Reactions of 4-morpholino-1,2-naphthoquinone with enamines and *o*-phenylenediamine

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The reactions of 4-morpholino-1,2-naphthoquinone with enamines, cyclohexanone derivatives, afford 7a-amino-5-morpholinohexahydrobenzo[*b*]naphtho[1,2][1,4]dioxines, while the reaction with *o*-phenylenediamine yields 5-morpholinobenzo[*a*]phenazine.

Key words: 4-morpholino-1,2-naphthoquinone, enamines, *o*-phenylenediamine, cycloaddition, 7a-amino-5-morpholinohexahydrobenzo[*b*]naphtho[1,2][1,4]dioxines, 7a-hydroxy-5-morpholinohexahydrobenzo[*b*]naphtho[1,2][1,4]dioxine, 5-morpholinobenzo[*a*]phenazine.

The reactions of 1,4-benzoquinones with enamines yielding 5-hydroxyindole or 5-hydroxybenzofuran derivatives (the Nenitzescu reaction) have been studied previously.[1–3] Analogous conversions of 1,2-benzoquinones are unknown. It was demonstrated[4] that, as in the case of the Nenitzescu reaction, the first stage of the reaction of 4-methyl-1,2-benzoquinone with anilinocrotonic ester involves the Michael addition. However, the subsequent stages of the last-mentioned reaction proceed differently, without the participation of the carbonyl group of quinone. [1+4]-Cycloaddition of *o*-quinones to olefins is one of the methods for the synthesis of benzo-1,4-dioxanes.[5] One would expect that these reactions involving enamines derived from cyclohexanone will afford hexahydrodibenzodioxine derivatives, which are potential biologically active compounds.[6]

Recently,[7] we have reported the synthesis of 4-morpholino-1,2-naphthoquinone (**1**). An alternative procedure for the preparation of **1** has been described previously.[8] When studying reactions of quinone **1**, we found that heating of this compound with an excess of enamines **2a—c** over a short period afforded 7a-amino-5-morpholino-7a,8,9,10,11,11a-hexahydrobenzo[*b*]naphtho[1,2][1,4]dioxines (**3a—c**) (Scheme 1).

The formation of compound **3a** proceeded smoothly without noticeable resinification. Compound **3a** is readily crystallized from methanol and acetonitrile.

Dioxines **3b** and **3c** are apparently thermally and hydrolytically less stable. The reaction of compound **1** with **2b** at 170 °C was accompanied by the formation of resinification products, and 7a-hydroxy-5-morpholino-7a,8,9,10,11,11a-hexahydrobenzo[*b*]naphtho[1,2][1,4]-dioxine (**4**) was isolated along with compound **3b**. Compound **4** can be considered as the hydrolysis product of **3b**. A decrease in the reaction temperature and the addition of the corresponding free amines to the reaction mixtures made it possible to obtain compounds **3b** and **3c** in moderate yields. Compounds **3b** and **3c** are readily soluble in most organic solvents, which prevents their purification by recrystallization.

Compounds **3** contain two asymmetrical carbon atoms, due to which these compounds can exist as two diastereomers. The ^{1}H NMR spectrum of dioxine **3a** is indicative of the diastereoselectivity of its formation. The splitting of the signals for the protons of the C(6)H and Me groups in the ^{1}H NMR spectra of compounds **3b** and **3c** is, apparently, associated with the presence of small amounts of configurational isomers.

