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Features of Quinoxaline Reactions with C-Nucleophiles: Examples of Dimerization of Heterocycle in Course of Hydrogen Substitution

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Abstract—Reaction of quinoxaline or its 6,7-difluoroderivative with C-nucleophiles in nitrogen atmosphere afforded along with the products of hydrogen substitution in the heterocyclic ring the corresponding bis-quinoxalines. An ESR signal of the cation-radical of the diprotic salt of quinoxaline was detected in the DMSO solution of quinoxaline and dimedone.

Keywords: quinoxalines, C-nucleophiles, hydrogen substitution, dimers of quinoxaline

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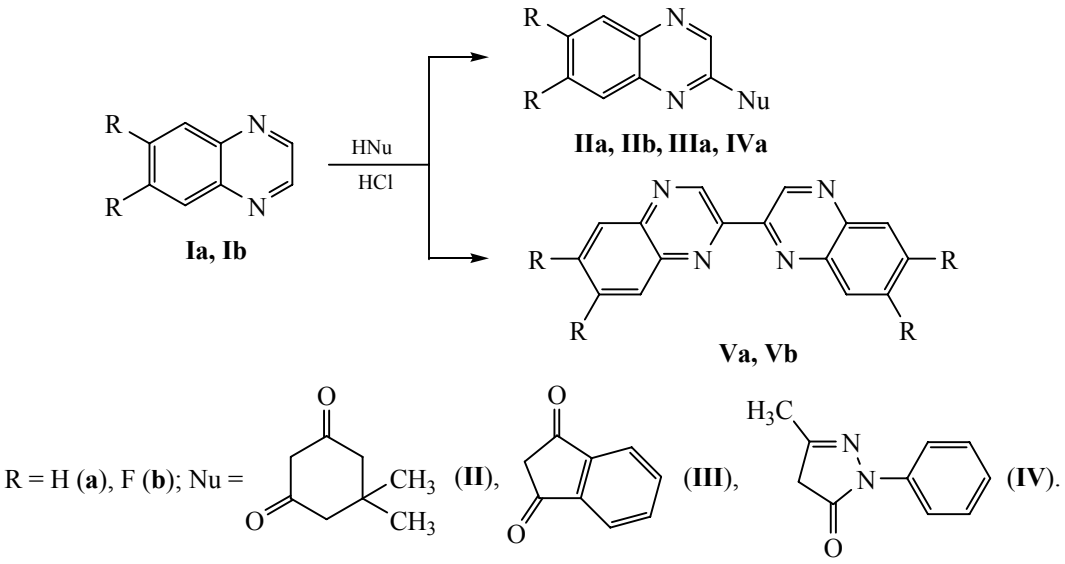
N-Alkyl salt of quinoxaline is known to react with 1,3-diketones to form the 2,3-diadducts of tetrahydroquinoxaline or the products of cycloaddition to the C^2–C^3 bond [1, 2]. The unsubstituted quinoxaline reacts in DMSO with 1,3-dimethylbarbituric acid at room temperature to form the product of hydrogen substitution [3]. *N,N*-Dimethylaniline when fused with quinoxaline hydrochloride in the presence of three-fold excess of sulfur gives 2-(*N,N*-dimethylaminophenyl)quinoxaline and 3-(*N,N*-dimethylaminophenyl)quinoxalinethione-2 in 12 and 71% yield respectively [4]. In the reaction of the same reagents in DMF solution in an inert atmosphere at 140°C 2,2'-bisquinoxaline is formed. At the same time, quinoxaline hydrochloride does not form any products when heated with *N,N*-dimethylaniline in DMF in the air at 140°C [4]. Recently, we reported that quinoxaline and its 6,7-difluoroderivatives smoothly reacted with C-nucleophiles in DMSO solution in the presence of acid at room temperature to form the products of monosubstitution of hydrogen atoms in the pyrazine ring [5, 6]. In the present work we have found that quinoxalines **Ia, Ib** react with C-nucleophiles in nitrogen atmosphere with the formation of not only the products of substitution **IIa, IIb–IVa, IVb**, but also 2,2'-bisquinoxalines **Va, Vb** (Scheme 1). The largest amount (7–11%) of dimers **Va, Vb** was observed in the reaction of quinoxalines **Ia, Ib** with dimedone. At the same time, when air was bubbling air through the reaction mixture of quinoxaline **Ib** with dimedone, the yield of dimer **Vb** did not exceed 2–3%.

