The interaction of 2-(4-acetylphenylamino)-3-piperidino-1,4-naphthoquinone with hydroxylamine and hydrazines

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With acid catalysts 2-(4'-acetylphenylamino)-3-piperidino-1,4-naphthoquinone reacts with hydroxylamine and aryl hydrazines exclusively at the carbonyl group of its side chain. The products corresponding to the condensation at the naphthoquinone C=O group could not be detected.

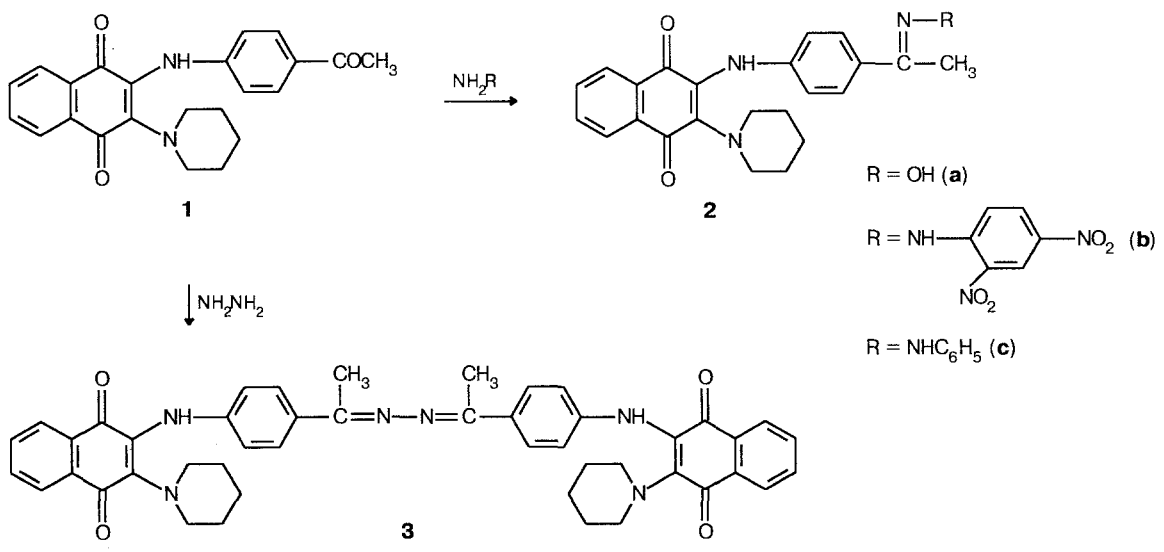
Key words: 2-(4'-acetylphenylamino)-3-piperidino-1,4-naphthoquinone; hydroxylamine, hydrazines; regioselectivity of reaction.

It is known that 1,4-naphthoquinone, as well as chloro- and hydroxysubstituted 1,4-napthoquinones react, like acetophenone, with hydroxylamine and phenylhydrazines in the presence of acid catalysts to give products of condensation of the C=O group: oximes and hydrazones.[1—3] Previously we synthesized 2-(4-acetylphenylamido)-3-piperidino-1,4-naphthoquinone (1) (see Ref. 4). The purpose of this work is to investigate the behavior of compound **1** in the reaction with hydroxylamine and substituted hydrazines. In the presence of an acid catalyst, compound **1** was found to react with the above reactants to form oxime (**2a**) and hydrazones (**2b,c**) (Scheme 1).

The conditions of the reaction and the yields of oxime **2a** and hydrazones **2b,c** depend on the starting reactants. Thus, compound **1** undergoes condensation with hydroxylamine, 2,4-dinitrophenylhydrazine and hydrazine when heated in alcohol in the presence of hydrochloric acid.[5] The reaction with hydrazine cannot be stopped at the stage of hydrazone production and proceeds on to give the respective azine (**3**). Under similar conditions phenylhydrazine did not react with compound **1**; the reaction was successfully carried out only in acetic acid at room temperature.

The formation of condensation products at the carbonyl group of the quinone system was not detected.