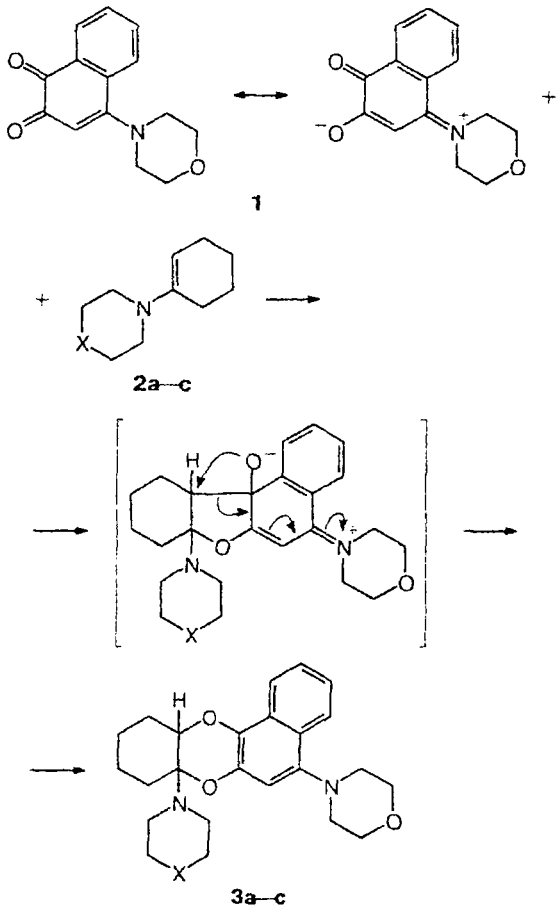
The structure of compound **3a** was established by X-ray diffraction analysis (Fig. 1, Tables 1 and 2).

The dihydrodioxine ring in molecule **3a** adopts a half-chair conformation. The C(11) and C(16) atoms deviate from the plane passing through the remaining atoms of the ring by 0.2312(7) and −0.5091(8) Å,

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 4, pp. 729—732, April, 2000.

1066-5285/00/4904-0732 $25.00

Scheme 1



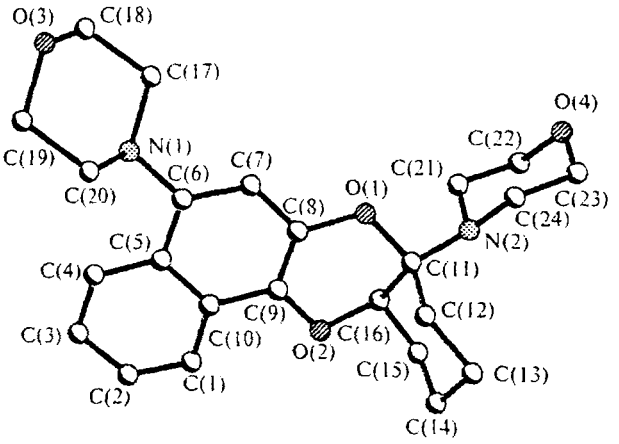


Fig. 1. Structure of molecule **3a**.

respectively. The saturated six-membered C(11)...C(16) ring adopts a chair conformation with the C(11) and C(14) atoms deviating from the plane through the remaining atoms of the ring by 0.7076(7) and −0.6439(7) Å, respectively. The fusion of these rings results in the following shortened intramolecular contacts: C(8)...H(12a), 2.80 Å (the sum of the van der Waals radii[9] is 2.87 Å); C(9)...C(12), 3.26 Å (3.42 Å); and C(9)...H(12a), 2.75 Å.

Table 1. Bond lengths (*d*) in the structure of **3a**

Bond	*d*/Å	Bond	*d*/Å
N(1)—C(6)	1.444(5)	C(4)—C(5)	1.409(6)
N(1)—C(17)	1.458(6)	C(5)—C(6)	1.418(6)
N(1)—C(20)	1.466(6)	C(5)—C(10)	1.421(6)
N(2)—C(11)	1.437(6)	C(6)—C(7)	1.361(6)
N(2)—C(21)	1.462(6)	C(7)—C(8)	1.418(6)
N(2)—C(24)	1.467(6)	C(8)—C(9)	1.371(6)
O(1)—C(8)	1.364(5)	C(9)—C(10)	1.431(6)
O(1)—C(11)	1.489(5)	C(11)—C(12)	1.518(7)
O(2)—C(9)	1.374(5)	C(11)—C(16)	1.539(6)
O(2)—C(16)	1.443(5)	C(12)—C(13)	1.534(7)
O(3)—C(19)	1.411(5)	C(13)—C(14)	1.529(7)
O(3)—C(18)	1.419(6)	C(14)—C(15)	1.514(7)
O(4)—C(22)	1.404(6)	C(15)—C(16)	1.533(6)
O(4)—C(23)	1.410(6)	C(17)—C(18)	1.523(6)
C(1)—C(2)	1.363(6)	C(19)—C(20)	1.506(6)
C(1)—C(10)	1.401(6)	C(21)—C(22)	1.514(7)
C(2)—C(3)	1.416(7)	C(23)—C(24)	1.519(6)
C(3)—C(4)	1.371(6)		

