Chemical properties of pyrimidoquinoxaline 6-oxides

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Ma. Beatriz García, Liliana R. Orelli and Isabel A. Perillo*

Department of Organic Chemistry. Faculty of Pharmacy and Biochemistry, University of Buenos Aires, Junín 956 (1113), Buenos Aires, Argentina. E-mail: iperillo@ffyb.uba.ar

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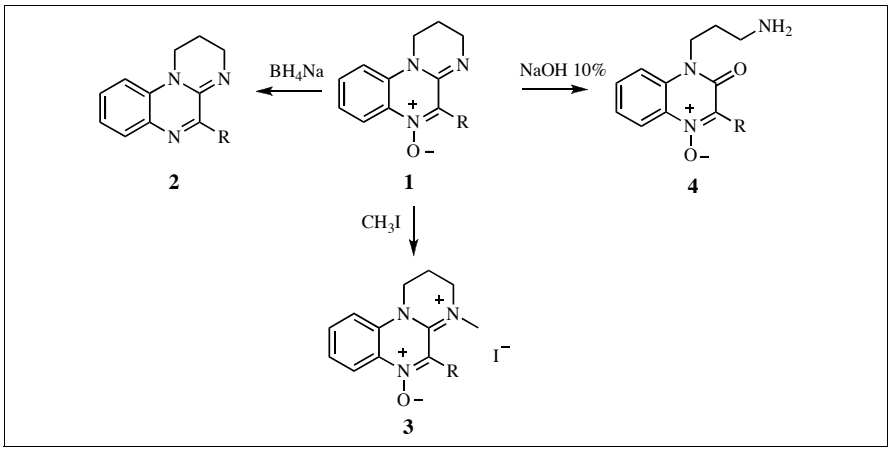

The reactivity of some representative 5-arylpyrimidoquinoxaline 6-oxides **1** was investigated. Reduction with sodium borohydride afforded the corresponding *N*-deoxy compounds **2**. Reaction with methyl iodide in excess led selectively to *N*-methyl derivatives **3**. The preference for *N vs. O*-alkylation is analyzed considering electronic effects. Alkaline hydrolysis of compounds **1** involved initial nucleophilic attack to the amidine carbon (C4a), and subsequent regioselective ring opening leading to 4-(3-aminopropyl)-2-aryl-quinoxaline-3-one 1-oxides **4**. The regioselectivity observed in alkaline hydrolysis is also discussed.

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Introduction.

Amidinoquinoxaline *N*-oxides have received attention due to their pharmacological properties, acting as antibacterials, antiamoebics and antineoplastics [1]. The first reported synthetic procedure for 5-aryl-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinoxaline 6-oxides involves a displacement-cyclization reaction of 2-benzyl-1,4,5,6-tetrahydropyrimidines with 2-nitrohalobenzenes, and leads in general to poor yields (30% or less) of the desired heterocycles [1a,b]. More recently, we reported an alternative synthetic procedure by ring closure of *N*-acyl-*N´*-(2-nitrophenyl)-1,3-propanediamines with ethyl polyphosphate (PPE) followed by spontaneous heterocyclization [2]. This method allowed for the preparation of 5-aryl derivatives with high yields and was extended to the corresponding 5-alkyl (and aralkyl) pyrimidoquinoxalines as well as to the homologous 6-aryldiazepinoquinoxalines, a novel heterocyclic nucleus. To our knowledge, the reactivity of pyrimidoquinoxaline *N*-oxides has not been studied yet. The chemical features of such system are interesting due to its polyfunctionality, resulting from the presence of two heterocyclic moieties: pyrimidine as tetrahydro derivative and quinoxaline *N*-oxide. The chemical behaviour of the heterocycles under study could thus result alternatively from the reactivity of each individual component or from the interaction of both. Due to the biological activity of the parent heterocycles, the investigation of new structurally related compounds is also interesting. Among them, derivatives bearing the quinoxalinone core are of particular interest as an important pharmacophore in numerous biologically active compounds [3].

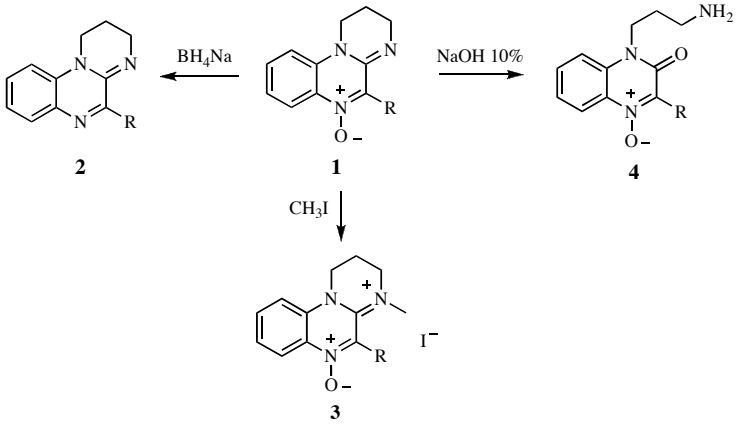
In the present paper we have investigated the reduction, methylation and alkaline hydrolysis of some representative 5-arylpyrimidoquinoxaline 6-oxides **1** (Scheme 1).

Results and Discussion.

Reactions of pyrimidoquinoxaline 6-oxides **1a-d** are summarized in Scheme 1. Treatment of compounds **1** with sodium borohydride led to pyrimidoquinoxalines **2** as the main products. However, variable amounts of colateral products are observed probably resulting from overreduction. This behaviour was also reported by Haddadin in the deoxygenation of quinoxaline *N,N´*-dioxides with sodium borohydride [4].

