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Dedicated to Full Member of the Russian Academy of Sciences N.S. Zefirov on His 70th Anniversary

Ring–Chain Transformations of Dihydroisoxazolo[4,5-*b*]quinoxaline

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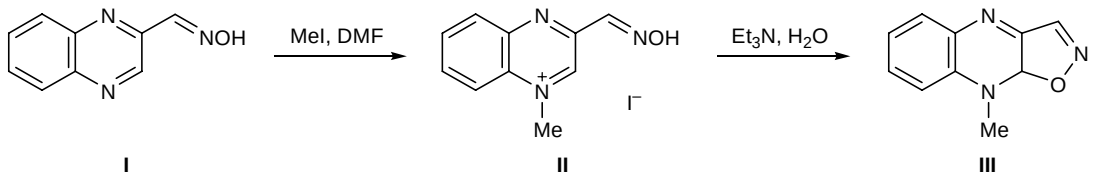
Abstract—Ring–chain transformation of 3-hydroxyiminomethyl-1-methylquinoxalinium iodide into 9-methyl-9,9a-dihydroisoxazolo[4,5-*b*]quinoxaline was studied. The isoxazole ring in the latter was cleaved by the action of alcohols.

In the recent years, methods for the synthesis of fused azine systems were developed on the basis of tandem reactions of azines and azinium ions with difunctional nucleophiles. Depending on the nature of the group replaced by nucleophile and the mechanism of new bond formation, these cyclizations may be regarded as S_N^H–S_N^H [1–3], A_N–A_N [4–9], A_N–S_N^H [7–9], A_N–S_N^{ipso} [10, 11], or S_N^H–S_N^{ipso} [11, 12]. As a rule, the key stage in these multistep processes is attack on unsubstituted carbon atom in the heteroring. Here, information on the properties of σ^H adducts and conditions of their formation is very important for understanding their reactivity. Studies on σ^H adducts derived from azines and nucleophiles are often complicated due to reversibility of the corresponding processes, whereas cyclic adducts of 1,4-diazines with difunctional nucleophiles are more stable. There are published data on equilibrium addition of S-, O-, and N-nucleophiles to 1-alkylquinoxalinium salts [13–15]; furthermore, isolation of stable crystalline σ^H adducts derived from 1-ethyl-2,3-dicyanopyrazinium ion has been reported in a few publications [16].

We previously reported on tandem reactions of 1,4-diazines and their quaternary salts containing an exocyclic carbonyl group with difunctional nucleophiles, resulting in fusion of five-, six-, and seven-membered heterorings to the pyrazine ring. These cyclizations occur as intramolecular nucleophilic substitution of hydrogen and give rise to aromatic systems [7–9, 12]. In the present communication we report on specific features of isoxazole ring fusion and properties of the dihydroisoxazolo[4,5-*b*]quinoxaline system. It is known that 2-quinoxalinecarbaldehyde oximes are capable of being involved in intramolecular nucleophilic substitution of hydrogen [8] or other readily departing groups [17, 18] with formation of isoxazolo[4,5-*b*]quinoxalines. We examined ring–chain transformations of *N*-alkyl-2-hydroxyiminomethylquinoxalinium salts.

