THERMAL CONVERSIONS OF 2-AZIDO-3-PIPERAZINO-SUBSTITUTED 1,4-NAPHTHOQUINONES

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2-Chloro-3-morpholino- or piperidino-1,4-naphthoquinones are known to react readily with NaN_3 [1], but it was only possible to isolate the azide corresponding to the morpholino derivative of naphthoquinone when the reaction was carried out in acetone. The use of DMF as a solvent on heating results in the formation of the heterocyclic quinones – 1,2-dihydro-4H-[1, 4]-oxazino[3,4-a]- and 1,2,3,4-tetrahydropyrido[1,2-a]-naphth [2,3-d]imidazole-6,11-dione – together with the corrsponding 2-amino derivatives of naphthoquinone. In the present work we have studied the reaction of the 3-(4-acylpiperazino)-2-chloronaphthoquinones (Ia, b), previosly obtained by us [2], with NaN_3 in DMF at different temperatures. It was found that 2-azido-3-(4-acylpiperazino)-1,4-naphthoquinones (IIa, b) are initially formed, which, during the reaction and also during storage, undergo further conversions to give compounds (IIIa, b)-(Va, b) in different ratios (Table 1).

Scheme 1

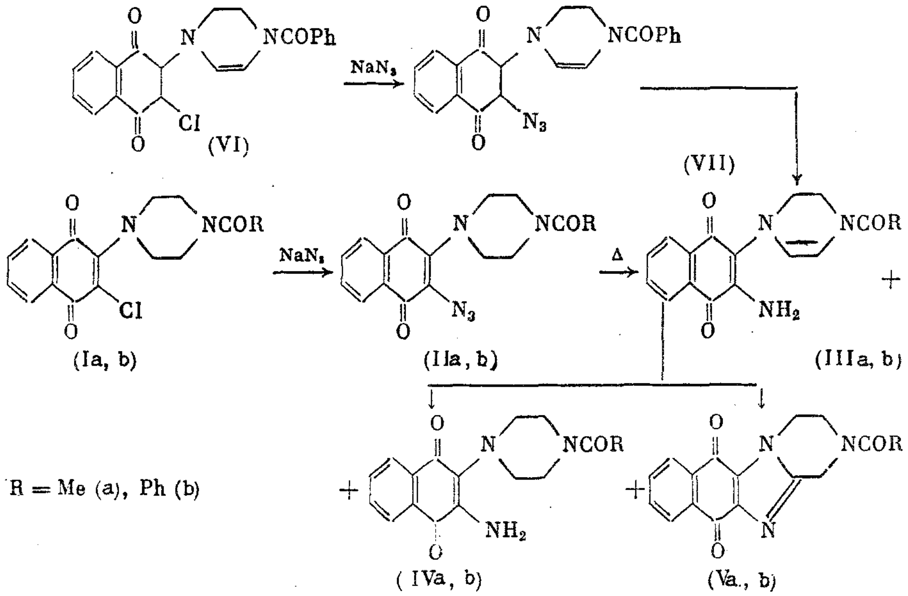

TABLE 1. Reaction of 2-Chloro-3-(4-acylpiperazino)-1,4-naphthoquinones with NaN_3 in DMF

Compound	T, °C	Time of reaction, h	Yield of reaction products, %			
			(II)	(III)	(IV)	(V)
(Ia)	20	20	47	35	Traces	–
	40–50	3	67	Traces	»	Traces
	80	1,5	–	»	23	31
(Ib)	20	20	18	40	10	6
	40–50	3	2	36	25	21
	80	1,5	Traces	–	67	31
	100 *	1	–	–	53	21

*Conditions as in [1].