Table 2. Bond angles (ω) in the structure of **3a**

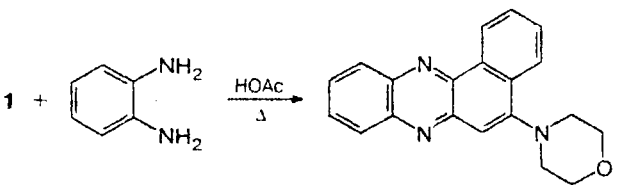
Angle	ω/deg	Angle	ω/deg
C(6)—N(1)—C(17)	116.0(4)	O(2)—C(9)—C(10)	117.2(4)
C(6)—N(1)—C(20)	112.6(3)	C(1)—C(10)—C(5)	120.9(4)
C(17)—N(1)—C(20)	109.5(4)	C(1)—C(10)—C(9)	120.0(4)
C(11)—N(2)—C(21)	116.6(4)	C(5)—C(10)—C(9)	119.1(4)
C(11)—N(2)—C(24)	115.4(4)	N(2)—C(11)—O(1)	107.3(4)
C(21)—N(2)—C(24)	108.1(4)	N(2)—C(11)—C(12)	113.2(4)
C(8)—O(1)—C(11)	116.5(3)	O(1)—C(11)—C(12)	108.7(4)
C(9)—O(2)—C(16)	113.0(3)	N(2)—C(11)—C(16)	111.2(4)
C(19)—O(3)—C(18)	109.6(4)	O(1)—C(11)—C(16)	107.6(3)
C(22)—O(4)—C(23)	110.1(4)	C(12)—C(11)—C(16)	108.6(4)
C(2)—C(1)—C(10)	119.9(4)	C(11)—C(12)—C(13)	111.7(4)
C(1)—C(2)—C(3)	121.0(5)	C(14)—C(13)—C(12)	109.9(4)
C(4)—C(3)—C(2)	118.8(4)	C(15)—C(14)—C(13)	112.6(4)
C(3)—C(4)—C(5)	122.5(4)	C(14)—C(15)—C(16)	110.6(4)
C(4)—C(5)—C(6)	123.7(4)	O(2)—C(16)—C(15)	105.2(4)
C(4)—C(5)—C(10)	116.8(4)	O(2)—C(16)—C(11)	109.9(4)
C(6)—C(5)—C(10)	119.4(4)	C(15)—C(16)—C(11)	111.4(4)
C(7)—C(6)—C(5)	119.9(4)	N(1)—C(17)—C(18)	108.8(4)
C(7)—C(6)—N(1)	122.6(4)	O(3)—C(18)—C(17)	111.0(4)
C(5)—C(6)—N(1)	117.6(4)	O(3)—C(19)—C(20)	112.0(4)
C(6)—C(7)—C(8)	121.7(4)	N(1)—C(20)—C(19)	109.5(4)
O(1)—C(8)—C(9)	122.3(4)	N(2)—C(21)—C(22)	111.2(4)
O(1)—C(8)—C(7)	118.0(4)	O(4)—C(22)—C(21)	112.0(4)
C(9)—C(8)—C(7)	119.7(4)	O(4)—C(23)—C(24)	111.7(4)
C(8)—C(9)—O(2)	122.5(4)	N(2)—C(24)—C(23)	109.7(4)
C(8)—C(9)—C(10)	120.2(4)		

The morpholine ring at the C(11) atom adopts a chair conformation with the N(2) and O(4) atoms deviating from the plane through the remaining atoms of the ring by 0.6710(7) and −0.6328(8) Å, respectively. The C(8)—O(1)—C(11)—N(2) and N(2)—C(11)—C(16)—C(15) torsion angles are 157.6(4)° and 67.1(5)°, respectively. The presence of this substituent is responsible for the existence of the following shortened intramolecular contacts: C(16)...H(21b), 2.57 Å; H(16)...C(21), 2.62 Å; H(16)...H(21b), 1.98 Å (2.32 Å); C(12)...H(24a), 2.51 Å; H(12b)...C(24), 2.56 Å; and H(12b)...H(24a), 1.95 Å.