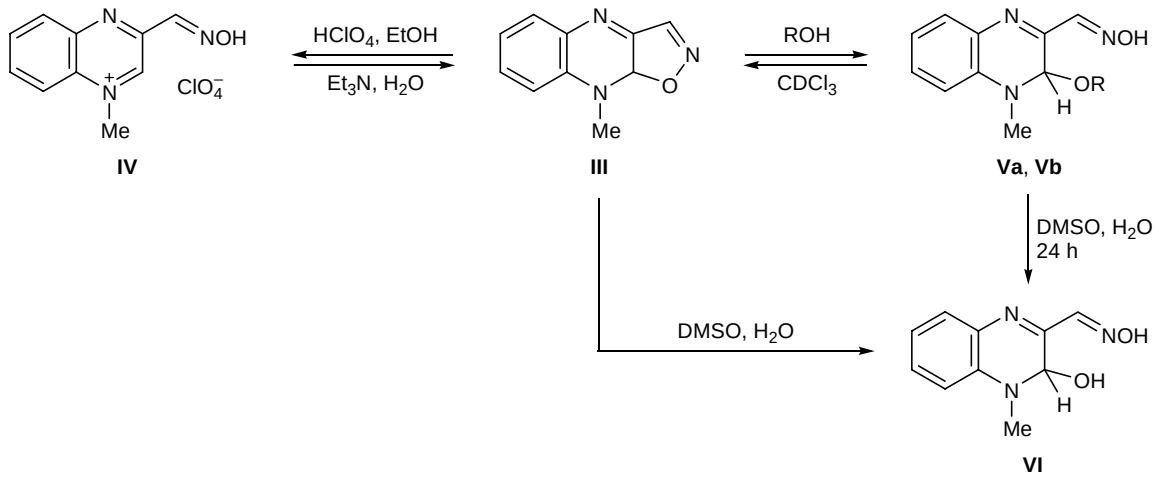
2-Quinoxalinecarbaldehyde oxime (**I**) [8] was treated with methyl iodide in DMF to give quinoxalinium salt **II** (Scheme 1). The ^{1}H NMR spectrum of salt **II** contained a three-proton signal at δ 4.73 ppm from the *N*-methyl group; its position is typical of *N*-methyl-

Scheme 1.



I **II** **III**

Scheme 2.



IV **III** **Va**, **Vb** **VI**

R = Me (**a**), Et (**b**).

quinoxalinium salts [15]. The position of the methyl group follows from the existence of spin–spin coupling between protons of the *N*-methyl group (a doublet with $^4J_{1\text{-Me},2\text{-H}}$ = 0.6 Hz) and 2-H in the pyrazine ring (a broadened signal). Addition of triethylamine to an aqueous solution of salt **II** resulted in its complete transformation into intramolecular nucleophilic addition product, 9-methyl-9,9a-dihydroisoxazolo[4,5-*b*]-quinoxaline (**III**). The ^{1}H NMR spectrum of **III** lacked OH proton signal, while the chemical shifts of the *N*-methyl protons (δ 3.34 ppm) indicated that the methyl group is attached to an uncharged nitrogen atom. Signals from protons in the benzene rings were located at positions characteristic of neutral quinoxaline derivatives. In addition, the signal from proton in the heteroring was displaced strongly upfield: it appeared at δ 6.79 ppm, i.e., at a position typical of a proton at an sp^3-carbon atom attached to oxygen [15]. It should be noted that no coupling between protons in the *N*-methyl group and proton of the 1,4-diazine ring was observed. In the ^{13}C NMR spectrum of **III**, the *N*-methyl carbon signal appeared as a quartet of doublets at δ_C 35.96 ppm, $^1J_{CH}$ = 137, $^3J_{C,9a\text{-H}}$ = 2.8 Hz, and the sp^3-hybridized carbon atom in the pyrazine ring gave a doublet of quartets at δ_C 87.30 ppm, $^1J_{CH}$ = 169.4, $^3J_{CH}$ = 3.9 Hz; also, a doublet at δ_C 147.48 ppm ($^1J_{CH}$ = 171.6 Hz) was present due to the C^3 atom in the isoxazole ring.

9-Methyl-9,9a-dihydroisoxazolo[4,5-*b*]quinoxaline (**III**) is capable of undergoing ring–chain transformations. Treatment of an alcoholic solution of compound **III** with perchloric acid induces cleavage of the C–O bond in the isoxazole ring with formation of quaternary salt **IV** (Scheme 2). Addition of triethylamine to an aqueous solution of salt **IV** restores cyclic structure **III**. Both opening and closure of the isoxazole ring are characterized by quantitative yield. Opening of the isoxazole ring also occurs in neutral medium by the action of nucleophiles. In particular, heating of compound **III** in alcohols gives the corresponding O-adducts, 3-methoxy- and 3-ethoxy-4-methyl-3,4-dihydroquinoxaline-2-carbaldehyde oximes **Va** and **Vb**. The ^{1}H NMR spectra of **Va** and **Vb**, apart from signals of protons of the alcohol residue and *N*-methyl group (δ 3.25 and 3.26 ppm, respectively), contain a signal from the oxime OH proton at δ 11.98 and 12.04 ppm and a singlet from 2-H (δ 5.62 and 5.65 ppm); the chemical shift of the latter proton is typical for such systems [14].

