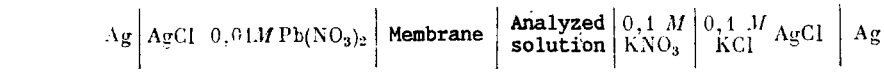

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REACTION OF 2-(4-ALKYLPIPERAZINO)-3-CHLORO-1,4-NAPHTHOQUINONES WITH SODIUM AZIDE

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It was shown that 2-(4-alkylpiperazino)-3-chloro-1,4-naphthoquinones react on heating with NaN_3 in DMF to form new heterocyclic quinones – 1,2,3,4-tetrahydro-13-alkyl-3,1-(iminoethano)benzo[g]quinoxaline-5,10-diones as well as the corresponding 2-(4-alkylpiperazino)-3-aminonaphthoquinones and naphthimidazopyrazinediones.

It is known that 2-morpholino- and 2-piperidino-3-chloro-1,4-naphthoquinones react on heating with NaN_3 in DMF with the formation of the corresponding 3-amino derivatives and naphth[2',3':4,5]imidazo-6,11-diones [1]. The precursors of the latter, as has been shown with the example of 2-(4-acylpiperazino)-3-azido-1,4-naphthoquinones, are dehydrogenation products of the piperazine ring – enaminonaphthoquinones [2]. In continuation of these investigations, the reaction of NaN_3 with 2-(4-alkylpiperazino)-3-chloro-1,4-naphthoquinones (Ia-c) was carried out in DMF at 80°C, and it was found that unlike 2-(4-acylpiperazino)-naphthoquinones [2], the reaction produced, besides the 3-amino derivatives (IIIa-c) and 2-alkyl-1,2,3,4-tetrahydronaphth[2',3':4,5]imidazo[1,2,a]pyrazine-6,11-diones (IVa-c), new heterocyclic compounds – 1,2,3,4-tetrahydro-13-alkyl-3,1(iminoethano)benzo[g]quinoxaline-5,5-diones (Va-c) (see Scheme 1). The yield of the reaction products is given in Table 1.

The thermolysis of azide (IIa), which separated out on reacting compound (Ia) with NaN_3 at 20°C leads to the same set of products (IIIa)-(Va).

It can be assumed that, like naphthimidazopyrazinediones (IV), the (3,1-iminoethano)-benzoquinoxaline derivatives (Va-c) are products of the intramolecular cyclization of the intermediately formed unstable enaminonaphthoquinones (A). Attempts to isolate them, unlike 4-acylpiperazino-substituted naphthoquinones [2], were unsuccessful as could be expected [3]. The direction of the cyclization of 1-(3-amino-1,4-naphtho-2-quinolyl)-4R-tetrahydropyrazines of type (A) is clearly influenced by the character of the substituent in the partially hydrogenated pyrazine ring: in the presence of an acyl group, the attack of the amine proceeds at the nearest α-carbon atom at the double bond with the formation of an imidazole ring [2], while in the presence of an alkyl group (R), the reaction occurs at the α- and β-carbon atoms with the formation of both five-membered (IV) and six-membered (V) rings.