The morpholine ring at the C(6) atom also has a chair conformation with the N(1) and O(3) atoms deviating from the plane through the remaining atoms of the ring by −0.6730(8) and 0.6520(8) Å, respectively. Apparently, this conformation of the ring leads to the appearance of the following shortened intramolecular contacts: N(1)...H(4), 2.54 Å (2.66 Å); C(4)...C(20), 3.24 Å (3.42 Å); C(4)...H(20b), 2.67 Å; H(4)...C(20), 2.80 Å; C(5)...H(20b), 2.79 Å; C(7)...H(17a), 2.83 Å; C(7)...H(17b), 2.75 Å; H(7)...C(17), 2.54 Å; and H(7)...H(17b), 2.19 Å.

Quinone **1** undergoes condensation with *o*-phenylidenediamine on heating in acetic acid to form 5-morpholinobenzo[*a*]phenazine **5** (Scheme 2).

Scheme 2



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Experimental

The IR spectra were recorded on a Specord IR-75 instrument in Nujol mulls. The ^{1}H NMR spectra were measured on Varian UNITY-300 (**3a—c** and **4**) and Bruker AM-300 (**5**) instruments.

Enamines were synthesized according to a procedure reported previously.[10]

5,7a-Dimorpholino-7a,8,9,10,11,11a-hexahydrobenzo[*b*]naphtho[1,2][1,4]dioxine (3a). A mixture of quinone **1** (1 g, 4 mmol) and 1-morpholinocyclohexene **2a** (2 mL, 10 mmol) was heated to 120 °C, and the color of the solution changed from dark-red to pale-red. Then acetonitrile (5 mL) was added. The reaction mixture was refluxed for 5 min and triturated with cooling. The colorless crystalline precipitate that gradually formed was filtered off, washed several times with cold acetonitrile, and dried. Compound **3a** was obtained in a yield of 0.98 g (60%), m.p. 153—154 °C (from MeCN). Found (%): C, 70.34; H, 7.18; N, 7.02. $C_{24}H_{30}N_2O_4$. Calculated (%): C, 70.22; H, 7.37; N, 6.82. IR, ν/cm^{-1}: 1634, 1607 (Ar); 1114 (C—O—C). ^{1}H NMR ($CDCl_3$), δ: 1.5—2.0 (m, 8 H, CH_2); 2.8—3.0 (m, 8 H, CH_2N); 3.67 (m, 4 H, CH_2O); 3.94 (t, 4 H, CH_2O, J = 4.5 Hz); 4.34 (m, 1 H, C(11a)H); 6.73 (s, 1 H, C(6)H); 7.37 and 8.10 (both m, 2 H each, H arom.).

5-Morpholino-7a-piperidino-7a,8,9,10,11,11a-hexahydrobenzo[*b*]naphtho[1,2][1,4]dioxine (3b). A mixture of quinone **1** (0.24 g, 1 mmol), 1-piperidinocyclohexene **2b** (0.6 mL, 3.5 mmol), and piperidine (0.1 mL, 1 mmol) was heated at 140 °C for 2 min, cooled, and dissolved in EtOH (10 mL). An oil, which was precipitated with water, rapidly solidified upon trituration. The precipitate was filtered off and dissolved in MeOH (10 mL). The mixture was decolorized with activated carbon and filtered. Water was added to the filtrate and the colorless crystalline precipitate that formed was filtered off, washed several times with 50% MeOH, and dried. Compound **3b** was obtained in a yield of 0.2 g (49%), m.p. 102—104 °C (from MeOH). Found (%): C, 73.49; H, 7.85; N, 7.11. $C_{25}H_{32}N_2O_3$. Calculated (%): C, 73.50; H, 7.90; N, 6.86. IR, ν/cm^{-1}: 1637, 1607 (Ar); 1127 (C—O—C). ^{1}H NMR ($CDCl_3$), δ: 1.5—2.0 (m, 14 H, CH_2); 2.7—3.0 (m, 8 H, CH_2N); 3.93 (t, 4 H, CH_2O, J = 4.5 Hz); 4.40 (m, 1 H, C(11a)H); 6.73 and 6.77 (both s, 1 H, C(6)H); 7.36 and 8.08 (both m, 2 H each, H arom.).