The stability of the isoxazole ring appreciably depends on the solvent polarity. According to the ^{1}H and ^{13}C NMR data, compound **III** in $CDCl_3$ exists exclusively in the cyclic form. After dissolution of **III** in DMSO-d_6, the intensity of signals belonging to the cyclic structure decreases, and those corresponding to covalent hydrate **VI** appear in the ^{1}H NMR spectrum of the solution. After 24 h, isoxazoloquinoxaline **III** is completely converted into compound **VI**. In the ^{1}H NMR spectrum of **VI** we observed two one-proton doublets belonging to 3-H (δ 5.65 ppm) and hydroxy proton (δ 6.16 ppm) with a coupling constant $^3J_{HH}$ of 6.5 Hz; the downfield region of the spectrum contained resonance signals from the oxime OH (δ 11.92 ppm) and CH=N protons (δ 7.80 ppm). The chemical shift of the *N*-methyl protons (δ 3.07 ppm) suggests the absence of positive charge on the nitrogen atom.

A conclusion may be drawn that dissolution of adduct **III** in DMSO containing water is accompanied by opening of the isoxazole ring with formation of quinoxalinium ion which reacts with water to give hydrate **VI**. Adducts **V** in moist DMSO are also converted into compound **VI**. The latter process occurs at a considerably lower rate due to higher polarity of compounds **V** as compared to cyclic structure **III**.

Slight heating of compounds **V** in chloroform leads to elimination of the alkoxy group with quantitative formation of isoxazoloquinoxaline **III**. The ^{1}H NMR spectra of solutions of compounds **V** in $CDCl_3$ contained only signals belonging to cyclic structure **III** and those of the corresponding alcohol with an intensity ratio of 1:1, while open-chain form **V** was not detected. The same pattern was observed in the ^{13}C NMR spectrum of compound **Va** in $CDCl_3$: the positions of carbon signals were fully identical to those in the spectrum of fused isoxazole derivative **III**; in addition, a signal belonging to free methanol was present.

Thus isoxazoloquinoxaline **III** is stable in nonpolar solvents while polar solvents stabilize more polar compounds **V**. Hydroxy derivative **VI**, which is the most polar among the examined 1,2-dihydroquinoxalines, is formed in dimethyl sulfoxide possessing a strong solvating power.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker WM-250 spectrometer at a frequency of 250 MHz and on a Bruker DRX-400 instrument at a frequency of 400 MHz. The ^{13}C NMR spectra and two-dimensional NMR experiments were run on a Bruker DRX-400 spectrometer at 100 MHz. Tetramethylsilane was used as internal reference. The melting points were not corrected. The mass spectra were obtained on a Varian MAT-311A spectrometer (accelerating voltage 3 kV, cathode emission current 300 μA, energy of ionizing electrons 70 eV) with direct sample admission into the ion source).

1-Methyl-3-hydroxyiminomethylquinoxalinium iodide (II). A solution of 0.5 g (2.89 mmol) of oxime **I** in a mixture of 2 ml of DMF and 2 ml of methyl iodide was heated for 6 h at 75°C. The mixture was cooled and diluted with diethyl ether, and the precipitate was filtered off and recrystallized from alcohol. Yield 0.6 g (71%), mp 205–206°C. ^{1}H NMR spectrum (DMSO-d_6, 250 MHz), δ, ppm: 4.76 d (3H, CH_3, $^3J_{HH}$ = 0.59 Hz), 8.05–8.31 m (2H, 6-H, 7-H), 8.33–8.75 m (2H, 5-H, 8-H), 8.38 s (1H, CH=N), 9.94 br.s (1H, 3-H), 12.71 s (1H, OH). Found, %: C 38.2; H 3.0; N 13.4. $C_{10}H_{10}IN_3O$. Calculated, %: C 38.1; N 3.2; N 13.3.