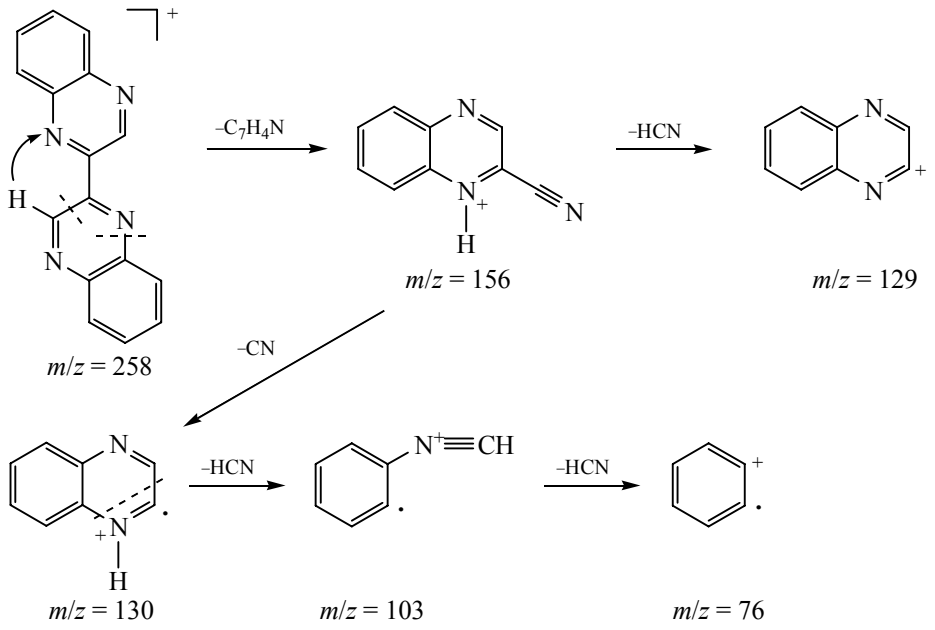
The base peaks in the mass spectra of dimers **Va, Vb** are the peaks of molecular ions. The fragmentation of molecular ions of compounds **Va, Vb** occurs similarly. In both cases peaks of low intensity of ions $[M - 28]^{+\bullet}$ are registered, whose formation, apparently, results from two consecutive processes and which correspond to fragments $[M - H - HCN]^{+\bullet}$. The main route of fragmentation is the formation of an intense ion $[M - C_7H_4N]^+$ in the case of dimer **Va** (Scheme 2) or $[M - C_7H_2F_2N]^+$ in the case of **Vb**.

The ion formed by the fragmentation of compound **Va** corresponds to cyanoquinoxaline cation (HRMS, ESI: M = 157.0631, calculated for $[C_6H_6N_3 + H]^+$ = 157.0634, $\Delta m/m$ = 2 ppm). The mechanism of formation of cyanoquinoxaline cation can be rationalized by successive splitting of the C–C bond of one of heterocyclic rings, the rearrangement with migration of a hydrogen atom, and subsequent splitting of the C–N bond.

Scheme 1.



Scheme 2.



When studying transformations of quinoxaline **Ia** with dimedone in the DMSO solution in the presence of acid at room temperature in the probe of the ESR spectrometer, after 15–20 min an ESR signal appeared (see figure), whose intensity increased during 3–5 h.