Scheme 1



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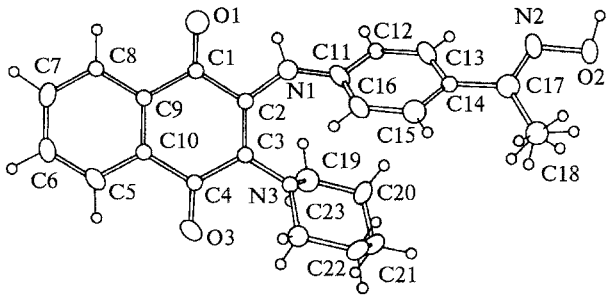

Fig. 1. Structure of the *N*-(3-piperidino-1,4-dihydro-1,4-dioxo-2-naphthyl)-4-aminoacetophenone oxime (**2a**) molecule.

This is also confirmed by the fact that 2-(4-ethoxycarbonylphenylamino)-3-piperidino-1,4-naphthoquinone did not undergo any visible changes when heated with 2,4-dinitrophenylhydrazine in alcohol with hydrochloric acid.

The condensation products, **2a—c** or **3**, are photosensitive compounds displaying two absorption maxima in the visible spectral region at 418—483 and 580—604 nm. The IR spectra of these compounds have absorption bands in the 3360—3300 cm^{-1} range characteristic of the stretching vibrations of NH groups, and in the 1680—1640 cm^{-1} range characteristic of C=O groups. A comparison of the ^{13}C NMR spectra of the starting compound **1** and oxime **2a** revealed that the signal at 196 ppm belonging to the carbon atom of the acetophenone C=O group in **1** is absent in the spectrum of oxime **2a**. Instead, there appears a signal at 153 ppm characteristic of the C=N group. Two signals from the carbon atoms of the naphthoquinone carbonyl groups appear at 181 ppm. A separate X-ray study was carried out for oxime **2a**, the results of which are given in Table 1 and Fig. 1.

The bond lengths in molecule **2a** are normal. Steric repulsions of the amine fragments of N(1) and N(2), as well as an intermolecular hydrogen bond N(1)—H...O(1) (H...O 2.13(2) Å, N—H...O 113(2)°) lead to a significant diminution of the C(1)—C(2)—N(1) bond angle which is only 111.3(2)° in **2a**. At the same time, the bond angle N(3)—C(3)—C(4) is changed only a little and amounts to 119.9(2)°. The rotations of the respective planes about the C(2)—N(1), N(1)—C(11) and C(14)—C(17) bonds are 31.6(2), 21.4(1) and 22.5(1)°, respectively. The O(2)—H...N(2) hydrogen bond (H...O 1.87(4) Å, O—H...N 156°) binds the molecules in centrosymmetric pairs.

Table 1. Coordinates ($\times 10^4$) and equivalent thermal factors ($Å^2$, $\times 10^3$) of the N-(3-piperidino-1,4-napthoquinone-2)-4-aminoacetophenone oxime (**2a**) atoms

Atom	x/a	y/b	z/c	U_{eq}
C(1)	3539(4)	1452(2)	9963(2)	49(1)
C(2)	3299(3)	2155(2)	10890(2)	45(1)
C(3)	4701(3)	3217(2)	11289(2)	44(1)
C(4)	6555(4)	3609(2)	10803(2)	52(1)
C(5)	8801(4)	3090(3)	9570(2)	54(1)
C(6)	9124(5)	2394(3)	8748(2)	60(1)
C(7)	7618(5)	1421(3)	8299(2)	67(1)
C(8)	5785(5)	1125(3)	8682(2)	64(1)
C(9)	5457(4)	1799(2)	9521(2)	48(1)
C(10)	6968(4)	2794(2)	9962(2)	46(1)
C(11)	912(3)	1661(2)	12161(2)	45(1)
C(12)	−1111(4)	1510(3)	12306(2)	50(1)
C(13)	−1747(4)	1453(3)	13211(2)	53(1)
C(14)	−392(3)	1533(2)	14009(2)	45(1)
C(15)	1628(4)	1693(2)	13859(2)	49(1)
C(16)	2271(4)	1742(2)	12945(2)	48(1)
C(17)	−1124(4)	1442(2)	14973(2)	51(1)
C(18)	223(6)	1966(4)	15858(2)	73(1)
C(19)	2734(5)	4683(3)	11944(2)	58(1)
C(20)	1930(5)	5045(3)	12888(2)	67(1)
C(21)	3622(6)	5754(3)	13612(2)	74(1)
C(22)	5212(5)	4966(3)	13722(2)	65(1)
C(23)	6012(4)	4658(3)	12762(2)	59(1)
N(1)	1457(3)	1676(2)	11223(2)	52(1)
N(2)	−2959(3)	857(2)	14985(1)	57(1)
N(3)	4333(3)	3975(2)	12084(1)	46(1)
O(1)	2180(3)	574(2)	9598(1)	67(1)
O(2)	−3624(3)	839(2)	15914(1)	68(1)
O(3)	7724(3)	4629(2)	11058(2)	88(1)

