Organic Chemistry

Reaction of 2-chloro-3-(4-*N,N*-dimethylaminoanilino)-1,4-naphthoquinone with cyclic amines (piperidine, morpholine, and pyrrolidine)

T. V. Mikhalina, S. V. Rubashko, E. P. Fokin, I. Yu. Bagryanskaya, and Yu. V. Gatilov*

Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 9 prosp. Akad. Lavrent'eva, 630090 Novosibirsk, Russian Federation. Fax: +7 (383 2) 354 752

It was shown that the reaction of 2-chloro-3-(4-*N,N*-dimethylaminoanilino)-1,4-naphthoquinone with piperidine in the absence of a solvent gives not only a product of replacement of the chlorine atom by a piperidino group, 3-(4-*N,N*-dimethylaminoanilino)-2-piperidino-1,4-naphthoquinone, but also 2-(4-*N,N*-dimethylaminoanilino)-1,4-naphthoquinone and 2-(4-*N,N*-dimethylaminoanilino-2-piperidino)-1,4-naphthoquinone. The latter compounds are the only reaction products formed in dimethyl sulfoxide. The reaction with morpholine occurs in a similar way, whereas that with pyrrolidine gives only a product of replacement of the chlorine atom by hydrogen.

Key words: 2-chloro-3-(4-*N,N*-dimethylaminoanilino)-1,4-naphthoquinone, cyclic amines.

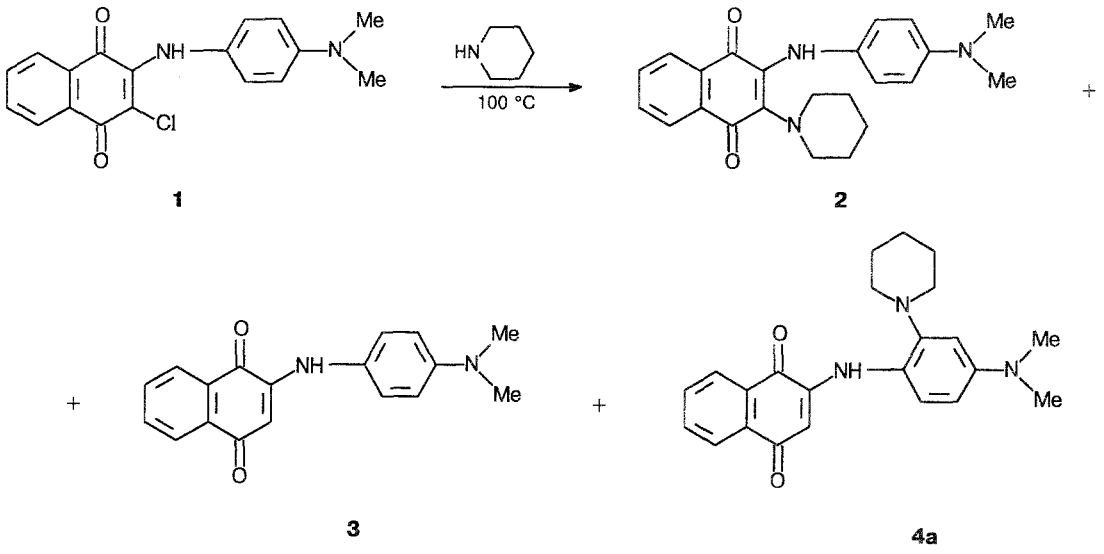
It has been shown previously that the replacement of the chlorine atom in 3-arylamino-2-chloro-1,4-naphthoquinones by a second amino group is hindered, particularly when electron-donating substituents are present in the aromatic amine.[1] In a continuation of studies on amino derivatives of 1,4-naphthoquinone,[2—4] we synthesized 2-chloro-3-(4-*N,N*-dimethylaminoanilino)-1,4-naphthoquinone (**1**) and studied its reactions with various secondary cycloalkylamines (piperidine, morpholine, and pyrrolidine).

