QUINOXALINE DERIVATIVES OF SEVERAL ALKALOIDS

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New quinoxaline derivatives were prepared by reaction of 2-quinoxalinehydroximoylbromide with the alkaloids anabasine, cytisine, and salsoline.

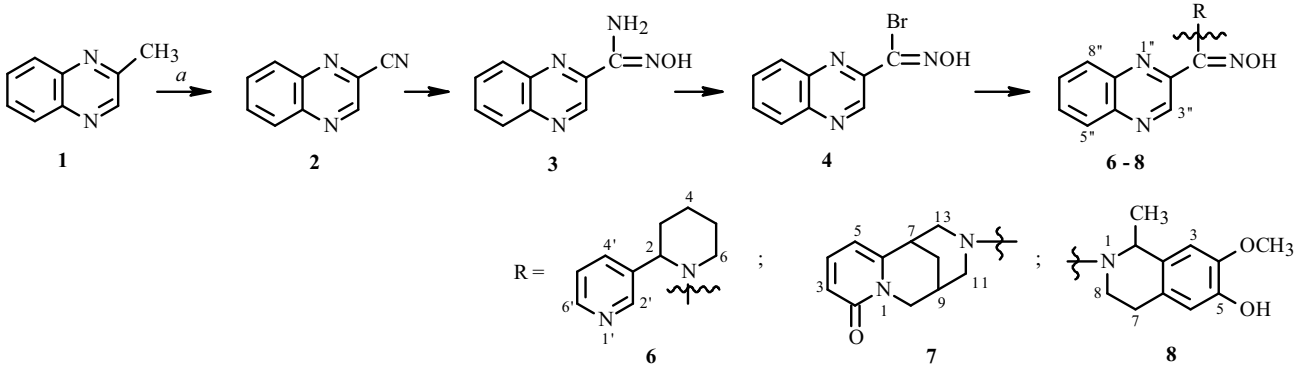
Keywords: quinoxaline, anabasine, cytisine, salsoline.

Quinoxaline derivatives, which exhibit a broad spectrum of biological activity, are some of the most synthesized of all classes of N-containing heterocyclic compounds [1]. The quinoxaline ring in nature is most often condensed into more complicated cyclic systems, the most well-known of which is riboflavin (vitamin B_2).

Two quinoxaline drugs are currently widely used in medical practice. These are quinoxidine and dioxidine, which have significant chemotherapeutic activity and are used for acute bacterial infections that are difficultly treated by other antimicrobial agents [2].

Our goal was to synthesize new quinoxaline derivatives containing fragments of several alkaloids of plant origin in their structure.

The key compound in the synthesis of the alkaloid derivatives of quinoxaline-2-hydroxamic acid was 2-quinoxalinehydroximoylbromide, which was synthesized by successive transformations of 2-methylquinoxaline (**1**). In the first step, 2-quinoxalinecarbonitrile (**2**) was prepared in 50% yield from 2-methylquinoxaline by oxidative ammonolysis by the method developed by us previously [3]. Then, amidoxime **3** was synthesized in good yield from **2** by the action of NH_2OH under mild conditions and was converted by diazotization with $NaNO_2$ in dilute HBr into hydroximoylbromide **4**.



a. t°, O_2, NH_3, H_2O, cat.

The resulting bromo derivative could easily add primary and secondary amines with elimination of HBr. In our instance, the secondary amines were the alkaloids anabasine (**5a**), cytisine (**5b**), and salsoline (**5c**). The reaction between **4** and the alkaloids at the NH center occurred smoothly under mild conditions to produce the corresponding quinoxaline alkaloid derivatives **6**-**8**.

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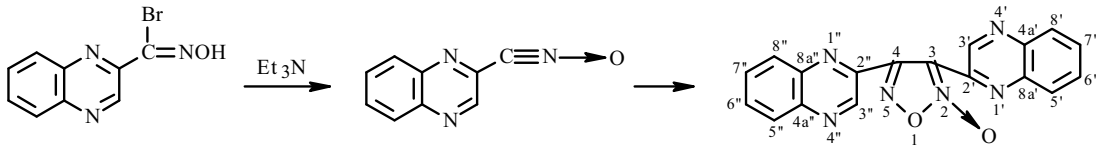
The oxime group, which is a pharmacophore and is responsible for the biological activity in compounds containing it, was retained. Also, the oxime could be further functionalized.