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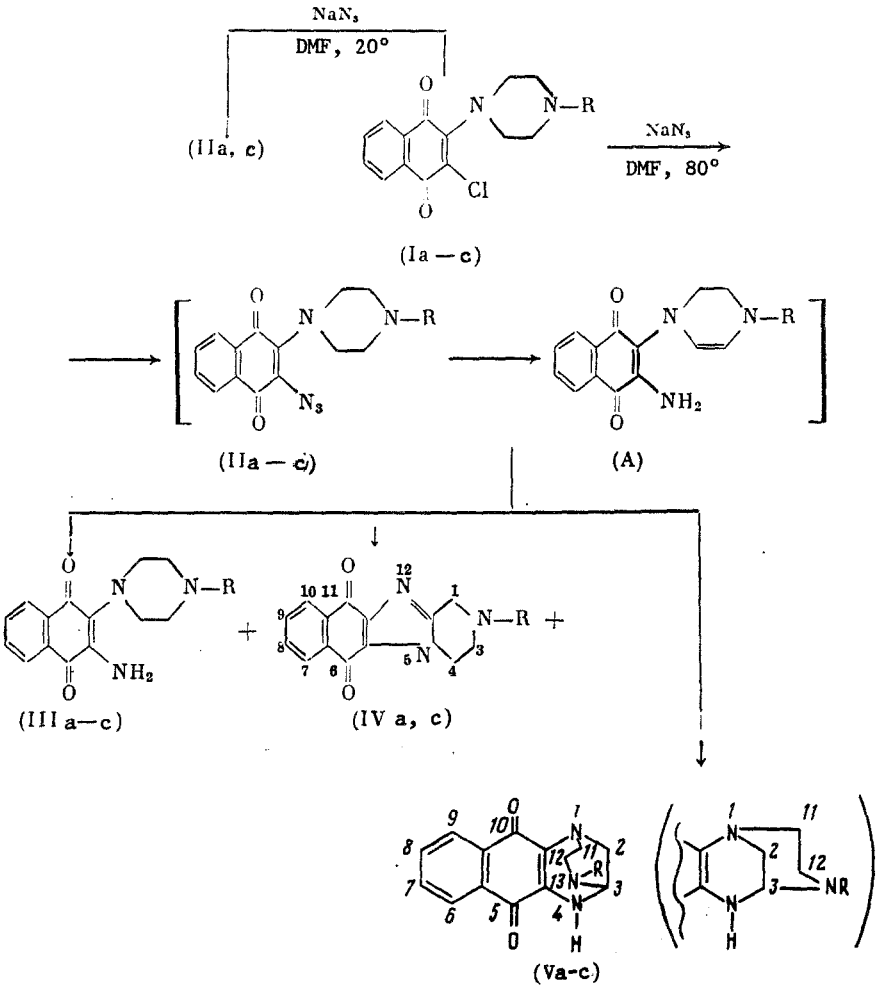
TABLE 1. Yield of Naphthoquinone Derivatives (DMF, 80°C)

Starting compound	Yield of reaction products, %		
	(III)	(IV)	(V)
(Ia)	32	11	15
(Ib)	54	–	3
(Ic)	55	11	22

Scheme 1



R = CH_2CH_2CN (a), CH_2Ph (b), CH_3 (c).

The structure of the compounds obtained was proved by physicochemical methods. The spectral characteristics of compounds (II)-(IV) are similar to those of the previously obtained 2-(4-acylpiperazino)-1,4-naphthoquinones [2] (Tables 2, 3). The 1,2,3,4-tetrahydro-13-alkyl-3,1-(iminoethano)benzo[g]quinoxaline-5,10-diones (Va-c) have a molecular weight 2 units higher than naphtimidazopyrazinediones (IV), but 2 units lower than amino derivatives (III). In the IR spectra of compounds (Va-c) there are absorption bands which correspond to the stretching vibrations of carbonyl groups and the NH group. The character of the PMR spectra confirms their structure. For example, in the PMR spectrum of compound (Va), in addition to the three multiplets of aromatic protons and a broadened singlet of an NH group proton, there are six multiplets of aliphatic protons, the assignment of which was carried out by the double resonance method on a spectrometer with a frequency of 400 MHz. The signal at 4.51 ppm was assigned to the H^3 proton; during its irradiation with a frequency corresponding to the NH group proton, merging of the multiplet into a doublet of doublets took place. The H^{2e} (3.52 ppm) and H^{2a} (2.54 ppm) protons were assigned in the following way: during the irradiation of the H^3 proton, the doublet of multiplets of the H^{2e} proton con-