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TABLE 2. Properties of Compounds Synthesized

Compound	Mp, °C (solvent)	Empirical formula	Molec. wt., m/z		R_f	IR spectrum, ν, cm^{-1}	Electronic absorption spectra, λ_{max}, nm (log ε)
			found	calculated			
(IIa)	95–96 (decomp.)	$C_{16}H_{15}N_5O_3$	297 *	325	0,26	2125 (N_3), 1680–1650 (C=O)	248 (4,28), 273 (4,26), 527 (3,34)
(IIb)	110–111 (decomp.)	$C_{21}H_{17}N_5O_3$	359 *	387	0,82	2125 (N_3), 1680–1645 (C=O)	238 (4,31), 272 (4,36), 294 **sh**(4,30), 527 (3,68)
(IIIa)	150 (decomp.)	$C_{16}H_{15}N_3O_3$	–	297	0,16	3433, 3355 (NH_2), 1680, 1645 (C=O)	267 (4,40), 281 **sh**(4,37), 310 **sh**(3,98), 436 (3,82), 576 **sh**(3,57)
(IIIb)	171–173 (C_6H_6)	$C_{21}H_{17}N_3O_3$	359,1239	359,1270	0,40	3390, 3280 (NH_2), 1680, 1620 (C=O)	258 (4,40), 291 (4,28), 315 **sh**(4,18), 415 **sh**(3,29), 581 (3,12)
(IVa)	234–235 (C_6H_6)	$C_{16}H_{17}N_3O_3$	299,1269	299,1270	0,11	3433, 3310 (NH_2), 1690, 1680 (C=O)	233 (4,16), 242 (4,13), 271 (4,26), 277 **sh**(4,24), 328 **sh**(3,45), 465 (3,20)
(IVb)	205–207 (C_6H_6)	$C_{21}H_{19}N_3O_3$	361,1428	361,1426	0,39	3477, 3355 (NH_2), 1680, 1630 (C=O)	231 (4,29), 240 (4,26), 271 (4,28), 280 **sh**(4,24), 326 **sh**(3,44), 465 (3,31)
(Va)	226–227 ($C_6H_4Cl_2$-o)	$C_{15}H_{13}N_3O_3$	295,0969	295,0957	0,04	1690, 1670 (C=O)	227 (4,13), 249 (4,97), 277 **sh**(4,20), 282 **sh**(4,22), 328 (3,56)
(Vb)	262–264 ($C_6H_4Cl_2$-o)	$C_{21}H_{15}N_3O_3$	357,1113	357,1113	0,23	1680 (C=O)	226 **sh**(4,27), 249 (4,72), 275 **sh**(4,19), 281 (4,20), 333 (3,56)
(VII)	130–133	$C_{21}H_{15}N_5O_3$	357 *	385	0,67	2120 (N_3), 1640 (C=O)	250 (4,38), 283 (4,18), 592 (3,00)

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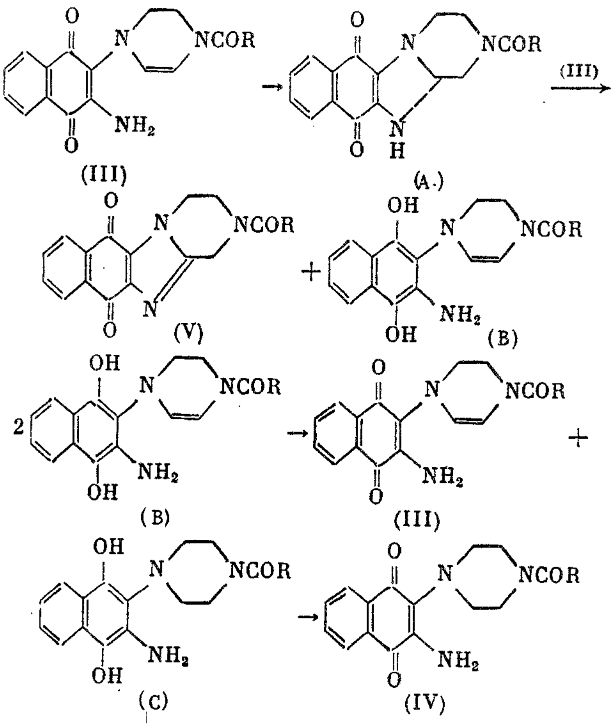
*[M−28].