The investigation of the hyperfine structure of the ESR spectrum obtained by the reaction of compound **Ia** with dimedone in DMSO is indicative of the presence of radical cation of the diprotic salt of quinoxaline in the reaction mixture. Indeed, the hyperfine structure corresponds to interaction of the unshared electron with two equivalent nitrogen nuclei (α_N^{NH} = 0.68 Gs) and two protons coupled with them (α_H^{NH} = 0.62 Gs), as well as with the groups of the in pair equivalent protons ($\alpha_H^{2,3}$ = 0.39 Gs, $\alpha_H^{5,8}$ = 0.14 Gs, $\alpha_H^{6,7}$ = 0.08 Gs).

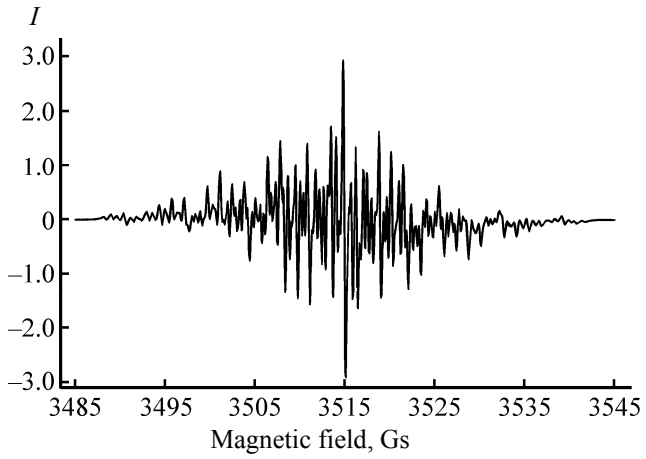
Note that hyperfine structure of the radical we have detected is fully consistent with that of the earlier described for the radical cation of the diprotic salt of quinoxaline [4].

It can be assumed that the formation of the products of monosubstitution **IIa, IIb, IIIa, IVa** when carrying out the reaction in nitrogen atmosphere is due to the addition of nucleophiles to the C_2 atom of quinoxaline and the oxidation of the formed intermediates $\mathbf{I_1}$, $\mathbf{I_2}$ by the starting quinoxalines **I** or their protic salts. In turn, intermediates $\mathbf{I_1}$, $\mathbf{I_2}$, when oxidized, can form radical cations in the process of one-electron reduction of the starting protic salts of quinoxaline. The reaction of cation-radical with the starting quinoxalines is a typical reaction of hetarylation to form the final dimers **Va, Vb** (Scheme 3).

To the best of our knowledge, the described examples of the reaction of hydrogen substitution, when the role of the oxidant of the formed σ-adducts was played by the starting quinoxalines or their protic salts, which, in turn, were converted into the dimers of quinoxalines, were observed for the first time. At the same time, the examples of reduction of pyridines, quinoxalines with active metals to radical anions and the use of the latter in the syntheses of bisheterocyclic derivatives in the reactions of hetarylation of nucleophilic aromatic compounds have been described earlier [7–9].

EXPERIMENTAL

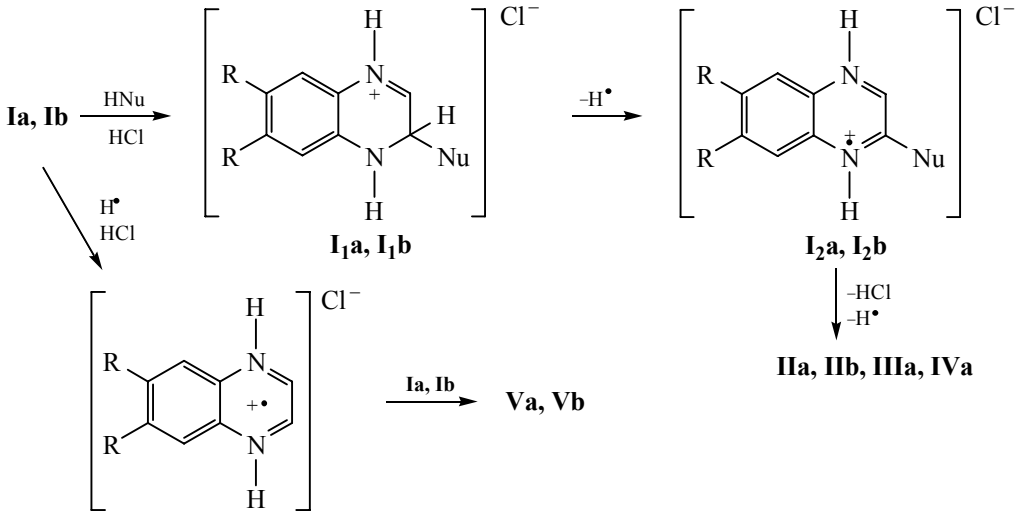
^{1}H NMR spectra were registered on a Bruker DRX-400 spectrometer (400 MHz). Mass spectrum (HRMS-ESI) was recorded on a micrOTOF-Q II Bruker Daltonics mass spectrometer. EI mass spectra were obtained on a Varian MAT 311A spectrometer at 200°C (70 eV) with direct admission of the sample into the ion source. ESR spectrum was obtained on an ELEXSYS E500 instrument in the CW mode in the range of 9.5 GHz.



