SYNTHESIS OF SOME NEW 7-SUBSTITUTED AMINOMETHYL-6-CHLOROQUINOLINE-5,8-QUINONE

Amal S. YANNI and Zarif H. KHALIL

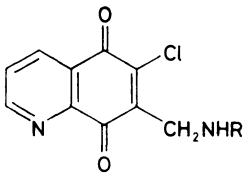
Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt

Received April 18, 1990
Accepted August 3, 1990

Some new 7-substituted aminomethyl-6-chloroquinoline-5,8-quinone (*II*—*IV*) have been obtained by the Mannich reaction on 6-chloroquinoline-5,8-dione and biologically evaluated.

The Mannich products obtained from 6-hydroxyquinoline-5,8-quinone with 1-hexylamine displayed significant amoebicidal activity against induced *E. histolytica* infection in the guinea pig[1-4]. Therefore it was of interest to prepare a new series of 6-chloro-7-aryl (or alkyl) aminomethylquinoline-5,8-quinone (*II*) which may be of some biological interest. 7-Piperidino- and morpholinomethyl-6-chloroquinoline--5,8-quinone (*III*, *IV*) were also prepared.

Oxidation and halogenation of 5-amino-8-hydroxyquinoline had been carried out using a mixture of anhydrous ferric chloride and concentrated hydrochloric acid to give 6-chloroquinoline-5,8-dione hydrochloride[5] (*I*). Refluxing *I* with an alcoholic solution of equimolecular amounts of the amine (primary aromatic or aliphatic) and paraformaldehyde for about 10 h afforded compounds *II* (cf. Table I). Using secondary amine such as piperidine and morpholine gave the 7-piperidino and morpholino derivatives under the same conditions. These derivatives were identified by elemental analysis and spectral (IR, UV) data.



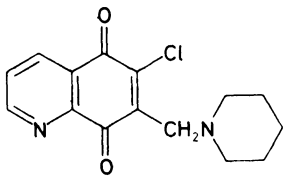
II

IIa, R = C_6H_5	*IIf*, R = C_6H_4—*p*-COOH	*IIk*, R = 1-naphthyl
IIb, R = C_6H_4—*p*-CH_3	*IIg*, R = C_6H_4—*o*-OH	*III*, R = 2-pyridyl
IIc, R = C_6H_4—*p*-OH	*IIh*, R = C_6H_4—*o*-Cl	*IIm*, R = CH_3
IId, R = C_6H_4—*p*-Cl	*IIi*, R = C_6H_4—*o*-NO_2	*IIn*, R = CH_2CO_2H
IIe, R = C_6H_4—*p*-NO_2	*IIj*, R = C_6H_4—*o*-COOH	

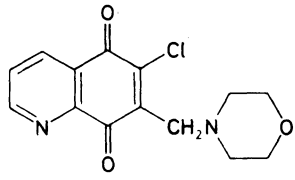
TABLE I

Characteristics of compounds *IIa—IV*

Compound Colour	M.p., °C Yield, %	Formula (M.w.)	Calculated/Found			
			% C	% H	% Cl	% N
IIa	>350	$C_{16}H_{11}ClN_2O_2$	64·30	3·68	11·89	9·38
Brownish violet	50	(298·5)	64·65	3·90	11·94	9·57
IIb	>350	$C_{17}H_{13}ClN_2O_2$	65·28	4·16	11·36	8·96
Reddish brown	80	(312·5)	65·49	4·32	11·49	8·88
IIc	>350	$C_{16}H_{11}ClN_2O_3$	61·05	3·50	11·29	8·90
Violet brown	54	(314·5)	61·20	3·68	11·39	8·80
IId	>350	$C_{16}H_{10}ClN_2O_2$	57·83	3·01	21·32	8·40
Brownish violet	50	(332·4)	57·99	3·20	21·21	8·08
IIe	>350	$C_{16}H_{10}ClN_3O_4$	55·89	2·91	10·36	12·22
Brown	55	(343·5)	56·02	3·12	10·18	12·08
IIf	>350	$C_{17}H_{11}ClN_2O_4$	59·56	3·21	10·36	8·17
Violet brown	45	(342·5)	9·82	3·50	10·20	8·07
IIg	170	$C_{16}H_{11}ClN_2O_3$	61·05	3·50	11·28	8·90
Violet brown	70	(314·5)	61·31	3·72	11·12	8·75
IIh	145	$C_{16}H_{10}Cl_2N_2O_2$	57·83	3·01	12·32	8·43
Violet brown	61	(332·4)	58·03	3·25	12·16	8·25
IIi	>350	$C_{16}H_{10}ClN_3O_4$	55·89	2·91	10·33	12·22
Dark brown	35	(343·5)	56·05	3·15	10·15	12·06
IIj	250 (dec.)	$C_{17}H_{11}ClN_2O_4$	59·56	3·21	10·36	8·17
Violet brown	55	(342·5)	59·88	3·40	10·19	8·04
IIk	>350	$C_{20}H_{13}ClN_2O_2$	68·87	3·73	10·18	8·03
Black violet	70	(348·5)	68·99	3·91	10·30	7·92
III	290	$C_{15}H_{10}ClN_3O_2$	63·04	3·50	12·43	9·81
Brown	38	(285·5)	63·35	3·69	12·75	9·98
IIm	>350	$C_{11}H_9ClN_2O_2$	55·81	3·80	15·01	11·83
Brown violet	40	(236·5)	55·99	3·96	15·32	12·05
IIn	>350	$C_{12}H_9ClN_2O_4$	51·37	3·70	12·67	9·98
Dark violet	45	(280·5)	51·60	3·35	12·50	9·80
III	>360	$C_{15}H_{15}ClN_2O_2$	61·97	5·15	12·22	9·64
Brownish violet	75	(290·7)	61·88	5·31	12·31	9·49
IV	260 (dec.)	$C_{14}H_{13}ClN_2O_3$	57·44	4·44	12·14	9·57
Brown	60	(292·7)	57·61	4·52	12·27	9·39