When the reaction is carried out above 50°C, amino derivatives (IVa, b) and heterocyclization products (Va, b) are mainly obtained. At ~20°C, in addition to azides (IIa, b), it was possible for the first time to isolate products (IIIa, b) derived from dehydrogenation of the piperazine ring and containing a primary amino group at the 2-position of the quinone. The formation of tetrahydropyrazine derivatives (III) from azides probably occurs as a result of attack by nitrene on the C—H bond of the neighboring piperazine ring. It was also shown that compounds (IIIa, b) are precursors of compounds (IVa, b) and (Va, b). Thus, 1-(3-amino-1,4-naphthoquinonyl-2)-4-benzoyl-1,4,5,6-tetrahydropyrazine (IIIb) in benzene at 20°C is converted to amino derivative (IVb), which is completely hydrogenated in the pyrazine ring, and naphthimidazoledione (Vb). The conversion process can be represented by Scheme 2.

Scheme 2



The intramolecular addition of the amine to the double bond in compound (III) gives the dihydroimidazole (A), which is oxidized by quinone (III) to give imidazoles (V) and hydroquinone (B). The latter, probably in a manner similar to that reported for a morpholino derivative of naphthohydroquinone [3], disproportionates to give compound (III) again and aminohydroquinone (C), which is oxidized to 2-amino derivative (IV). It cannot also be ruled out that the formation of aminoquinones (IV) results from the known disproportionation of partially hydrogenated derivatives of pyrazine [4, 5].

The structure of the compounds obtained was proved by physicochemical methods. Thus, in the IR spectra of 2-azido-3-acylpiperazinonaphthoquinones (IIa, b) there is a strong band at 2125 cm^{-1} corresponding to the antisymmetric vibrations of the N_3 group. In the mass spectra of compounds (IIa, b) the peak due to the molecular ion is absent, but a peak ($[M - 28]^+$) corresponding to the loss of two N atoms occurs, which is typical for arylazides [6].

Amino derivatives (IVa, b) have absorption bands in their IR spectra that correspond to stretching vibrations of carbonyl groups and an NH_2 group. In the PMR spectrum of compound (IVb), in addition to a triplet at 8.00 ppm ($2H_\alpha$), a sextet at 7.64 ppm ($2H_\beta$), a multiplet at 7.41 ppm (5H, Ph), and three multiplets due to methylene protons at 3.76, 3.42, and 3.20 ppm (1:1:2), there is a broad singlet at 5.55 ppm corresponding to the two protons of the NH_2 group.

The electronic absorption spectra of compounds (Va, b) are similar to the spectra of the naphthimidazolediones obtained from piperidino and morpholino derivatives of naphthoquinone [7]. In the IR spectra of cyclization products (Va, b) there are absorption bands due to carbonyl groups and there are no bands in the region 3600-3200 cm^{-1}. In the PMR spectrum of compound (Vb) there are four multiplets from aromatic protons at 8.20, 8.06, 7.71, and 7.46 ppm (1:1:2:5), a singlet and two multiplets from the methylene protons of the piperazine ring at 5.01, 4.56, and 4.10 ppm (2:2:2), on the basis of which it was assigned the structure of 1,2-dihydro-3-benzoyl-4H-[1,4]-pyrazino[1,2-a]naphth[2,3-d]imidazole-6,11-dione.

The intensely colored compounds (IIIa, b) have bands due to stretching vibrations of carbonyl groups and an NH_2 group in their IR spectra. In the PMR spectrum of compound (IIIb) there are two multiplets from aromatic protons at 8.02 ($2H_\alpha$) and 7.57 ppm (7H: $2H_\beta$ and 5H, Ph), two doublets from methine protons at 5.80 and 5.44 ppm, a singlet at 5.26 ppm (2H, NH_2), and two triplets from methylene protons at 4.10 and 3.66 ppm. From all this it is possible to propose the structure of 1-(3-amino-1,4-naphthoquinonyl-2)-4-benzoyl-1,4,5,6-tetrahydropyrazine for compound (IIIb). The formation of compound (IIIb) by reaction of 1-(3-chloro-1,4-naphthoquinonyl-2)-4-benzoyl-1,4,5,6-tetrahydropyrazine (VI) [2] with NaN_3 is additional confirmation of its structure.