Experimental

IR spectra were recorded in chloroform on an UR-20 instrument. UV spectra were recorded in ethanol on a Specord UV-VIS instrument. The ^1H NMR spectra were recorded using a Bruker WP-200-S4 and Bruker AC-200 instruments, with $CDCl_3$ used as the solvent. The ^{13}C NMR spectra were obtained on a Bruker AC-400 instrument in DMSO-d_6. Chemical shifts, δ , are given in ppm. Molecular weight was determined on a Finnigan Mat 8200 mass spectrometer.

X-ray structural study of oxime 2a. Oxime **2a** belongs to the triclinic crystal system: a = 6.804(1), b = 10.732(2), c = 14.094(3) Å, α = 94.99(3), β = 93.70(3), γ = 101.85(3)°, V = 999.8 $Å^3$, $C_{23}H_{23}N_3O_3$, M = 389.44, space group, $P\bar{1}$, Z = 2, d_{calc} = 1.294 g cm^{-3}, μ(Cu-K_α) = 0.70 cm^{-1}. The intensities of 2700 independent reflections with 2θ < 114° were measured using the θ/2θ-scan technique on a SYNTEX $P2_1$ diffractometer (graphite monochromator). Corrections were applied for the intensity fall of the control reflections and the absorption by the actual crystal shape (transmission 0.88-0.97). The structure was solved by direct methods using the SHELX-86 program and refined by the least squares technique in a full-matrix anisotropic-isotropic approximation to wR2=0.1236 for 2700 F^2, S =1.01, R = 0.446, for 1948 $F_0 > 4\sigma(F_0)$ using the SHELX-93 program. The positions of the hydrogen atoms were determined from the difference synthesis, which confirmed the disorder in the two positions of the methyl group (the population factors of the positions were equalled to 0.5). The obtained atomic coordinates are listed in Table 1.

***N*-(3-piperidino-1,4-dihydro-1,4-dioxo-2-naphthyl)-4-aminoacetophenone oxime (2a).** Hydroxylamine hydrochloride (2 g) was added to 2 g of compound **1** in ethanol (150 mL) and the mixture was boiled for 5 h. Then the reaction mixture was cooled, poured out onto ice, and the precipitate was collected by filtration and dried. The yield of **2a** was 1.25 g (65%), m.p. 183—185 °C (from ethanol). IR, ν/cm^{-1}: 3580(OH),

3350(NH), 1645(C=O). UV spectrum, λ_{max}/nm (lg ε): 254(4.36), 323(4.38), 448(3.47), 604(3.45). ^{1}H NMR ($CDCl_3$), δ: 1.40 (m, 6 H, CH_2); 2.26 (s, 3 H, CH_3); 3.13 (m, 4 H, CH_2—N); 6.80 (d, 2 H, H(2) and H(6), J = 7 Hz); 7.11 (br.s, 1 H, NH); 7.53 (d, 2 H, H(3) and H(5), J = 7 Hz); 7.60 (m, 2 H(6,7)); 7.99 (m, 2 H(5,8)). ^{13}C NMR spectrum, δ: 181.1 and 181.3 (C(1) and C(4)), 152.6 (C(17)), 141.7—118.3 (C arom), 49.3—11.3 (C aliph). Found: *m/z* 389.1738. $C_{23}H_{23}N_3O_3$. Calculated: *m/z* 389.1470.