7a-(*N*-Methylpiperazino)-5-morpholino-7a,8,9,10,11,11a-hexahydrobenzo[*b*]naphtho[1,2][1,4]dioxine (3c). A mixture of quinone **1** (0.48 g, 2 mmol), 1-(*N*'-methylpiperazino)cyclohexene **2c** (1.2 mL, 7 mmol), and *N*-methylpiperazine (0.2 mL, 2 mmol) was heated at 140 °C for 2 min and cooled. Then EtOH (20 mL) was added. A sticky substance was precipitated with water, separated, and dissolved in MeOH (20 mL). The mixture was refluxed with activated carbon and filtered. A pale crystalline substance was precipitated from the filtrate with water. The precipitate was filtered off, washed several times with a 1 : 2 EtOH—H_2O mixture, and dried. Compound **2c** was obtained in a yield of 0.4 g (47.6 %), m.p. 104—114 °C. Found (%): C, 70.23; H, 7.68; N, 9.42. $C_{25}H_{33}N_3O_3$. Calculated (%): C, 70.89; H, 7.85; N, 9.92. IR, ν/cm^{-1}: 1621, 1594 (Ar); 1114 (C—O—C). ^{1}H NMR ($CDCl_3$), δ: 1.4—2.0 (m, 8 H, CH_2); 2.57 and 2.60 (both s, 3 H, Me); 2.41 (m, 4 H, CH_2N); 3.83—3.03 (m, 8 H, CH_2N); 3.93 (t, 4 H, CH_2O, J = 4.5 Hz); 4.37 (m, 1 H, C(11a)H); 6.71 and 6.76 (both s, 1 H, C(6)H); 7.36 and 8.08 (both m, 2 H each, H arom.).

7a-Hydroxy-5-morpholino-7a,8,9,10,11,11a-hexahydrobenzo[*b*]naphtho[1,2][1,4]dioxine (4). A mixture of quinone **1** (1 g, 4 mmol) and enamine **2b** (2 mL, 10 mmol) was heated to 170 °C, cooled, and dissolved in acetonitrile (10 mL) upon heating. A sticky oil was precipitated with water. The oil was separated, dissolved in $CHCl_3$, and passed through a column with Al_2O_3. The solvent was evaporated, the residue was dissolved in EtOH, and a pale crystalline substance was precipitated with water. The precipitate was filtered off, washed with water, and dried. Then the precipitate was extracted several times with boiling light petroleum, the undissolved portion was recrystallized from acetonitrile, and colorless crystalline compound **4** was obtained in a yield of 0.06 g, m.p. 235—237 °C. Found (%): C, 69.87; H, 7.22; N, 4.23. $C_{20}H_{23}NO_4$. Calculated (%): C, 70.36; H, 6.79; N, 4.10. IR, ν/cm^{-1}: 3380 (OH); 1621, 1600 (Ar); 1107, 1087 (C—O). ^{1}H NMR ($CDCl_3$), δ: 1.4—2.3 (m, 8 H, CH_2); 3.02 (m, 4 H, CH_2N); 3.28 (s, 1 H, OH); 3.86 (dd, 1 H, C(11a)H, J = 4.8 and 11.6 Hz); 3.94 (t, 4 H, CH_2O, J = 4.5 Hz); 6.76 (s, 1 H, C(6)H); 7.41 and 8.10 (both m, 2 H each, H arom.).

