SYNTHESIS AND PHOTOCHEMICAL CONVERSIONS OF PIPERAZINE DERIVATIVES OF 2-CHLORO-1,4-NAPHTHOQUINONE

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Continuing our investigation of the photochemical conversions of 2-dialkylamino-1,4-naphthoquinone [1, 2] we have brought about the synthesis and photolysis of 3-piperazino derivatives of 2-chloro-1,4-naphthoquinone. The methyl and halogeno derivatives of 1,4-naphthoquinone readily react with diamines, moreover, the character of the product formed depends on the structure of the diamine and the conditions of carrying out the reaction. Aliphatic diamines, depending on the number of methylene groups, form two types of products with quinones: a) tetra, penta and hexamethylenediamines- compounds with an open chain [3-5] and b) ethylene and propylenediamines (which can cyclize during the reaction to form stable six- and seven-membered rings)- benzoquinoxaline derivatives [5, 6]. The reaction of piperazine with 1,4-benzoquinone precludes the possibility of cyclization of the secondary amino group at the carbonyl atom. In this case the rigidity of the piperazine (in which the chair form is more favored) does not permit formation of a cyclic structure despite the common length of the hydrocarbon fragment compared with ethylenediamine [7]. It is considered that the reaction proceeds via a classical scheme with formation of amino derivatives of benzoquinone. For 2,3-dichloro-1,4-naphthoquinone (I) the mono-reaction product with piperazine was not obtained even with excess piperazine [4], only the product of condensation of two piperazine amino groups was produced, viz., 1,4-bis(3-chloro-1,4-naphthoquinon-2-yl) piperazine (II).

By carrying out the reaction at ~20°C we obtained 2-chloro-3-piperazino-1,4-naphthoquinone, III. Using an excess of 2,3-dichloro-1,4-naphthoquinone (I) and adding $NaHCO_3$ there was obtained almost exclusively the naphthoquinonylpiperazine II (Table 1). Thus, varying the reaction conditions can lead selectively to one product or the other.

2-Chloro-3-piperazino-1,4-naphthoquinone (III) was used for the synthesis of N-substituted piperazinonaphthoquinones. Compound III is acylated by acid anhydrides and chlorides. Thus, Ac_2O at ~20°C gave 2-chloro-3-(4'-acetylpiperazino)-1,4-naphthoquinone (IV) and PhCOCl gave 2-chloro-3-(4'-benzoylpiperazino)-1,4-naphthoquinone (V).

Under the conditions used for unsubstituted piperazine [9], quinone III slowly reacts with n-BuBr and $PhCH_2Cl$ with the formation of 2-chloro-3-(4'-butylpiperazino)- and 2-chloro-3-(4'-benzylpiperazino)-1,4-naphthoquinones (VI and VII), the reaction going only in the presence of $NaHCO_3$. In analogous conditions MeI reacts quite rapidly with III to give the quaternary salt VIII. Compound III can also be alkylated using olefin oxides: with propylene oxide there is formed 2-chloro-3-[4'-β-hydroxypropyl)-piperazino]-1,4-naphthoquinone (IX).

N-substituted 2-chloro-3-piperazino-1,4-naphthoquinones may be obtained by direct reaction of N-substituted piperazines with 2,3-dichloro-1,4-naphthoquinone (I). In this way 2-chloro-3-[4'-(β-cyanoethyl)piperazino]-1,4-naphthoquinone X and 2-chloro-3-(4'-benzoylpiperazino)-1,4-naphthoquinone V were prepared, the latter also being obtained by acylation of III. As for other aminoalkylquinones, these derivatives of 2-chloro-1,4-naphthoquinone are hydrolyzed by the action of mineral acids to form 2-chloro-3-hydroxy-1,4-naphthoquinone XI.

All of the piperazino derivatives proved to be light sensitive. Photolysis of N-substituted piperazinonaphthoquinones in C_6H_6 and EtOH takes place with the formation of 1,4,5,6-tetrahydropyrazine derivatives, the stability of which depends upon the substituent in the piperazine ring. Thus, when 2-chloro-3-(4'-acetylpiperazino)-1,4-naphthoquinone (IV) is irradiated using either fluorescent light at ~20°C or an incandescent lamp at the temperature of the refluxing solvent, there is produced a blue-violet product (XII). The electronic spectrum shows a bathochromic shift of 78 nm when compared with starting material IV which points to an increase in chain conjugation. Comparison of the position of the signals in the PMR spectrum

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of XII with starting IV allows one to assign a singlet at 2.20 ppm to the acetyl group, a singlet at 3.90 to the piperazine ring, a multiplet at 6.00 ppm to the two protons of the double bond, and a multiplet at 7.80 ppm to aromatic ring protons. On the basis of elemental analysis, spectral data, and comparison with reference data [2], compound XII is assigned the structure 1-(3-chloro-1,4-naphthoquinon-2-yl)-4-acetyl-1,4,5,6-tetrahydropyrazine. 1-(3-Chloro-1,4-naphthoquinone-2-yl)-4-benzoyl-1,4,5,6-tetrahydropyrazine (XIII) was obtained by irradiation of 2-chloro-3-(4'-benzoylpiperazino)-1,4-naphthoquinone (V).