TABLE 2. Characteristics of the Obtained Compounds

Compound	mp, °C (solvent)	Mol. mass, m/z: found	Mol. mass, m/z: calculated	Empirical formula	IR spectrum ν, cm^{-1}	Electronic absorption spectrum, λ_{max}, nm (log ε)
(IIa)	88–90 (dec.)	308 *	336	$C_{17}H_{16}N_6O_2$	2220 (C≡N), 2125 (N_3), 1670 (C=O)	234(4,21), 276(4,20), 295 sh(4,15), 546(3,47)
(IIc)	97–99 (dec.)	297, 1226	297, 1226	$C_{15}H_{15}N_5O_2$	2125 (N_3), 1670, 1645 (C=O)	233(4,25), 274(4,06), 301 sh(3,86), 523(3,11)
(IIIa)	174–176 (EtOH)	310, 1430	310, 1430	$C_{17}H_{18}N_4O_2$	3506, 3385 (NH_2), 2266 (C≡N), 1680, 1640 (C=O)	247(4,13), 271(4,15), 280 sh(4,13), 332a(3,38), 465(3,18)
(IIIb)	145–147 (EtOH)	347, 1633	347, 1634	$C_{21}H_{21}N_3O_2$	3470, 3350 (NH_2), 1670, 1630 (C=O)	242(4,11), 270(4,19), 277 sh(4,18), 468(3,19)
(IIIc)	154–155 (EtOH)	271, 1317	271, 1321	$C_{15}H_{17}N_3O_2$	3400, 3230 (NH_2), 1680 (C=O)	241(4,07), 271(4,23), 291 sh(4,08), 328 sh(3,41), 465(3,29)
(IVa)	220–222 ($C_6H_4Cl_2$-o)	306, 1115	306, 1117	$C_{17}H_{14}N_4O_2$	2255 (C≡N), 1690, 1670 (C=O)	225sh(4,08), 250(4,65), 276(4,22), 282(4,23), 336(3,56)
(IVc)	221–224 ($C_6H_4Cl_2$-o)	267, 1007	267, 1008	$C_{15}H_{13}N_3O_2$	1670 (C=O)	225 sh(3,92), 250(4,51), 276 sh(4,05), 283(4,14), 371(3,04)
(Va)	200–203 (C_6H_6 – EtOH)	308, 1273	308, 1273	$C_{17}H_{16}N_4O_2$	3355 (NH), 2260 (C≡N), 1680, 1640 (C=O)	241(4,18), 281(4,38), 332 sh(3,48), 498(3,28)
(Vb)	85–90 **	345, 1503	345, 1477	$C_{21}H_{19}N_3O_2$	3400 (NH), 1670, 1630 (C=O)	244(4,25), 278(4,33), 328 sh(3,48), 498(3,22)
(Vc)	137–140 **	269, 1164	269, 1164	$C_{15}H_{15}N_3O_2$	3410 (NH), 1680, 1640 (C=O)	247(4,26), 281(4,20), 326 sh(3,51), 498(2,94)

*(M–28)

**Precipitated by hexane from C_6H_6.

verted into a doublet of doublets (the splitting of the doublets is caused by interaction of the H^{2e} proton with an NH group proton – a 1,5-interaction), and during irradiation at a frequency corresponding to the H^{2e} proton, the doublet of multiplets of the H^{2a} proton in the complex multiplet at 2.54 ppm merges into a broadened singlet. The H^{11a},H^{11e} protons (3.40 ppm) and the H^{12e} proton can be differentiated by suppressing the H^{12a} proton (2.22 ppm).

EXPERIMENTAL

The electronic absorption spectra were recorded on a "Specord UV-VIS" spectrophotometer in EtOH, IR spectra – on a UR-20 spectrophotometer in $CHCl_3$ and in KBr tablets. The PMR spectra were recorded in $CDCl_3$ on a "Bruker WP-200SY" and "Bruker AM-400" spectrometers. The molecular weights and the empirical formulas of the compounds were determined according to an accurate value of the mass number of the molecular ions on a "Finnigan MAT 8200" mass-spectrometer. The elemental analysis corresponded to the calculated values. The preparative chromatography was carried out on SiO_2 (L 100/160 μm) and Silufol plates in systems: 1) C_6H_6–$CHCl_3$ (4:1), 2) $CHCl_3$, 3) C_6H_6–$CH_3)_2CO$ (4:1), 4) $CHCl_3$–$CH_3)_2CO$ (4:1). The TLC was carried out on Silufol plates in system 3. The synthesis of compounds (Ia-c) was described in [3]. All the reactions were carried out in the absence of direct sunlight.

Reaction of Compounds (Ia-c) with NaN_3 on Heating. A solution of 2 mmoles of NaN_3 in 0.5 ml of H_2O was added to a solution of 1 mmole of (Ia-c) in 4 ml of DMF and the mixture