5-Morpholinobenzo[*a*]phenazine (5). A solution of quinone **1** (0.72 g, 3 mmol) and *o*-phenylenediamine (0.36 g, 3.3 mmol) in acetic acid (9 mL) was refluxed for 1 h and cooled. The yellow crystalline precipitate that formed was filtered off, washed several times with cold MeOH, and dried. Benzophenazine **5** was obtained in a yield of 0.77 g (84%), m.p. 178—180 °C (from EtOH). Found (%): C, 76.20; H, 5.30; N, 13.39. $C_{20}H_{17}N_3O$. Calculated (%): C, 76.17; H, 5.43; N, 13.32. IR, ν/cm^{-1}: 1627, 1594, 1541 (Ar); 1114 (C—O—C). ^{1}H NMR

(DMSO-d_6), δ: 3.29 (m, 4 H, CH_2N); 4.03 (t, 4 H, CH_2O, J = 4.5 Hz); 7.44 (s, 1 H, C(6)H); 7.80 (m, 4 H, H arom.); 8.20 (m, 2 H, H arom.); 8.30 and 9.42 (both m, 1 H each, H arom.).

X-ray diffraction study of compound 3a. Crystals of $C_{24}H_{30}O_4N_2$ are monoclinic, at 203(2) K a = 13.424(4) Å, b = 9.928(4) Å, c = 17.258(5) Å, β = 107.88(2)°, V = 2189(1) Å^3, crystal dimensions 0.5×0.4×0.3 mm, space group $P2_1/c$, Z = 4, d_{calc} = 1.246 g cm^{-3}, $F(000)$ = 880, μ = 0.085 mm^{-1}.

The intensities of 4038 reflections (3864 independent reflections, R_{int} = 0.092) were measured on an automated four-circle Syntex $P2_1/PC$ diffractometer (graphite monochromator, Mo-Kα radiation, θ/2θ scanning technique, $2\theta_{max}$ = 50°).

The structure was solved by the direct method with the use of the SHELXTL PLUS program package.[11] The positions of the hydrogen atoms were located from the difference electron density synthesis and refined using the riding model with fixed U_{iso} = 1.2U_{eq} of the corresponding nonhydrogen atoms to which the hydrogen atoms are attached. The structure was refined based on F^2 with anisotropic thermal parameters for nonhydrogen atoms (271 parameters) by the full-matrix least-squares method using 3804 reflections to R_1 = 0.078 (for 1455 reflections with $F > 4\sigma(F)$), wR_2 = 0.221, S = 0.92. The bond lengths and bond angles in the structure of **3a** are given in Tables 1 and 2, respectively. The atomic coordinates were deposited with the Cambridge Structural Database.

References

1. G. Domschke, *J. Prakt. Chem.*, 1966, **32**, 140; 144.
2. U. Kucklander and H. Toberich, *Chem. Ber.*, 1981, **114**, 2238.
3. T. I. Mukhanova, L. M. Alekseeva, E. F. Kuleshova, Yu. N. Sheinker, and V. G. Granik, *Khim.-Farm. Zh.*, 1993, **27**, No. 3, 60 [*Russ. Pharm. Chem. J.*, 1993, **27** (Engl. Transl.)].
4. M. G. Peter and F. Speckenbach, *Helv. Chim. Acta*, 1982, **65**, 1279.
5. V. I. Ivanskii, *Khimiya geterotsiklicheskikh soedinenii (Chemistry of Heterocyclic Compounds)*, Vysshaya shkola, Moscow, 1978, 367 pp. (in Russian).
6. A. D. Kuntsevich, V. F. Golovkov, and V. R. Rembovskii, *Usp. Khim.*, 1996, 65, 29 [*Russ. Chem. Rev.*, 1996, **65** (Engl. Transl.)].
7. L. Yu. Ukhin, Z. S. Morkovnik, O. S. Philipenko, S. M. Aldoshin, and O. V. Shishkin, *Mendeleev Commun.*, 1997, 153.
8. W. Brackman and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, 1955, **74**, 937.
9. Yu. V. Zefirov and P. M. Zorkii, *Usp. Khim.*, 1989, **58**, 713 [*Russ. Chem. Rev.*, 1989, **58** (Engl. Transl.)].
10. *Organicum*, VEB Deutscher Verlag der Wissenschaften, Berlin, 1976.
11. G. M. Sheldrick, *SHELXTL PLUS Version, A System of Computer Programs for the Determination of Crystal Structure from X-ray Diffraction Data*, Rev. 5. 02, Siemens Analytical X-ray Instruments Inc., Germany, 1994.

Received June 28, 1999;
in revised form December 21, 1999