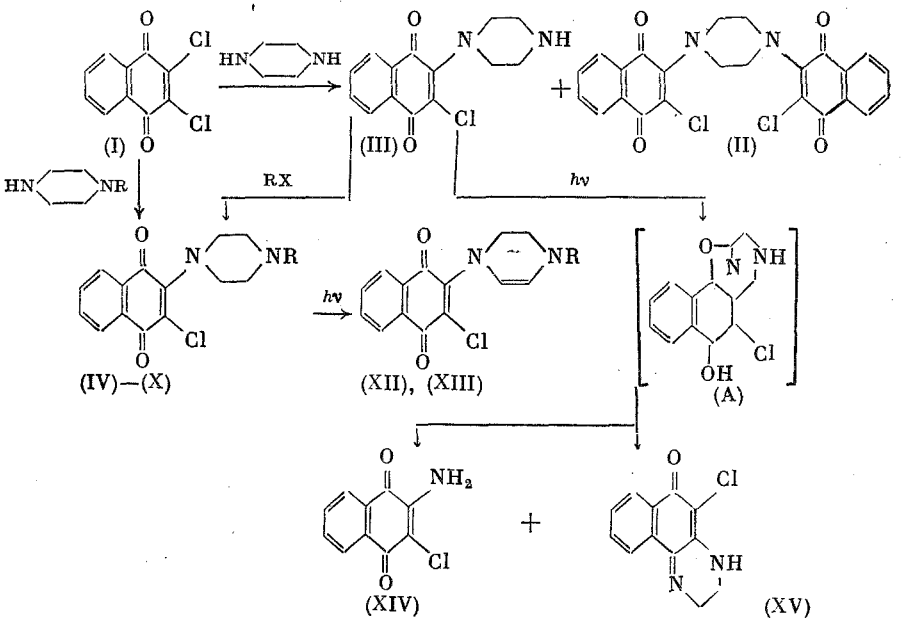
Upon photolysis of naphthoquinonylpiperazines with alkyl substituents (n-Bu, CH_2Ph, CH_2-CH_2CN, $CH_2CH(OH)CH_3$) in the quaternary position of the piperazine ring, blue products of the tetrahydropyrazine type (XII, XIII) are also formed but they are unstable and easily decomposed.

The type of photolysis product of 2-chloro-3-piperazino-1,4-naphthoquinone (III) depends on the solvent used. Irradiation of benzene solutions of III, both at ~20°C and at the reflux temperature of benzene lead to formation of a yellow precipitate, apparently the naphthdihydroxazole (A), analogously obtained earlier by photolysis of other dialkylaminonaphthoquinones [1]. This product is poorly soluble in organic solvents and on chromatography decomposes to give a complex mixture from which there was obtained 2-chloro-3-amino-1,4-naphthoquinone (XIV) [10] and 2,3,4-trihydro-5-chloro-benzo[f]quinoxalin-6-one (XV), the structure of which was confirmed by independent synthesis according to [6]. Photolysis of III in alcohol solution leads immediately to decomposition products (XIV, XV). The formation of the latter is probably a result of further reaction of A, as described earlier [11] (Scheme 1).

EXPERIMENTAL

TLC was carried out on Silufol plates, eluting solvents were $CHCL_3$ and $CHCl_3$—EtOH—25% NH_3 (10:10:1). Preparative chromatography was carried out on KSK silica gel (0.315-0.125 mμ) and Al_2O_3 (activity II), eluting solvent was $CHCl_3$. Electronic absorption spectra (EAS) were recorded on a Specord UV-VIS spectrophotometer using EtOH. IR spectra were recorded on a UR-20 spectrophotometer using KBr tablets or chloroform solutions. PMR spectra were recorded on a Varian A-56/60 machine and referenced to hexamethyldisiloxane. Molecular weights were determined using an AEI MS-902 machine, resolving power ~10,000, direct injection entry. The properties of the obtained compounds are given in Table 2.

Scheme 1



R = COMe (IV), (XII); COPh (V), (XIII); *n*-Bu (VI); CH_2Ph (VII); $NR = \overset{+}{N}Me_2\bar{I}$ (VIII); $CH_2CH(OH)Me$ (IX); CH_2CH_2CN (X).