EXPERIMENTAL

Electronic absorption spectra were recorded on a Specord UV-VIS spectrophotometer in EtOH, and IR spectra were recorded on a UR-20 spectrometer in KBr and $CHCl_3$. PMR spectra were recorded in $CDCl_3$ on a Bruker WP-200 SY instrument. Molecular weights and element composition of the compounds were determined according to the precise value of the mass number of molecular ions on a Finnigan MAT 8200 mass spectrometer. TLC was performed on Silufol plates and preparative chromatography was carried out on SiO_2 (L 100/160 μm) and Al_2O_3 (activity II) in the systems: A) $C_6H_6-CHCl_3$ (4:1); B) $C_6H_6-CHCl_3$ (1:1); C) $CHCl_3$; D) $C_6H_6-(CH_3)_2CO$ (4:1); E) $CHCl_3-(CH_3)_2CO$ (1:1). The R_f values were determined on Silufol plates in system D.

Reaction of Compounds (Ia, b) with NaN_3. To a solution of 0.5 mmole of (Ia, b) in 2 ml of DMF was added a solution of 1 mmole of NaN_3 in 0.2 ml of water, and the mixture was kept at a fixed temperature until the initial compound had disappeared according to TLC. The mixture was poured into water, extracted with $CHCl_3$, evaporated under vacuum, and chromatographed on Al_2O_3 in the systems A-E in succession. The yield of compounds (II)-(V) are given in Table 1, and the properties listed in Table 2.

2-Azido-3-(4-acetylpiperazino)-1,4-naphthoquinone (IIa). To a solution of 0.16 g of (Ia) in 2 ml of DMF was added a solution of 0.07 g of NaN_3 in 0.2 ml of water, and the mixture was kept at 20°C for 13 h. It was poured into water, the dark violet precipitate that had formed was filtered off, washed with water, and dried in the dark. Yield of azide (IIa) was 0.13 g (77%).

Conversion of Compound (IIIb). A solution of 0.15 g of compound (IIIb) in 5 ml of C_6H_6 was kept at 20°C in the dark for 17 h, then chromatographed on SiO_2 plates in system C. The following yields were obtained: 0.056 g (38%) of (IVb) and 0.023 g (16%) of naphthimidazoledione (Vb).

Reaction of 1-(3-Chloro-1,4-naphthoquinonyl-2)-4-benzoyl-1,4,5,6-tetrahydropyrazine (VI) with NaN_3. (a) To a supspension of 0.38 g of compound (VI) [2] in 30 ml of methanol was added a solution of 0.14 g of NaN_3 in 0.4 ml of water, and the mixture was agitated at 20°C for 4.5 h. The precipitate that had formed was filtered off and washed with MeOH and water. Yield of 1-(3-azido-1,4-naphthoquinonyl-2)-4-benzoyl-1,4,5,6-tetrahydropyrazine (VII) was 0.23 g (60%). (b) The same quantities of reagents were kept at 20°C for 96 h, and the mixture was concentrated under vacuum and chromatographed on Al_2O_3 plates in system C. The following yields were obtained: 0.04 g (10%) of (VII) and 0.06 g (18%) of (IIIb).

CONCLUSIONS

The 2-azido derivatives which are formed when 2-chloro-3-(4-acylpiperazino)-1,4-naphthoquinones are reacted with NaN_3 in DMF are converted during the reaction to the corresponding 2-amino derivatives and the cyclization products—naphthimidazolediones.

2. It is shown that the precursors of the naphthimidazolediones are 1-(3-amino-1,4-naphthoquinonyl-2)-1,4,5,6-tetrahydropyrazines, which are products from dehydrogenation of the piperazine ring.

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