III



IV

IR spectra showed well defined bands at 3 200–3 400 cm^{-1} (ν(NH)), 2 800 to 2 950 cm^{-1} ($\nu(CH_2)$) 1 640–1 680 cm^{-1} (ν(C=O) of quinones), and 1 580 to 1 640 cm^{-1} (ν(C=N)). The UV spectra of these compounds in dioxane displayed the π–π^* transition bands due to phenyl and heterocyclic rings around 250(s), 270 (shoulder) and 320–335 nm (shoulder).

Biological testing of selected compounds *IIa*, *IIe*, *IIm* and *III*, was done by the usual disc assay method against *Bacillus cereus*, *Micrococcus luteus*, *Staphylococcus aureus*, *Escherichia coli*, *Serratia sp.*, *Pseudomonas aeruginosa* and showed that alkylaminomethyl substitution induced greater bactericidal activity than aryl aminomethyl substitution while substitution by *p*-nitrophenylaminomethyl eliminates this activity.

EXPERIMENTAL

Melting points are uncorrected. IR spectra in KBr were recorded on a Unicam SP 200 G spectrophotometer. UV spectra were recorded on a Unicam SP 8000 UV Recording spectrophotometer using 1 cm matched silica cells.

TABLE II

Effect of selected compounds on some Gram positive and Gram negative bacterial species using disc plate method (disc diameter 5 mm) expressed as diameter of inhibition zone in mm

Organism	Compound			
	IIa	*IIe*	*IIm*	*III*
Bacillus cereus	8	—	12	10
Micrococcus luteus	—	—	10	—
Staphylococcus aureus	9	—	11	12
Escherichia coli	9	—	10	11
Serratia sp.	—	—	—	—
Pseudomonas aeruginosa	—	—	—	—

6-Chloro-7-aryl(alkyl)aminomethylquinoline-5,8-quinone (*II*—*IV*)

A mixture of *I* (0·004 mol), paraformaldehyde (0·004 mol) and the primary aromatic or aliphatic amine (0·004 mol) was refluxed in ethanol (50 ml) for 30—50 h, during which most of the starting material dissolved before precipitation of the product. The separated products *IIa*—*IIn* were filtered and crystallized from acetic acid, yield 40—80%. These compounds are highly colored from brown-brownish violet, insoluble in chloroform, carbon tetrachloride, ether, moderately soluble in acetone, dioxane, pyridine, and soluble in acetic acid and dilute HCl, sparingly soluble in methanol and ethanol. Compounds *III* and *IV* were also prepared following the above procedure. Physical and analytical data are given in Table I.

Determination of Antibacterial Activity of Some Selected Compounds *II*, *III*

The antibacterial activity of compounds *IIa*, *IIe*, *IIm* and *III* were determined by the usual disc assay method against *Staphylococcus aureus*, *Bacillus cereus*, *Micrococcus luteus*, *Escherichia coli*, *Serratia sp.*, *Pseudomonas aeruginosa* at concentrations 5 microgram per disc (see Table II). The culture medium used was of normal nutrient agar containing one gram yeast/liter. The bactericidal 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.

REFERENCES

1. Taylor D. J., Greenburg J.: Am. J. Hyg. *56*, 58 (1952).
2. Pratt Y. T., Drake N. L.: J. Am. Chem. Soc. *79*, 5024 (1957).
3. Robertson D. N., Link K. P.: J. Am. Chem. Soc. *75*, 1883 (1953).
4. Porter T. H., Skelton F. S., Folkers K.: J. Med. Chem. *15*, 34 (1972).
5. Osman A. M., Hamam A. S., Khalil Z. H., Yanni A. S.: Indian J. Chem., B *21*, 325 (1982).