TABLE 1. Reaction of 2,3-Dichloro-1,4-naphthoquinone (I) with Piperazine

Reagent ratio		Yield of reaction product, %	In the presence of $NaHCO_3$	
quinone (I)	piperazine		(II)	(III)
1	1	0,5	14	54
1	2	0,2	8	79
1	10	0,1	Traces	96
2	1	18	48	42
2*	1	24	85	Traces

*In the presence of $NaHCO_3$.

Reaction of 2,3-dichloro-1,4-naphthoquinone (I) with piperazine. Quinone I (0.01 mole) was added with stirring to piperazine (0.005-0.1 mole) in EtOH (50 ml) and held at ~20° (see Table 1). The precipitated 1,4-bis(3-chloro-1,4-naphthoquinon-2-yl)piperazine (II), if formed, was filtered off, washed with EtOH and dried. It decomposed without melting above 200°C (from benzene), (compare [5], mp 264-265°C (decomp)). Found: mol. wt. 466. $C_{24}H_{16}Cl_2N_2O_4$. Calculated: 466. Water was added to the filtrate to give a precipitate of 2-chloro-3-piperazino-1,4-naphthoquinone (III) which was filtered off, washed with water, and dried — mp 91-93°C. Infrared spectrum (ν, cm^{-1}): 3330 (NH), 2920, 2840 (CH_2), 1680, 1650 (two C=O). EAS (λ_{max}, nm (log ε): 242(4.20), 248(4.31), 506(3.72). Found: mol. wt. 276.0631. $C_{14}H_{13}ClN_2O_2$. Calculated, 276.0665.

Reaction of I with N-substituted piperazines. Quinone I (0.01 mole) was added to solutions of 0.02 mole of N-benzoyl or N-(β-cyanoethyl)piperazine in EtOH (50 ml) and stirring continued for 6 or 2 h, respectively. The precipitated V or X was filtered off, washed with EtOH and dried. If precipitation did not occur during the reaction, the reaction mass was poured into water, the precipitated material filtered off, washed with water, and dried.

2-Chloro-3-(4'-acetylpiperazino)-1,4-naphthoquinone (IV). To III (0.001 mole) was added Ac_2O (0.006 mole). After 15 min the mixture was poured onto ice, filtered, washed with water, the tarry precipitate formed dissolved in $CHCl_3$, and evaporated.

2-Chloro-3-(4'-benzoylpiperazino)-1,4-naphthoquinone (V). PhCOCl (0.01 mole) was added to a solution of III (0.001 mole) in benzene (20 ml). After 1 h the mixture was poured into water, the organic layer washed with water, evaporated, and chromatographed on a silica gel column to give a basic red fraction. Infrared spectroscopy indicated the compound (V) identical to that obtained above. Yield 80%.

2-Chloro-3-(4'-butylpiperazino)- and 2-chloro-3-(4'-benzylpiperazino)-1,4-naphthoquinones (VI) and (VII). To a solution of III (0.001 mole) in EtOH (20 ml) there was added $NaHCO_3$ (0.008 mole) and n-BuBr or $PhCH_2Cl$ (0.008 mole). The mixture heated at 60°C, and subsequently at ~20°C for 7 days. The precipitate was filtered off, evaporated, and chromatographed on silica.

Methyliodide of 2-chloro-3-(4'-methylpiperazino)-1,4-naphthoquinone (VIII). To a suspension of quinone III (0.001 mole) in ethanol (7 ml) was added MeI (0.002 mole) and Et_3N (2-3 drops). The mixture was heated until the solid dissolved and then was allowed to stand at ~20°C for 17 h. The precipitate was filtered off and washed with alcohol.

2-Chloro-3-[4'-(β-hydroxypropyl)piperazino]-1,4-naphthoquinone (IX). A suspension of III (0.001 mole) in propylene oxide (2 ml) was allowed to stand at ~20°C until a solution was formed (~7 days). The oxide was distilled off and the residue chromatographed on SiO_2.

2-Chloro-3-hydroxy-1,4-naphthoquinone (XI). A solution of III (0.001 mole) in conc. HCl (5 ml) was allowed to stand for 2 h at ~20°C. The precipitate formed was washed with water and dried. The yield of XI was 81%, mp 191-193°C (from EtOH) (compare [11]).

Photolysis Method 1. A solution of the piperazino substituted quinone (0.5 mmole) in absolute solvent (500 ml) was placed in a cylindrical glass tube, inside of which was inserted an LB-40 fluorescent lamp. Irradiation was continued until the disappearance of the starting quinone, the solvent was distilled off in vacuum at ~30°C, and the residue dissolved in $CHCl_3$ on an alumina column.