ESR spectrum (first derivative) of the radical cation of quinoxaline.

Reaction of quinoxalines Ia, Ib with dimedone. 1.0 mmol of quinoxaline **Ia** or **Ib** was stirred with 1.0 mmol of dimedone in 1 mL of DMSO in the presence of 0.1 mL of conc. HCl at 20–25°C in nitrogen atmosphere during of 48–50 h. The formed precipitate was filtered, washed with chloroform (3 × 3 mL),

Scheme 3.



and crystallized from DMF to obtain the corresponding dimer **Va** or **Vb**. The chloroform solutions from washing the solid products of the reaction were evaporated in a vacuum to obtain the products of substitution **IIa, IIb**.

2,2'-bisquinoxaline (Va). Yield 7.5%. mp 273–274°C (mp 272–274°C [7]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.80–7.92 m (4H, H_{Ar}); 8.20–8.25 m (2H, H_{Ar}); 8.22–8.32 m (2H, H_{Ar}); 10.15 s (2H, H_{Ar}). Mass spectrum (EI), *m/z* (I_{rel}, %): 258 (98), 257(4), 230 (8), 156 (100), 130 (35), 103 (45), 76 (45).

6,6',7,7'-Tetrafluoro-2,2'-bisquinoxaline (Vb). Yield 11.0%. mp >250°C. ^{1}H NMR spectrum (DMF-d_7) δ, ppm: 8.20–8.34 m (4H, H_{Ar}); 10.00 s (2H, H_{Ar}). Mass spectrum (EI), *m/z* (I_{rel}, %): 330 (94), 329 (3), 302 (4), 192(100), 166 (31), 165 (27), 139 (52), 112 (53), 88 (16). Found, %: C 58.09; H 1.93; N 16.88. $C_{16}H_6F_4N_4$. Calculated, %: C 58.19; H 1.83; N 16.97.

2-(1,3-Dioxo-5,5-dimethylcyclohexan-2-ylidene)-1*H*-1,2-dihydroquinoxaline (IIa). Yield 32%. mp 173–174°C (mp 173–174°C [5]).

2-(6,7-Difluoroquinoxalin-2(1*H*)-ylidene)-5,5-dimethylcyclohexan-1,3-dione (IIb). Yield 37%. mp 228–230°C (mp 228–230°C [6]).

The reaction of quinoxaline **Ia** with indandione was carried out similarly to the reaction of **Ia** with dimedone. Dimer **Va** (1.5%) and 2-(1,3-dioxoindan-2-ylidene)-1*H*-1,2-dihydroquinoxaline **IIIa** (25%) were obtained, mp > 250°C (mp > 250°C [5]).

Reaction of quinoxaline **Ia** with 1-phenyl-3-methyl-pyrazolone-5 was carried out similarly. Dimer **Va** (2.8%) and 2-(1-phenyl-3-methyl-5-oxypyrazol-4-ylidene)-1*H*-1,2-dihydroxyquinoxaline **IVa** (28%) were obtained, mp 158–160°C (mp 158–160°C [5]).

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