Pyridine and Et_3N were used at first as the HBr acceptor. However, both allowed competing reactions to occur and decrease the yields of the desired products. Therefore, an equimolar excess of the corresponding alkaloid turned out to be optimal. In the case of pyridine, the bromo derivative formed the corresponding salt; with Et_3N, intermolecular condensation that passed through an intermediate of quinoxaline nitrile *N*-oxide that dimerized to form 3,4-di-(quinoxalin-2′,2″-yl)-1,2,5-oxadiazol-2-oxide (**9**) in 88% yield occurred.



4 **9**

Many compounds containing a furoxane ring act as plant growth regulators [4]. Compound **9** can act as a synthon for further chemical transformations leading to new polyheterocyclic structures.

EXPERIMENTAL

We used 2-methylquinoxaline (**1**) (Aldrich, USA), HBr solution (48%), hydroxylamine hydrochloride, Et_3N, $NaNO_2$ (Reakhim, Russia), cytisine (**5b**), and salsoline (**5c**) (AO Khimfarm, Kazakhstan).

2-Quinoxalinecarbonitrile (**2**) was synthesized by oxidative ammonolysis of 2-methylquinoxaline by the literature method [3]. Anabasine was isolated from *Anabasis aphylla* as before [5].

The course of reactions and purity of products were monitored by TLC on Silufol UV-254 plates. Melting points were determined on a Boetius heating stage. IR spectra were measured in KBr on a Nicolet Avatar Fourier spectrophotometer. PMR spectra were recorded in DMSO-d_6 on a Bruker DRX500 spectrometer (500 MHz) relative to TMS internal standard. ^{13}C NMR spectra were recorded in DMSO-d_6 at 300 MHz. Mass spectra were measured in a Finnigan MAT INCOS50 (ionization energy 70 eV). Elemental analyses were performed on a Eurovector 3000c CNHS-analyzer and agreed with those calculated.

2-Hydroxyamidinoquinoxaline (3). An aqueous solution (10 mL) of hydroxylamine hydrochloride (0.42 g, 6.0 mmol) and $KHCO_3$ (0.60 g, 6.0 mmol) released CO_2. When the bubbling stopped, the solution was treated with an alcoholic solution (30 mL) containing 2-quinoxalinecarbonitrile (0.78 g, 5.0 mmol) and stirred. After 5 min a yellowish precipitate formed. The mixture was refluxed for 15 min and cooled. Solvent was evaporated to dryness in a rotary evaporator. The solid was washed with water and dried in air to constant weight. Crystallization from EtOH produced **4** (0.85 g, 90%), mp 223–225°C. IR spectrum (KBr, ν, cm^{-1}): 3511 (OH), 3397 (NH_2), 1645, 1546, 1493 (C=C, C=N, conj.).

2-Quinoxalinehydroximoylbromide (4). Compound **3** (0.10 g, 0.5 mmol) was dissolved with stirring in HBr solution (20 mL, 10%), cooled to –5°C, stirred vigorously, treated with small portions of aqueous $NaNO_2$ solution (2 mL, 0.06 g, 0.9 mmol) so that the temperature did not rise above 0°C, and stirred for 30 min. The resulting precipitate of quinoxaline-2-hydroximoylbromide was filtered off, washed with distilled water, and dried in air to afford quinoxaline-2-hydroximoylbromide (0.105 g, 79%), mp 179°C (dec.). IR spectrum (KBr, ν, cm^{-1}): 3124 (OH), 1650 (C=N), 933 (N–O), 599 (C–Br).

General Method for Synthesizing Quinoxaline Derivatives of Alkaloids (6-8). A solution of 2-quinoxaline-hydroximoylbromide (0.3 mmol) in EtOH (50 mL) was stirred vigorously, treated with the appropriate alkaloid (0.6 mmol) dissolved in EtOH (10 mL) (for salsoline, 20 mL hot EtOH:$CHCl_3$, 1:1). The mixture turned yellow, was stirred for 1 h, and then left for 24 h. Solvent was evaporated in a rotary evaporator. The solid was washed with distilled water, dried in air to constant weight, and separated by column chromatography over silica gel with elution by hexane:$CHCl_3$:EtOH (3:3:1).