TABLE 2. 2-Chloro-3-Piperazino Substituted 1,4-Naphthoquinones

Compound	Yield, %	mp, °C, (solvent)	Found, %				Empirical formula	Calculated, %				Electronic absorption spectrum in EtOH, λ_{max}, nm (log ε)
			C	H	Cl	N		C	H	Cl	N	
(IV)	89	142–144 (petr. ether)	60,48	4,72	11,22	8,78	$C_{16}H_{15}ClN_2O_3$	60,38	4,72	11,01	8,81	244(4,21), 249(4,20), 281(4,29), 498(3,66),
(V)	67	153–154 (ethanol)	66,21	4,43	9,64	7,20	$C_{21}H_{17}ClN_2O_3$	66,29	4,53	9,21	7,37	242(4,31), 248sh (4,30), 280(4,33), 498(3,68)
(VI)	39	73–75 (petr. ether)	64,88	6,06	10,47	8,15	$C_{18}H_{21}ClN_2O_2$	65,06	6,33	10,54	8,43	242–250(4,19), 283(4,28), 498(3,68)
(VII)	83	110–112 (petr. ether)	68,43	5,20	9,69	7,46	$C_{21}H_{19}ClN_2O_2$	68,85	5,19	9,56	7,65	242–250(4,18), 284(4,26), 502(3,68)
(VIII)	60	237–239	43,89	4,17	(–)	6,30	$C_{16}H_{18}ClIN_2O_2$ *	44,40	4,17	8,10	6,48	–
(IX)	88	138–140 (petr. ether)	61,11	5,65	10,54	8,30	$C_{17}H_{19}ClN_2O_3$	61,08	5,69	10,48	8,38	241(4,15), 249(4,16), 283(4,27), 502(3,68)
(X)	81	103–104 (methanol)	61,98	4,88	10,66	12,62	$C_{17}H_{16}ClN_3O_2$	62,01	4,86	10,67	12,77	243(4,20), 248(4,20), 282(4,31), 502(3,70)
(XII)	75–90	191–194 (ethanol)	60,74	4,12	11,14	8,86	$C_{16}H_{13}ClN_2O_3$ †	60,76	4,11	11,08	8,86	247(4,27), 251sh (4,26), 294(4,43), 576(3,78)
(XIII)	71–90	178–180 (ethanol)	66,71	4,09	9,41	7,39	$C_{21}H_{15}ClN_2O_3$ †	66,67	3,97	9,26	7,41	245(4,32), 251 sh (4,26), 294(4,43), 576(3,78)

*Found: I 28.93%. Calculated: I 29.40%.
†Found: mol. wt. 316. Calculated: mol. wt. 316.
‡Found: mol. wt. 378. Calculated: mol. wt. 378.

TABLE 3. Photolysis of 2-Chloro-3-(4'-acetylpiperazino)- and 2-Chloro-3-(4'-benzoylpiperazino)-1,4-naphthoquinone (IV and V)

Compound	Photolysis method	Solvent	Reaction time, h	Photolysis product	Yield, %
(IV)	1	C_6H_6	3,5	(XII)	90
	1	EtOH	5,25		75
	2	C_6H_6	1,25		86
(V)	1	C_6H_6	3,5	(XIII)	90
	1	EtOH	5,5		74
	2	C_6H_6	1,5		71

Method 2. A solution of the quinone (0.5 mmole) in absolute benzene (500 ml) was irradiated at reflux using a condenser and 300 watt incandescent lamp. The results of the photolysis of IV and V are given in Table 3.

Photolysis of 2-chloro-3-piperazino-1,4-naphthoquinone (III). a) An ethanol solution of III was irradiated using method 1 for 9 h and the residue, after distillation of ethanol, chromatographed on silica gel plates to give 2-chloro-3-amino-1,4-naphthoquinone (XIV, 0.031 g, 30%, [10]) and 2,3,4-trihydro-5-chloro-benzo[f]quinoxalin-6-one (XV, 0.040 g, 34%), mp 134-136°C (from EtOH) (compare [6]). EAS (λ_{max}, nm (log ε)) 240(4.18), 276(4.36), 442(3.58). Found: mol. wt. 232. $C_{12}H_9ClN_2O$. Calculated: mol. wt. 232. The infrared spectrum was identical to that obtained according to [6]. b) A benzene solution of III was irradiated according to method 1 for 3 h, the precipitated yellow solid (0.1 g) filtered off, and washed with benzene. It decomposed on standing in $CHCl_3$ giving (TLC) a complex mixture of products containing XIV and XV.

CONCLUSIONS

1. By reaction of 2,3-dichloro-1,4-naphthoquinone with piperazine, benzoyl, and β-cyanoethylpiperazine there were obtained the 3-piperazino derivatives of 2-chloro-1,4-naphthoquinone.

2. The N-alkylation and N-acylation of 2-chloro-3-piperazino-1,4-naphthoquinone was carried out.

3. Photolysis of N-acyl substituted piperazinonaphthoquinones in benzene or alcohol leads to the formation of 1-(3-chloro-1,4-naphthoquinon-2-yl)-4-acyl-1,4,5,6-tetrahydropiperazine.

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