Compound **1** does not react with piperidine on heating in alcohol. Refluxing with excess piperidine results in a mixture of products, and 3-(4-*N,N*-dimethylaminoanilino)-2-piperidino-1,4-naphthoquinone (**2**) was isolated therefrom in 40 % yield (Scheme 1). The yield of 2-(4-*N,N*-dimethylaminoanilino)-1,4-naphthoquinone (**3**), which has also been obtained previously from 1,4-naphthoquinone and *p*-nitroso-*N,N*-dimethylaniline,[5] was 4 %. According to mass spectroscopic data and elemental analysis, the third product **4a** (yield 16 %) has the same molecular formula as compound **2**, but their UV and ^{1}H NMR spectra differ considerably, *i.e.*, these compounds are isomers. It was unambiguously proved by X-ray diffraction study that compound **4a** is 2-(4-*N,N*-dimethylamino-2-piperidinoanilino)-1,4-naphthoquinone. Figure 1 presents the structure of compound **4a**. The 1,4-naphthoquinone moiety is planar to within ±0.034(5) Å, and its bond lengths (Table 1) coincide with those in 2-amino-1,4-naphthoquinone.[6] The C(2)—N(1)—C(11) bond angle is 133.8(4)°, which is close to 131.1° for the similar angle in di(2-pyridyl)amine.[7] However, the N(1)—C(2)—C(3) angle in naphthoquinone **4a** is markedly wider (129.3°) than the corresponding angles in di(2-pyridyl)amine, which are

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 12, pp. 2451—2454, December, 1995.

1066-5285/95/4412-2346 $12.50

Scheme 1



119.4 and 124.3°. The increase in the angle could originate not only from repulsion between the hydrogen atoms at the C(3) and C(16) atoms (the H...H distance is 1.98 Å), but also from the N(1)—H...O(1) intramolecular hydrogen bond with the following parameters: 0.90, 2.11, 2.592 Å, 112°. The naphthoquinone moiety and the phenyl ring are rotated 5.3(2) and 18.5(4)° around the N(1)—C(2) and N(1)—C(11) bonds, respectively. The orientation of the piperidyl moiety relative to the benzene ring is characterized by a C(21)—N(2)—C(12)—C(13) torsion angle of 34.4(5)°.

The unexpected formation of products **3** and **4a** prompted us to study the effect of solvents on this reaction. It is known that highly polar solvents, such as DMSO, increase the rate of nucleophilic substitution reactions.[8] When the reaction of compound **1** was carried out in DMSO, quinones **3** and **4a** formed as the main products, while the product of replacement of the chlorine atom for a piperidino group, *i.e.* compound **2**, was formed only as traces.

The mechanism for the formation of compounds **3** and **4a** requires additional studies. The reactions of quinone **1** with other cycloalkylamines, morpholine and pyrrolidine, in DMSO occurs in a similar manner. However, the ratio of products **3** and **4** depends on the structure of the cycloalkylamine (Table 2, Scheme 2). For example, quinone **3** is the only product of the reaction of compound **1** with pyrrolidine.