1-Anabasinyl-2″-quinoxalinaldoxime (6). Yield 78%, mp 83–85°C (dec.). IR spectrum (KBr, ν, cm^{-1}): 3154 (OH), 1612 (C=N).

PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.61–1.86 (6H, H-3,4,5), 3.22 (1H, t, J_1 = 6.6, J_2 = 5.8, J_3 = 12.4, H-6), 3.63 (1H, d, J = 12.2, H-6), 4.68 (1H, dd, J_1 = 3.2, J_2 = 3.4, J_3 = 9.2, H-2), 7.09 (1H, dd, J_1 = 4.7, J_2 = 4.7,

J_3 = 7.9, H-5′), 7.45 (1H, dd, J_1 = 3.86, J_2 = 3.8, J_2 = 3.8, J_3 = 8.0, H-4′), 7.83 (1H, td, J_1 = 1.5, J_2 = 2.7, J_3 = 1.5, J_4 = 7.6, J_5 = 7.6, H-8″), 7.88 (1H, td, J_1 = 1.5, J_2 = 2.7, J_3 = 1.6, J_4 = 7.6, J_5 = 7.6, H-7″), 7.99 (1H, dd, J_1 = 1.4, J_2 = 1.4, J_3 = 8.2, H-5″), 8.09 (1H, d, J = 2.1, H-2′), 8.13 (1H, dd, J_1 = 1.4, J_2 = 1.3, J_3 = 8.2, H-6″), 8.22 (1H, dd, J_1 = 1.6, J_2 = 1.6, J_3 = 4.7, H-6′), 8.50 (1H, s, H-3″), 11.27 (1H, s, NOH).

^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, δ, ppm): 25.14 (t, C-4), 26.64 (t, C-5), 36.57 (t, C-3), 50.57 (t, C-6), 60.95 (d, C-2), 124.09 (d, C-5′), 129.12 (d, C-6″), 130.67 (d, C-7″), 131.85 (d, C-8″), 131.79 (d, C-5″), 137.01 (d, C-4′), 141.50 (s, C-3′), 142.09 (s, C-4a″), 142.15 (s, C-8a″), 145.68 (d, C-3″), 148.21 (d, C-6′), 148.81 (d, C-2′), 149.81 (s, C-2″), 154.21 (s, C-9″).

12-Cytisinyl-2″-quinoxalinaldoxime (7). Yield 81%, mp 103–105°C (dec.). IR spectrum (KBr, ν, cm^{-1}): 3357 (OH-oxime), 1647 (C=N), 1640 (C=O).

PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.92 (2H, s, H-8), 2.40 (1H, s, H-9), 2.96 (1H, d, J = 11.7, H-11), 3.04 (1H, d, J = 11.7, H-13), 3.06 (1H, s, H-7), 3.28–3.32 (1H, s, H-11), 3.46 (1H, d, J = 12.4, H-13), 3.7 (1H, dd, J_1 = 6.5, J_2 = 6.4, J_3 = 15.3, H-10), 4.04 (1H, d, J = 15.3, H-10), 6.02 (1H, dd, J_1 = 1.2, J_2 = 1.2, J_3 = 6.9, H-5), 6.35 (1H, dd, J_1 = 1.3, J_2 = 1.3, J_3 = 9.0, H-3), 7.35 (1H, dd, J_1 = 6.8, J_2 = 6.8, J_3 = 9.0, H-4), 7.87–7.93 (2H, m, H-7″,8″), 8.01-8.04 (1H, m, H-5″), 8.09–8.12 (1H, m, H-6″), 8.59 (1H, s, H-3″), 9.67 (1H, s, NOH).