9-Methyl-9,9a-dihydroisoxazolo[4,5-*b*]quinoxaline (III). A solution of 0.5 g (1.58 mmol) of salt **II** in 15 ml of water was cooled, and a few drops of triethylamine were added. The precipitate was filtered off and washed with water. Yield 0.25 g (86%), mp 173–175°C. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz), δ, ppm: 3.34 s (1H, CH_3), 6.79 s (1H, 9a-H), 6.89–7.02 m (2H, 6-H, 7-H), 7.33 m and 7.54 m (2H, 5-H, 8-H), 7.81 s (1H, 3-H). ^{13}C NMR spectrum ($CDCl_3$, 100 MHz), δ_C, ppm: 35.96 q.d (CH_3, $^1J_{CH}$ = 137, $^3J_{C,9a\text{-}H}$ = 2.8 Hz); 87.30 d.q (C^{9a}, $^1J_{CH}$ = 169.4, $^3J_{C,3\text{-}H}$ = 3.9 Hz); 111.94 m, 119.75 m, 129.19 m, and 130.01 m (C^5–C^8); 133.28 m and 133.29 m (C^{4a}, C^{8a}); 147 d (C^3, $^1J_{CH}$ = 171.58 Hz), 147.88 m (C^{3a}). Found, %: C 64.1; H 4.8; N 24.3. $C_{10}H_9N_3O$. Calculated, %: C 64.2; N 4.8; N 22.4.

1-Methyl-3-hydroxyiminomethylquinoxalinium perchlorate (IV). Several drops of perchloric acid were added to a solution of 0.1 g (0.54 mmol) of compound **III** in 10 ml of ethanol. The mixture was cooled with ice, and the precipitate was filtered off and recrystallized from ethanol. Yield 0.14 g (91%), mp 283–285°C. ^{1}H NMR spectrum (DMSO-d_6, 250 MHz), δ, ppm: 4.77 d (1H, CH_3, $^3J_{HH}$ = 0.59 Hz), 8.22–8.32 m (2H, 6-H, 7-H), 8.46 m and 8.58 m (2H, 5-H, 8-H), 8.51 s (1H, CH=N), 9.90 d (1H, 3-H, $^3J_{HH}$ = 0.59 Hz), 12.87 s (1H, OH). Found, %: C 41.6; H 3.5; N 14.5. $C_{10}H_{10}ClN_3O_5$. Calculated, %: C 41.7; N 3.5; N 14.6.

3-Methoxy-4-methyl-3,4-dihydroquinoxaline-2-carbaldehyde oxime (Va). A mixture of 0.20 g (1.1 mmol) of compound **III** and 1 ml of methanol was heated to the boiling point. The mixture was cooled, and the precipitate was filtered off. Yield 0.18 g (72%), mp 170°C. ^{1}H NMR spectrum (DMSO-d_6, 250 MHz), δ, ppm: 3.17 s (3H, OCH_3), 3.26 s (3H, CH_3), 5.62 s (1H, 3-H), 6.77–7.12 m (2H, 6-H, 7-H), 7.18–7.48 m (2H, 5-H, 8-H), 7.87 s (1H, CH=N), 11.98 s (1H, OH). Mass spectrum, *m*/*z* (I_{rel}, %): 219 $[M]^+$ 188 (100), 170 (7), 144 (33), 129 (9), 102 (8). Found, %: C 60.2; H 6.1; N 19.2. $C_{11}H_{13}N_3O_2$. Calculated, %: C 60.3; N 6.0; N 19.2.

3-Ethoxy-4-methyl-3,4-dihydroquinoxaline-2-carbaldehyde oxime (Vb). A mixture of 0.20 g (1.1 mmol) of compound **III** and 1.5 ml of ethanol was heated to the boiling point. The mixture was cooled, and the precipitate was filtered off. Yield 0.22 g (88%), mp 190°C. ^{1}H NMR spectrum (DMSO-d_6, 250 MHz), δ, ppm: 0.99 t (3H, $OCH_2C\mathbf{H}_3$, $^3J_{HH}$ = 7.0 Hz), 3.24 s (3H, CH_3), 3.50 m (2H, $OC\mathbf{H}_2CH_3$, $^3J_{HH}$ = 7.0 Hz),

5.65 s (1H, 3-H), 6.84–7.02 m (2H, 6-H, 7-H), 7.27 m and 7.38 m (2H, 5-H, 8-H), 7.87 s (1H, CH=N), 12.04 s (1H, OH). Mass spectrum, *m*/*z* (I_{rel}, %): 233 $[M]^+$, 188 (100), 170 (6), 144 (26), 129 (7), 102 (7). Found, %: C 61.8; H 6.5; N 18.0. $C_{12}H_{15}N_3O_2$. Calculated, %: C 61.8; N 6.5; N 18.0.

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