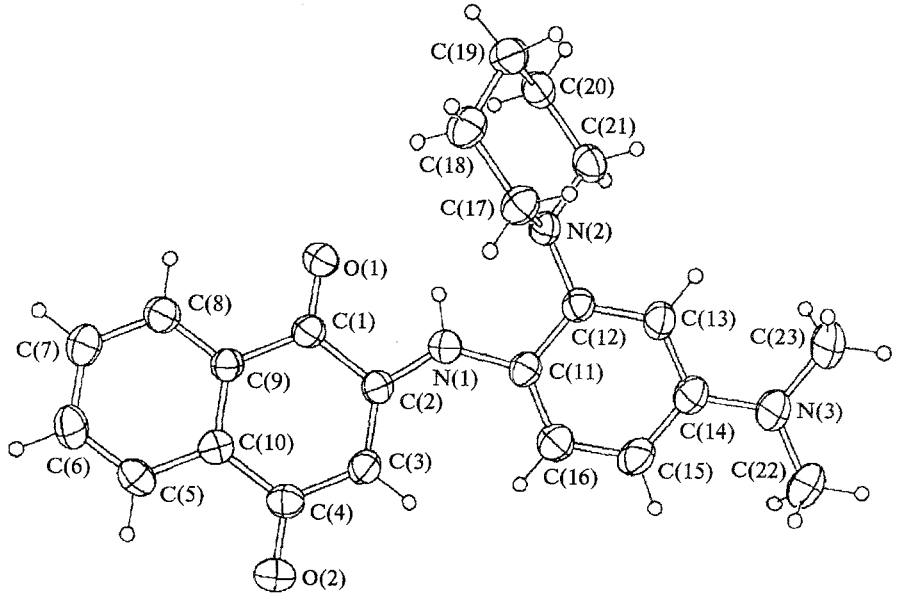


Fig. 1. Structural formula of 2-(4-*N*,*N*-dimethylamino-2-piperidinophenylamino)-1,4-naphthoquinone (**4a**).

Table 1. Bond lengths in the molecule of naphthoquinone **4a**

Bond	*d*/Å	Bond	*d*/Å
O(1)—C(1)	1.225(7)	O(2)—C(4)	1.246(7)
N(1)—C(11)	1.409(5)	C(2)—N(1)	1.348(6)
N(2)—C(12)	1.412(6)	N(2)—C(17)	1.465(5)
N(2)—C(21)	1.467(7)	N(3)—C(14)	1.381(6)
N(3)—C(22)	1.404(7)	N(3)—C(23)	1.426(9)
C(2)—C(1)	1.498(5)	C(9)—C(1)	1.476(7)
C(2)—C(3)	1.363(5)	C(3)—C(4)	1.433(7)
C(10)—C(4)	1.478(6)	C(5)—C(6)	1.368(6)
C(10)—C(5)	1.392(7)	C(7)—C(6)	1.379(9)
C(8)—C(7)	1.376(8)	C(9)—C(8)	1.372(6)
C(10)—C(9)	1.392(8)	C(12)—C(11)	1.413(7)
C(11)—C(16)	1.374(7)	C(13)—C(12)	1.377(5)
C(13)—C(14)	1.383(7)	C(14)—C(15)	1.408(8)
C(16)—C(15)	1.388(6)	C(17)—C(18)	1.499(6)
C(19)—C(18)	1.527(9)	C(19)—C(20)	1.501(6)
C(21)—C(20)	1.511(6)		

Experimental

IR spectra were recorded on a UR-20 spectrophotometer in chloroform. UV spectra were recorded on a Specord UV-VIS instrument in ethanol. ^{1}H NMR spectra were obtained on Bruker WP-200-SY and AC-200 spectrometers using $CDCl_3$ as the solvent. Molecular masses were determined by mass spectrometry on an MS-330 instrument. The X-ray diffraction study was performed on a SYNTEX $P2_1$ diffractometer. The crystals of naphthoquinone **4a** are triclinic: a = 9.725(6), b = 10.360(6), c = 11.535(7) Å, α = 72.93(4), β = 68.63(4), γ = 67.70(4)°, V = 985.0(9) Å^3, space group $P\bar{1}$, Z = 2, d_{calc} = 1.27 g cm^{-3}, μ = 6.2 cm^{-1}, Cu-Kα irradiation (graphite monochromator). The intensities of 2628 independent reflections with $2\theta < 114°$ were measured by $4\theta/3\omega$-scanning using a 0.02 × 0.28 × 1.3 mm^3 sample. The calculations used 1665 observed reflections ($I > 2\sigma$) corrected for absorption by the DIFABS program (the absorption coefficients were within the range 0.59—1.26). The structure was solved by the direct method using the SHELX86 program and refined by the SHELX76 program in anisotropic-isotropic approximation to R = 0.037, R_w = 0.045, s = 1.4, $w^{-1} = \sigma_F^2$. The positions of hydrogen atoms were calculated geometrically and were not refined. The obtained coordinates of nonhydrogen atoms are presented in Table 3.

