Photo-Oxidation of 2-Methylamino-3-(1-piperidinylmethyl)-1,4-naphthoquinone

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2-Methylamino-3-(1-piperidinylmethyl)-1,4-naphthoquinone (7) was prepared *via* several steps from 2-methyl-1,4-naphthoquinone (vitamin K_3, 3). The quinone (7) was photochemically oxidized to 2-methylamino-3-(1-piperidinylcarbonyl)-1,4-naphthoquinone (8) and/or 2-alkoxycarbonyl-3-methylamino-1,4-naphthoquinone (9), depending on the solvent used.

Keywords 2-methyl-1,4-naphthoquinone; 1,4-naphthoquinone-2-carboxylate; photooxidation; amination

In the course of our study on the syntheses of oxazine (**1**) and quinazoline (**2**) derivatives starting from 2-methyl-1,4-naphthoquinone (vitamin K_3, **3**), we became interested in the photochemical behavior of 2-alkylamino-3-alkylaminomethyl-1,4-naphthoquinones (**4**).[1,2]

On treatment of two equivalents of various amines with **3** in methanol, monoamino compounds (**5**) and demethylated compounds (**6**) were obtained, but the diamino compound (**4**) was not isolated. The results are summarized in Table I. Similar demethylation *via* a reverse Mannich reaction of generated aminomethyl hydroquinone intermediates has been reported in the reaction of methyl-substituted quinones with amines.[3]

On the treatment of **3** with a large excess (30—36 eq) of heterocyclic secondary amines as the reaction solvent (*e.g.* pyrrolidine and piperidine) the diamino products (**4a**, **b**) were obtained, while with primary amines (*e.g.* methylamine and propylamine), monoamino compounds (**5c**, **d**) were obtained.[2] In the case of the reaction with an acyclic secondary amine such as *N*,*N*-diethylamine, the reaction was complicated, giving an inseparable resinous material.

In order to generate **4c** ($R^1=R^3=CH_3$, $R^2=R^4=H$), **4a** and **4b** were treated with a large excess of methylamine in methanol. However, the 2-piperidinyl group in **4b** was

TABLE I. Amination of **3** with Two Equivalents of Amines

Run	Amine		Product			
	R^1	R^2	Isolated yield (%)			
1	$-(CH_2)_4-$		**5a**[4]	53.2	**6a**[1]	11.0
2	$-(CH_2)_5-$		**5b**[4]	54.3	**6b**[5]	10.4
3	Me	H	**5c**[2,4]	64.2	**6c**[2,6]	4.2
4	*n*-Pr	H	**5d**[2]	59.3	**6d**[2,6]	7.1
5	iso-Pr	H	**5e**[2]	52.9		
6	*n*-Pr	H	**5f**[2]	52.6	—	
7	*sec*-Bu	H	**5g**[2]	21.8	—	
8	*tert*-Bu	H	—		—[a]	
9	Ph	H	—		—[a]	

a) No reaction.

