	+	–	–
Sarcina luteus	+++	++	++	+++	+++	++
Anthracoid	–	–	–	–	–	–
Micrococcus luteus	–	–	–	–	–	–

7- and 9-Substituted-6*H*-pyrido[2,3-*b*]carbazole-5,11-dione (*Va*— *VI*) and Dipyrido[3,2-*b*;2,3-*f*]indole-6,11-dione (*VI*)

A mixture of *II* (0·001 mol) and arylamine (0·001 mol) was refluxed in pyridine (30 ml) for 15—18 h. The reaction mixture was concentrated, cooled and the separated product was filtered off, washed with dilute acid and alcohol. Crystallization from ethanol or dilute acetic acid gave fine crystals of highly coloured (brown to violet) compounds and of high melting points. Yield 55—78%. The results are given in Table I.

Cyclisation of *IVa*, *IVd* to 6*H*-Pyrido[2,3-*b*]carbazole-5,11-dione (*Va*, *Vb*)

6-Amino-7-chloroquinoline-5,8-dione (*IVa* or *IVd*; 0·5 g) was refluxed in pyridine (30 ml) for 18 h. The isolated product after concentration and cooling was washed with dilute acid, and alcohol, dried and crystallized from ethanol into fine deep violet crystals of *Va*, m.p. 250°C and violet brown crystals of *Vb*, m.p. 230°C (see Table I).

Antibacterial Activity of Prepared Compounds

The antibacterial activity of compounds *IIIa*—*IIIc*, *IVa*—*IVc* were determined by the usual disc assay method against *Streptococci*, *Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus albus*, *Staphylococcus citrus*, *Sarcna luteus*, *Anthracoid* and *Micrococcus luteus*, at concentrations 5 μg per disc. The culture medium used was of normal nutrient agar containing 1 g of yeast/l. The bacterial suspension was prepared by adding 1 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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