2-Chloro-3-(4-*N,N*-dimethylaminoanilino)-1,4-naphthoquinone (1). 2,3-Dichloro-1,4-naphthoquinone (10 g) and *N,N*-dimethyl-*p*-phenylenediamine (14 g) in ethanol (150 mL) were stirred for 5 h at ~20 °C. The reaction mixture was poured into water. The precipitate that formed was filtered off, washed with water, and dried in air to give 13.7 g (98 %) of quinone **1**, m.p. 180—183 °C (from ethanol). Found (%): C, 65.83; H, 4.62; N, 8.25; Cl, 11.06. $C_{18}H_{15}ClN_2O_2$. Calculated (%): C, 66.26; H, 4.60; N, 8.59; Cl, 10.89. IR, ν/cm^{-1}: 3325 (N—H); 1645 (C=O). UV, λ_{max}/nm (log ε): 279 (4.44), 560 (3.55). ^{1}H NMR, δ: 2.85 (s, 6 H, Me); 6.51 and 6.86 (dd, 4 H, H arom., J = 8 Hz); 7.70 and 7.61 (td, 2 β-H, J_1 = 7.5 Hz, J_2 = 1.5 Hz); 7.66 (br.s, NH); 8.03 (dd, 2 α-H, J_1 = 7.5 Hz, J_2 = 1.5 Hz). MS, m/z (I_{rel} (%)): 326 (38), 292 (100), 278 (27).

Reaction of quinone 1 with piperidine. *A.* Compound **1** (2 g) was refluxed in piperidine (50 mL) for 8 h. The reaction mixture was poured into ice water and neutralized with 10 % HCl. The resulting precipitate was filtered off to give a mixture of products, which was chromatographed on silica gel using benzene as the eluent to give 0.68 g (40 %) of 3-(4-*N,N*-dimethylaminoanilino)-2-piperidino-1,4-naphthoquinone (**2**), 0.37 g (16 %) of 2-(4-*N,N*-dimethylamino-2-piperidinoanilino)-1,4-naphthoquinone (**4a**), and 0.07 g (4 %) 2-(4-*N,N*-dimethylaminoanilino)-1,4-naphthoquinone (**3**).[5] Compound **2**: m.p. 138—140 °C (from hexane). Found (%): C, 73.24; H, 6.71; N, 11.22. $C_{23}H_{25}N_3O$. Calculated (%): C, 73.57; H, 6.71; N, 11.18. IR, ν/cm^{-1}: 3350 (N—H); 1670, 1655 (C=O). UV, λ_{max}/nm (log ε): 246 (4.38), 287 (4.37), 502 (3.63), 616 (3.55). ^{1}H NMR, δ: 1.32 (m, 6 H, CH_2); 2.91 (s, 6 H, Me); 3.01 (m, 4 H, NCH_2); 6.68, 6.78 (AB-system, 4 H arom., J = 9 Hz); 7.19 (br.s, NH); 7.53, 7.61 (td, 2 β-H,

Scheme 2

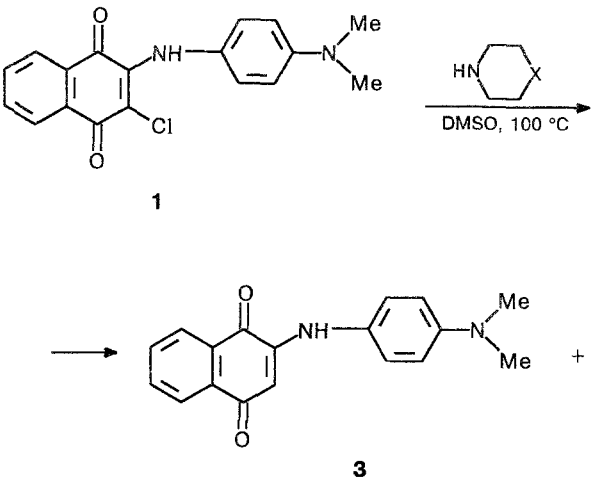


Table 2. Yields (%) of the products of reactions between quinone **1** and amines in DMSO