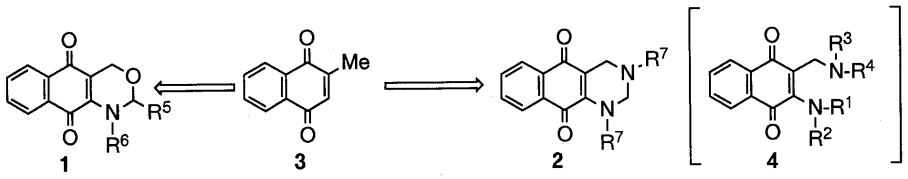

Chart 1

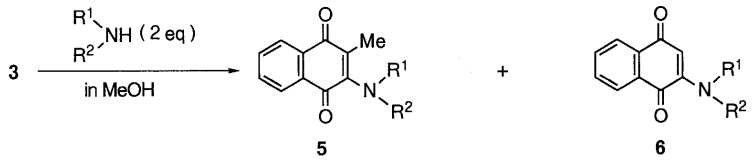

Chart 2

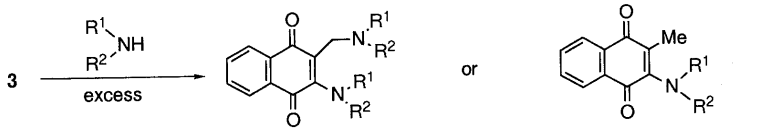

Chart 3

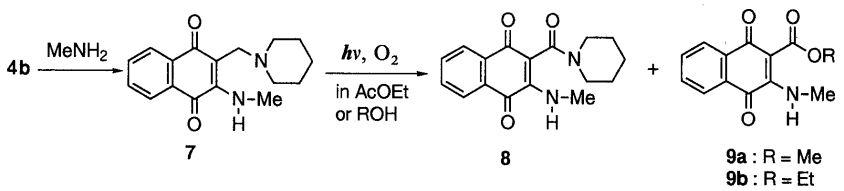

Chart 4

TABLE II. Photo-Oxidation of 7

Run	Light source	Solvent	R	Time (h)	Isolated yield (%)		
					8	9	Total yield (%)
1	A	AcOEt	—	6	—	—	—[a]
2	B	AcOEt	—	12	34.6	0	34.6
3	C	AcOEt	—	36	29.1	0	29.1
4	A	MeOH	Me	6	—	—	—[a]
5	B	MeOH	Me	12	0	**9a**[2]: 38.1	38.1
6	C	MeOH	Me	24	20.1	**9a**[2]: 16.3	36.3
7	C	MeOH	Me	36	8.9	**9a**[2]: 31.3	40.2
8	C	MeOH[b]	Me	36	20.1	**9a**[2]: 13.5	33.6
9	B	EtOH	Et	12	5.6	**9b** : 23.1	28.7
10	C	EtOH	Et	36	12.3	**9b** : 14.1	26.4
11	B	*tert*-BuOH	*tert*-Bu	12	13.4	0	13.4
12	C	*tert*-BuOH	*tert*-Bu	36	12.3	0	12.3
13	B	$C_6H_5CH_2OH$	Bn	12	8.9	0	8.9
14	C	$C_6H_5CH_2OH$	Bn	36	2.2	0	2.2

Light source: A, 500 W high-pressure Hg lamp; B, sunlight; C, 200 W incandescent lamp. *a*) A complex mixture was obtained. *b*) Rose bengal (1.0 eq) was added.

simply exchanged for the methylamino group to give **7** without the desired diamino compound (**4c**).[7]

We found that when a solution of the diaminoquinone (**7**) in ethyl acetate (AcOEt) was exposed to sunshine, several new spots appeared on thin-layer chromatography (TLC), accompanied with loss of **7**. We carefully separated the major product by preparative TLC (PTLC) and determined it to be the amide compound (**8**) on the basis of its spectral and analytical data. The reaction was carried out under various conditions and the results are summarized in Table II. Use of a 500 W high-pressure Hg-arc lamp as a light source gave a complex mixture (runs 1 and 4) while use of sunshine or a 200 W incandescent lamp afforded the amide (**8**). When methanol or ethanol was used as the reaction solvent, the corresponding ester (**9**)[1] was obtained together with **8** (runs 5—10). Increase of the reaction time increased the yield of the ester (**9**) (runs 6 and 7). When *tert*-butyl alcohol or benzyl alcohol was used, the reaction almost did not proceed (runs 11—14).

Photo-oxidation of an allylic or benzylic position in the presence of mercuric bromide ($HgBr_2$) or *N*-bromosuccinimide (NBS) was reported.[8] Also, bromo-substituted or bromine-catalyzed diphenylmethanes were photochemically oxidized to substituted benzophenones by irradiation in contact with air.[9] In the latter report, generation of bromine atoms was presumed to be crucial. In the present photochemical oxidation, the 1,4-naphthoquinone moiety in **7** itself might work as a photo-sensitizer to promote the oxidation of the benzylic position by oxygen in air.

The structure of the present photochemical products (**8** and **9**)[10] can be considered as a modification of the

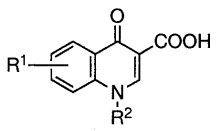

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Fig. 1

first-generation quinolone antibacterial agents such as **10**.[11,12]

Experimental

All melting points are uncorrected. Infrared (IR) spectra were taken with a Shimadzu IR-435 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured on a JEOL EX-270 (270 MHz) or a Varian XL-300 (300 MHz) with tetramethylsilane as an internal standard. Low-resolution mass spectrum (LRMS) was obtained on a Hitachi M-80 spectrometer. All solvents were removed under reduced pressure in the usual work-up procedure. Anhydrous sodium sulfate was used as a drying agent. Silica gel 60 PF_{254} (Nacalai Tesque Inc.) was used for PTLC.

General Procedure for Synthesis of 2-Amino-3-methyl-1,4-naphthoquinone (5). Synthesis of 2-Methyl-3-(1-pyrrolidinyl)-1,4-naphthoquinone (5a) as an Example Pyrrolidine (0.18 ml, 2.1 mmol) was added to a solution of **3** (172 mg, 1.0 mmol) in MeOH (20 ml) and the whole was stirred for 24 h at room temperature. After evaporation of the solvent, the residue was purified by PTLC (solvent, dichloromethane). **5a**: Red needles (recrystallized from AcOEt), mp 71.0—72.0 °C (lit. 71—72 °C).[4] Yield, 134 mg (53.2%). IR ($CHCl_3$): 1724, 1671 (C=O), 1592, 1521 (aromatic) cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$): 1.85—1.95 (m, 4H, $-CH_2CH_2-$), 2.15 (s, 3H, $-CH_3$), 3.70—3.85 (m, 4H, $-CH_2NCH_2-$), 7.54 (dt, 1H, J=1.3, 7.6 Hz, aromatic-H), 7.63 (dt, 1H, J=1.3, 7.6 Hz, aromatic-H), 7.88 (dd, 1H, J=1.3, 7.6 Hz, aromatic-H), 8.02 (dd, 1H, J=1.3, 7.6 Hz, aromatic-H). **6a**: Yield 25 mg (11.0%).[1]