***N*-(3-piperidino-1,4-dihydro-1,4-dioxo-2-naphthyl)-4-amnoacetophenone 2,4-dinitrophenylhydrazone (2b)**. 1 g of 2,4-dinitrophenylhydrazine and 10 mL of hydrochloric acid were added to 2 g of compound **1** in 200 mL of ethanol. The resulting solution was stirred for 2 h at 70 °C. Then the reaction mixture was cooled, and poured out onto ice. The precipitate was filtered off, washed with water, and dried in air. Obtained was 1.15 g of hydrazone **2b** (79%), m.p. 205-207 °C (from benzene—hexane). Found (%): H, 4.49; N, 15.25. $C_{29}H_{26}N_6O_6$. Calculated (%): H, 4.69; N, 15.16. IR, ν/cm^{-1}: 3355, 3330(NH), 1650(C=O). UV, λ_{max}/nm (lg ε): 242(4.43), 418(4.39), 598(3.52). ^{1}H NMR ($CDCl_3$), δ: 1.22 (m, 6 H, CH_2); 2.40 (s, 3 H, CH_3); 3.19 (m, 4 H, CH_2—N); 6.84 (d, 2 H, H(2) and H(6), J = 7.5 Hz); 7.14 (br.s, NH); 7.62 (m, 2 H(6,7)); 7.75 (m, 2 H, H(3) and H(5), J = 7.5 Hz); 7.98 (m, 2 H(5,8)); 8.06 (d, 1 H, H(6) J = 10 Hz); 8.30 (d.d, 1 H, H(5), J = 10 Hz, J = 2.5 Hz); 9.09 (d, 1 H, H(3), J = 2.5 Hz); 11.30 (br.s, 1 H, NH—N).

***N*-(3-piperidino-1,4-dihydro-1,4-dioxo-2-naphthyl)-4-aminoacetophenone phenylhydrazone (2c)**. 3 mL of phenylhydrazine was added to 0.7 g of compound **1** in 150 mL of acetic acid, and the mixture was stirred at room temperature for 1 h. Then the reaction mixture was poured out onto ice, the precipitate was filtered off, washed with water and dried in air. The yield of compound **3c** was 0.45 g (55%), m.p. 105 °C (with decomp.). IR, ν/cm^{-1}: 3350(NH), 1645(C=O). UV, λ_{max}/nm (lg ε): 244(4.34), 307(4.41), 344(4.32), 483(3.38), 589(3.39). ^{1}H NMR ($CDCl_3$), δ: 1.41 (m, CH_2); 2.17 (s, CH_3); 2.22 (s, CH_2); 3.17 (m, CH_2—N); 6.80—6.86 (m, H(3), H(4′), H(5′)); 7.18 (d, H(2) and H(6), J = 7.5 Hz); 7.15—7.37 (m, H(2′), H(6′), NH—N); 7.62 (m, H(6,7)); 7.71 (d, H(3) and H(5), J = 7.5 Hz); 8.01 (m, H(5,8)). High-resolution mass spectrometry: *m/z* 464.2216(M$^+$). $C_{29}H_{28}N_4O_2$. Calculated: *m/z* 464.221.

***N*-(3-piperidino-1,4-dihydro-1,4-dioxo-2-naphthyl)-4-aminoacetophenone azine (3)**. Hydrazine hydrate (1 mL) and hydrochloric acid (1 mL) were added to 0.3 g of compound **1** in 50 mL of ethanol. The mixture was stirred for 3 h at 60 °C. Then the reaction mixture was cooled and poured out onto ice. The precipitate was filtered off, washed with water, and dried in air. The obtained product was chromatographed on silica gel (140—315 μm). Elution with benzene afforded 0.24 g of the substance (49%), m.p. 239—241 °C (from benzene). Found (%): H, 6.01; N, 10.87. $C_{46}H_{44}N_6O_4$. Calculated: (%): H, 5.91; N, 11.29. IR, ν/cm^{-1}: 3350(NH), 1645(C=O). UV, λ_{max}/nm (lg ε): 244(4.79), 316(4.83), 358(4.86), 461(4.08), 604(3.88). ^{1}H NMR ($CDCl_3$), δ: 1.41 (m, 12 H, CH_2); 2.35 (s, 6 H, CH_3); 3.17 (m, 8 H, CH_2—N); 6.85 (d, 4 H, H arom., J = 7.5 Hz); 7.14 (br.s, 2 H, NH); 7.61 (m, 4 H, H(6,7)); 7.84 (d, 4 H, H arom, J = 7.5 Hz); 8.01 (m, 4 H, H(5,8)).

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