Amine	**3**	**4a—c**
Piperidine	10	65
Morpholine	34	54
Pyrrolidine	75	0

Table 3. Coordinates ($\times 10^4$) and thermal factors of nonhydrogen atoms in naphthoquinone **4a**

Atom	x/a	y/b	z/c	$U_{eq} \cdot 10^3/Å^2$
O(1)	1424(3)	7695(3)	5499(3)	75(2)
O(2)	1128(4)	4531(3)	2731(3)	87(2)
N(1)	3051(4)	5041(4)	5789(3)	60(2)
N(2)	3569(4)	4996(3)	7895(3)	53(2)
N(3)	6697(5)	4(4)	8084(4)	100(3)
C(1)	1362(5)	6996(4)	4837(4)	57(2)
C(2)	2246(4)	5448(4)	4939(4)	52(2)
C(3)	2130(5)	4656(4)	4240(4)	59(2)
C(4)	1201(5)	5262(5)	3380(4)	60(2)
C(5)	−658(5)	7406(5)	2479(4)	65(3)
C(6)	−1530(6)	8804(5)	2409(4)	77(3)
C(7)	−1470(6)	9617(5)	3136(5)	82(3)
C(8)	−514(6)	9027(5)	3912(4)	71(3)
C(9)	366(5)	7627(4)	3981(4)	54(2)
C(10)	309(4)	6786(4)	3264(4)	53(2)
C(11)	3957(5)	3722(4)	6301(4)	56(2)
C(12)	4235(5)	3715(4)	7423(4)	54(2)
C(13)	5147(5)	2484(5)	7976(4)	66(2)
C(14)	5810(5)	1236(5)	7500(5)	71(3)
C(15)	5540(5)	1275(5)	6370(5)	73(3)
C(16)	4638(5)	2507(5)	5789(4)	70(3)
C(17)	1968(4)	5218(4)	8709(4)	65(3)
C(18)	1235(5)	6720(4)	8923(4)	70(2)
C(19)	2179(5)	7161(5)	9460(4)	71(3)
C(20)	3833(5)	6828(4)	8651(4)	66(3)
C(21)	4487(5)	5293(4)	8494(4)	65(2)
C(22)	7356(5)	−1275(4)	7622(5)	98(3)
C(23)	7187(6)	52(5)	9090(5)	104(3)

J_1 = 8 Hz, J_2 = 1.5 Hz); 7.94, 7.99 (dd, 2 α-H, J_1 = 8.0 Hz, J_2 = 1.5 Hz). Compound **4a**: m.p. 149—150 °C (from ethanol). Found (%): C, 73.56; H, 6.78; N, 11.14. $C_{23}H_{25}N_5O$. Calculated (%): C, 73.57; H, 6.71; N, 11.18. IR, ν/cm^{-1}: 3355 (N—H); 1675 (C=O). UV, λ_{max}/nm (log ε): 244 (4.42), 290 (4.46), 604 (3.81). ^{1}H NMR, δ: 1.57 (m, 2 H, CH_2); 1.72 (m, 4 H, CH_2); 2.78 (m, 4 H, NCH_2); 2.91 (s, 6 H, Me); 6.46 (m, 3 H, H-3, H-3, H-5); 7.30 (d, 1 H, H-6, J = 7.5 Hz); 7.57 and 7.68 (td, 2 β-H, J_1 = 7.5 Hz, J_2 = 1.5 Hz); 8.04 and 8.08 (dd, 2 α-H, J_1 = 7.5 Hz, J_2 = 1.5 Hz); 8.40 (br.s, 1 H, NH). MS, m/z (I_{rel} (%)): 375 (100), 319 (20), 292 (90), 202 (20).