TABLE 3. PMR Spectra of Naphthoquinone Derivatives

Compound	δ, ppm, J, Hz
(IIIa)	2,56 m (6H, $H^{3',5'}$, CH_2CH_2CN), 2,75 m (2H, CH_2—CN), 3,19 m (4H, $H^{2',6'}$), 5,43 br.s (2H, NH_2), 7,60 m (2H, $H^{6,7}$), 7,95 m (2H, $H^{5,8}$)
(IIIb)	2,52 m (4H, $H^{3',5'}$), 3,19 m (4H, $H^{2',6'}$), 3,56 s (2H, CH_2—Ph), 5,42 br.s (2H, NH_2), 7,31 m (5H, Ph), 7,60 m (2H, $H^{6,7}$), 7,99 m (2H, $H^{5,8}$)
(IIIc)	2,32 s (3H, CH_3), 2,49 m (2H, $H^{3',5'}$), 3,20 m (4H, $H^{2',6'}$), 5,40 br.s (2H, NH_2), 7,60 m (2H, $H^{6,7}$), 7,98 m (2H, $H^{5,8}$)
(IVa)	2,63 t (2H, $C\underline{H}_2CH_2CN$), 2,96 t (2H, $CH_2C\underline{H}_2CN$), 3,08t (2H, H^3), 3,96 s (2H, H^1), 4,50 t (2H, H^4), 7,70 m (2H, $H^{8,9}$), 8,08 m (1H, $H^{7(10)}$), 8,20 m (1H, $H^{7(10)}$)
(IVc)	2,51 s (3H, CH_3), 2,90 t (2H, H^3), 3,80 s (2H, H^1), 4,46 t (2H, H^4), 7,68m (2H, $H^{8,9}$), 8,08 m (1H, $H^{7(10)}$), 8,20 m (1H, $H^{7(10)}$)
(Va)	2,20d.t (1H, H^{12a}, $J_{H^{12a}H^{12c}} = 13$, $J_{H^{12a}H^{11a}} = 12$, $J_{H^{12a}H^{11c}} = 6$), 2,54 m (5H: 1H, H^{2a}; 3H, CH_2CH_2CN; 1H, H^{12c}), 2,92 m (1H, $C\underline{H}_2CH_2CN$), 3,40m (2H, $H^{11a,11c}$), 3,52 d.m (1H, H^{2c}, $J_{H^{2c}H^{2a}} = 13$), 4,51m (1H, H^3), 6,24 m (1H, NH), 7,64 m (2H, $H^{7,8}$), 7,99 m (1H, $H^{6(9)}$), 8,09 m (1H, $H^{6(9)}$)
(Vb)	2,14 d.t (1H, H^{12a}, $J_{H^{12a}H^{12c}} = 12$, $J_{H^{12a}H^{11c}} = 5$), 2,34 m (1H, H^{12c}), 2,50d.t (1H, H^{2a}, $J_{H^{2a}H^{2c}} = 13$), 3,30 m (2H, $H^{11a,11c}$), 3,48 m (3H: 2H, CH_2—Ph; 1H, H^{2c}), 4,37 m (1H, H^3), 6,15 m (1H, NH), 7,34 m (5H, Ph), 7,64m (2H, $H^{7,8}$), 8,02 m (1H, $H^{6(9)}$), 8,10m (1H, $H^{6(9)}$)
(Vc)	2,12 d.t (1H, H^{12a}, $J_{H^{12a}H^{12c}} = 12$, $J_{H^{12a}H^{11a}} = 12$, $J_{H^{12a}H^{11c}} = 6$), 2,30 s (3H, CH_3), 2,38 m (1H, H^{12c}), 2,57d.m (1H, H^{2a}, $J_{H^{2a}H^{2c}} = 13$), 3,35 m (2H, $H^{11a,11c}$), 3,43d.m (1H, H^{2c}), 4,35 m (1H, H^3), 6,23 br.s (1H, NH), 7,62 m (2H, $H^{7,8}$), 8,04 m (2H, $H^{6,9}$)

was held at 80°C up to the disappearance of the starting compound (3.5, 1.5 and 1.5 h, respectively). The reaction mixture was poured into water, extracted with $CHCl_3$, evaporated under vacuum and chromatographed on SiO_2 plates in systems 1-4, successively separating compounds (III), (V) and (IV).

3-Azido-2-(4-β-cyanoethylpyrazino)- and 3-Azido-2-(4-methylpiperazino)-1,4-naphthoquinones (IIa) and (IIc). A solution of 2 mmoles of $NaaN_3$ in 0.5 ml of H_2O was added to a solution of 1 mmole of (Ia, c) in 4 ml of DMF, and the mixture was held for 40 h at 20°C. The reaction mixture was poured into water, the precipitate that separated out was filtered off, washed with water, and dried at 20°C. The yield of (IIa) and (IIc) was 76 and 59%, respectively.

Thermolysis of 3-Azido-2-(4-β-cyanoethylpiperazino)-1,4-naphthoquinone (IIa). a) A solution of 0.170 g of (IIa) in 2 ml of DMF was held for 1 h at 80°C (to the disappearance of the azide). The reaction mixture was poured into water and extracted with $CHCl_3$. The extract was evaporated under vacuum and the residue was chromatographed on SiO_2 in systems 1-4, successively separating 0.026 g (16%) of amine (IIIa), 0.057 g (38%) of compound (Va) and 0.004 g (3%) of (IVa).

b) A solution of 0.200 g of (IIa) in 30 ml of C_6H_6 was boiled for 1 h. The mixture was evaporated and chromatographed on SiO_2. Yield, 0.017 g (9%) of amine (IIIa), 0.053 g (30%) of (Va) and traces of imidazole (IVa).

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