Mass spectrum (70 eV, *m*/*z*, I_{rel}, %): 361.4 $[M]^+$, 190 (16.3), 189 (100.0), 185 (22.2), 172 (34.3), 160 (53.4), 157 (15.8), 156 (47.5), 155 (26.6), 148 (24.4), 147 (34.8), 146 (99.9), 143 (16.4), 134 (22.1), 130 (29.0), 129 (69.2), 118 (22.1), 117 (31.4), 104 (16.5), 103 (35.9), 102 (49.9), 77 (21.4), 76 (28.0), 68 (22.3), 65 (14.5), 51 (14.8), 44 (50.5), 43 (23.1), 42 (44.9), 41 (48.9), 39 (33.8).

1-Salsolinyl-2″-quinoxalinaldoxime (8). Yield 75%, mp 142–145°C (dec.). IR spectrum (KBr, ν, cm^{-1}): 3281 (OH-oxime), 1605 (C=N), 1368 (CH_3), 1218 (OH-phenol).

PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.36 (3H, d, J = 6.6, CH_3), 1.47 (1H, d, J = 6.6, H-2), 2.81–2.89 (1H, m, H-7), 3.19 (1H, td, J_1 = 3.7, J_2 = 3.4, J_3 = 4.0, J_4 = 12.2, J_5 = 12.8, H-7), 3.52 (1H, dd, J_1 = 4.8, J_2 = 4.8, J_3 = 8.4, H-8), 4.43 (1H, d, J = 6.8, H-8), 6.50 (1H, s, H-3), 6.59 (1H, s, H-6), 7.90–7.94 (2H, m, H-7″,8″), 8.15 (1H, t, J_1 = 2.3, J_2 = 3.0, J_3 = 5.3, H-5″), 8.16 (1H, t, J_1 = 3.0, J_2 = 2.2, J_3 = 5.2, H-6″), 8.73 (1H, s, Ar–OH), 8.99 (1H, s, H-3″), 9.43 (1H, s, NOH).

3,4-Di-(quinoxalin-2′,2″-yl)-1,2,5-oxadiazol-2-*N*-oxide (9). Compound **4** (0.25 g, 1.0 mmol) in EtOH (50 mL) was stirred vigorously, treated dropwise with freshly distilled Et_3N (2 mL), and left overnight at room temperature. Solvent was removed in a rotary evaporator. The solid was washed with distilled water, dried in air to constant weight, and purified by column chromatography over silica gel with elution by hexane:EtOAc (3:1) to isolate **9** (0.30 g, 88%), mp 167–168°C. IR spectrum (KBr, ν, cm^{-1}): 1631 (C=N), 1025 (C=N–O).

PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 7.75 (1H, dd, J_1 = 1.2, J_2 = 1.2, J_3 = 8.4, H-5′), 7.82 (1H, dd, J_1 = 1.3, J_2 = 1.3, J_3 = 8.4, H-5″), 7.88–7.91 (1H, m, H-8′), 7.91–7.94 (1H, m, H-8″), 7.97–8.00 (1H, dt, J_1 = 2.6, J_2 = 2.5, J_3 = 7.1, H-7″), 7.99–8.02 (1H, dt, J_1 = 2.3, J_2 = 2.5, J_3 = 7.0, H-7′), 8.21 (1H, dd, J_1 = 1.1, J_2 = 1.1, J_3 = 4.9, H-6″), 8.23 (1H, dd, J_1 = 1.1, J_2 = 1.1, J_3 = 4.9, H-6′), 9.44 (1H, s, H-3″), 9.52 (1H, s, H-3′).

^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, δ, ppm): 113.11 (s, C-4), 129.05 (d, C-7″), 129.174 (d, C-7′, C-6′), 129.22 (d, C-6″), 131.50 (d, C-8″), 131.67 (d, C-8′), 132.22 (d, C-5″, C-5′), 139.62 (s, C-4a″), 140.45 (s, C-4a′), 140.75 (s, C-8a″), 141.50 (s, C-8a′), 141.67 (s, C-2″), 142.09 (s, C-2′), 144.43 (d, C-3″), 145.24 (d, C-3′) 154.39 (s, C-3).

Mass spectrum (70 eV, *m*/*z*, I_{rel}, %): 342.3 $[M]^+$, 283 (17.1), 282 (85.2), 180 (100), 154 (17.2), 129 (36.7), 103 (49.5), 102 (55.4), 76 (75.1), 75 (18.9), 50 (22.1).

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