B. Compound **1** (0.7 g), piperidine (0.5 mL), and DMSO (100 mL) were stirred for 3 h at 100 °C. The reaction mixture was poured into ice water, and the precipitate that formed was filtered off and washed with water to neutral pH. The resulting mixture was chromatographed on silica gel (0.140—0.315 μm) using benzene as the eluent, giving 0.52 g (65 %) of compound **4a** and 0.06 g (10 %) of compound **3**.

Reaction of quinone 1 with morpholine. Compound **1** (0.7 g), morpholine (0.5 mL), and DMSO (10 mL) were stirred for 5 h at 100 °C. The reaction mixture was poured into ice water, and the precipitate that formed was filtered off and washed with water to neutral pH. The resulting mixture was chromatographed on silica gel using benzene—acetone (10 : 1) as the eluent to give 0.21 g (34 %) of compound **3** and 0.44 g (55 %) of 2-(4-*N*,*N*-dimethylamino-2-morpholinoanilino)-1,4-naphthoquinone (**4b**), m.p. 174—176 °C (from a benzene—hexane mixture). Found (%): C, 70.42; H, 6.31; N, 11.11. $C_{22}H_{23}N_3O_3$. Calculated (%): C, 70.00; H, 6.14; N, 11.13. IR, ν/cm^{-1}: 3335 (N—H); 1670 (C=O). UV, λ_{max}/nm (log ε): 236 (4.34), 287 (4.45), 598 (3.83). ^{1}H NMR, δ: 2.89 (t, 4 H, NCH_2), J = 4.5 Hz); 2.96 (s, 6 H, Me); 3.85 (t, 4 H, OCH_2, J = 4.5 Hz); 6.46 (m, 3 H, H-3, H-3′, H-6′); 7.32 (dd, H-5, J_1 = 7.0 Hz, J_2 = 1.5 Hz); 7.63 and 7.75 (td, 2 H, β-H, J_1 = 7.5 Hz, J_2 = 1 Hz); 8.08 and 8.12 (dd, 2 H, α-H, J_1 = 2 Hz, J_2 = 1 Hz); 8.31 (br.s, NH).

Reaction of quinone 1 with pyrrolidine. A similar reaction of compound **1** (1 g) with pyrrolidine (0.5 mL) in DMSO (10 mL) (heating at 100 °C for 3 h) followed by chromatography on silica gel (benzene as the eluent) gave 0.7 g (75 %) of compound **3**.

References

1. R. P. Shishkina, L. V. Ektova, K. I. Matoshina, and E. P. Fokin, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 1982, No. 5, 136 (in Russian).
2. T. V. Mikhalina, S. V. Rubashko, V. N. Krasheninina, and E. P. Fokin, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 1990, No. 6, 115 (in Russian).
3. S. V. Rubashko, T. V. Mikhalina, and E. P. Fokin, *Sib. Khim. Zh.*, 1992, **3**, 67 (in Russian).
4. S. V. Rubashko, T. V. Mikhalina, and E. P. Fokin, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 1990, No. 3, 46 (in Russian).
5. A. R. Forrester and R. H. Thomson, *Z. Naturforsch.*, 1985, **40**, 1515.
6. A. I. Kitaigorodskii, P. M. Zorkii, and V. K. Belskii, in *Stroenie organicheskogo veshchestva* [*Structure of Organic Compounds*], Nauka, Moscow, 1980, 194 (in Russian).
7. A. I. Kitaigorodskii, P. M. Zorkii, and V. K. Belskii, in *Stroenie organicheskogo veshchestva* [*Structure of Organic Compounds*], Nauka, Moscow, 1980, 375 (in Russian).
8. M. Dieter and G. H. Herman, *Dimethylsulfoxid*, Berlin, 1971, 174 pp.

Received February 13, 1995