Other compounds (**5b**,[4] **5c**,[2,4] **5d**—**g**,[2] **6b**,[5] and **6c**—**d**[2,6]) shown in Table I were obtained similarly from the corresponding amines. Spectral data and melting points were identical with those in the literature.

2-Methylamino-3-(1-piperidinylmethyl)-1,4-naphthoquinone (7) A so-

lution of **4b** (152 mg, 0.45 mmol) in methylamine (30% in MeOH, 1.0 ml, 9.0 mmol) was allowed to stand in the dark at room temperature for 24 h. After evaporation of the solvents, the residue was purified by PTLC and recrystallized from ether to give **7** as dark orange plates, mp 139.8—140.9 °C (lit. 140—141.5 °C).[3a] Yield, 127 mg (99.2%). IR ($CHCl_3$): 3348 (NH), 1668, 1601 (C=O), 1564, 1527 (aromatic) cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$): 1.33—1.68 (m, 6H, $-(CH_2)_3-$), 2.28—2.51 (m, 4H, $-CH_2NCH_2-$), 3.32 (s, 3H, $-CH_3$), 3.51 (s, 2H, $ArCH_2-$), 6.30—6.50 (br, 1H, –NH), 7.48—7.66 (m, 2H, aromatic-H), 7.85—8.05 (m, 2H, aromatic-H).

General Procedure for Photo-oxidation of 7 a) Sunshine as the light source and AcOEt as the solvent (run 2): A solution of **7** (86 mg, 0.3 mmol) in AcOEt (20 ml) was placed in a Pyrex reaction vessel and allowed to stand in the sunlight for 12 h. After evaporation of the solvent, the residue was purified by PTLC (solvent, AcOEt) and recrystallized from ether to give **8** as orange needles, mp 169.6—171.6 °C. Yield, 31 mg (34.6%). IR ($CHCl_3$): 3356 (NH), 1675, 1608 (C=O), 1570, 1522 (aromatic) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.40—1.85 (m, 6H, $-(CH_2)_3-$), 3.05 (d, 3H, J=5.8 Hz, $-CH_3$), 3.30—3.50 (m, 2H, $-CH_2N-$), 3.70—3.80 (m, 2H, $-CH_2N-$), 6.39 (br d, 1H, J=5.4 Hz, –NH), 7.62 (dt, 1H, J=1.4, 7.6 Hz, aromatic-H), 7.73 (dt, 1H, J=1.4, 7.6 Hz, aromatic-H), 8.03 (dd, 1H, J=1.3, 7.6 Hz, aromatic-H), 8.09 (dd, 1H, J=1.3, 7.6 Hz, aromatic-H). *Anal.* Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.01; H, 6.15; N, 9.29. LRMS m/z: 298 (M^+).

b) A 200 W incandescent lamp as the light source and EtOH as the solvent (run 10): A solution of **7** (86 mg, 0.3 mmol) in EtOH (20 ml) was placed in a Pyrex reaction vessel and irradiated with a 200 W incandescent lamp for 36 h. After evaporation of the solvent, the residue was purified by PTLC (solvent, AcOEt). **8**: Yield, 11 mg (12.3%). **9b**: Orange crystals (from hexane), mp 186.0—187.9 °C. Yield, 11 mg (14.1%). IR ($CHCl_3$): 3350 (NH), 1717, 1676, 1611 (C=O), 1574, 1524 (aromatic) cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.42 (t, 3H, J=7.1 Hz, $-CH_2C\underline{H}_3$), 3.00—3.20 (br, 3H, $-NCH_3$), 4.41 (q, 2H, J=7.1 Hz, $-C\underline{H}_2CH_3$), 6.30—6.50 (br, 1H, $-N\underline{H}CH_3$), 7.63 (dt, 1H, J=1.3, 7.6 Hz, aromatic-H), 7.76 (dt, 1H, J=1.3, 7.6 Hz, aromatic-H), 8.03 (d, 1H, J=7.6 Hz, aromatic-H), 8.13 (d, 1H, J=7.6 Hz, aromatic-H). *Anal.* Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.65; H, 4.89; N, 5.65.

Compound **9a** was obtained similarly, except for the use of MeOH instead of EtOH. Spectral data of **9a** were identical with those in ref. 1.

References and Notes

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