Treatment of compounds **1** with methyl iodide in excess led exclusively to the *N*-alkyl derivatives **3**. Although steric effects cannot be ruled out, the observed *N vs. O* selectivity can be explained considering the resonance stabilization of the resulting amidinium system and the electron releasing effect of the oxygen atom (Scheme 2,

Scheme 1



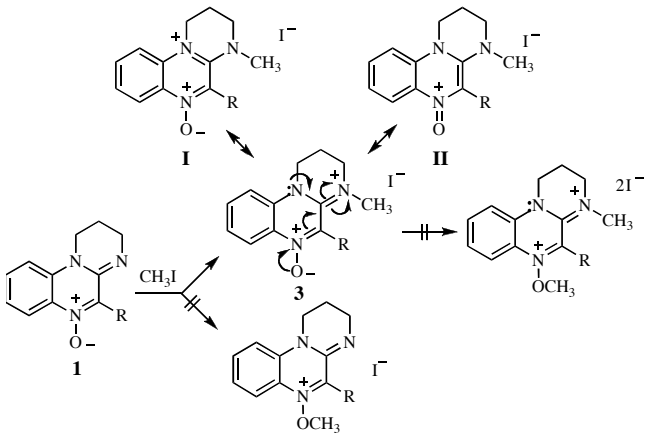
Compd.1-4	R
a	C_6H_5
b	4-ClC_6H_4
c	4-$CH_3OC_6H_4$
d	4-$NO_2C_6H_4$

structures I and II, respectively). The last effect can also account for the absence of *N,O*-dialkylation products.

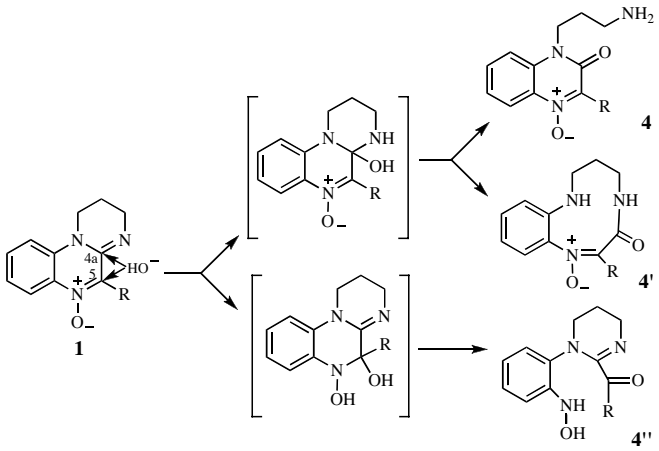
Treatment of compounds **1** with an excess 10% aqueous sodium hydroxide solution led to 4-(3-aminopropyl)-2-arylquinoxaline-3-one 1-oxides **4**.

According to previous data regarding cyclic amidines [5] and quinoxalines [6], the existence of two electrophilic sites can be anticipated in compounds **1**, namely C4a and C5. Accepting that alkaline hydrolysis of cyclic amidines [5b] and heterocyclic *N*-oxides [6] involves formation and cleavage of carbinolamines as reaction intermediates, a total of three products could, in principle, be expected (Scheme 3). The higher stabilization of isomer **4** could in part account for the observed regioselectivity. On the other hand, isolation of compounds **4** as the sole reaction products would result from initial hydroxyde attack on C4a and subsequent regioselective cleavage of C4a – N4 bond in the reaction intermediate. The higher electrophilicity of C4a if compared to C5 would be the consequence of electron delocalization involving both the *N*-oxide moiety and the 5-aryl substituent. The observed regioselective cleavage of the reaction intermediate can be rationalized considering the different basicities of the two potential leaving groups. It is accepted that, due to their strong basicity, nitrogen anions (RR´N⁻) are poor nucleofuges and require proton transfer previous or simultaneous to their departure [7]. C4a – N4 cleavage would then be the consequence of a thermodynamically

Scheme 2



Scheme 3



favored proton transfer from the solvent to the most basic nitrogen (N4), which becomes the best leaving group [8]. This behavior is opposite to that previously observed in the alkaline hydrolysis of *N*-aryltetrahydropyrimidines [5b], in which the less basic amino group is liberated. In the case of tetrahydropyrimidines, the observed regioselectivity was explained on the basis of stereoelectronic effects which might not be operating for pyrimidoquinoxaline 6-oxides due to geometry restrictions.

EXPERIMENTAL

Melting points were taken on a Büchi capillary apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker MSL 300 MHz spectrometer. Deuteriochloroform or methanol-d_4 was used as the solvents, and the standard concentration of the samples was 20 mg/mL. Chemical shifts are reported in ppm (δ) relative to TMS as an internal standard. Deuterium oxide was employed to confirm exchangeable protons (ex). Splitting multiplicities are reported as singlet (s), broad signal (bs), doublet (d), double doublet (dd), triplet (t), double triplet (dt), quartet (q), pentet (p) and multiplet (m). Electron impact mass spectra were recorded with a GC-MS Shimadzu QP-1000 spectrometer operating at 20 eV. TLC analyses were carried out on Silica gel 60 F_{254}. Column chromatographies were performed on Silica gel 60, with typically 30-50 g of stationary phase per gram substance. Reagents, solvents and starting materials were purchased from standard sources and purified according to literature procedures.

5-Aryl-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinoxaline 6-oxides **1a-d** were synthesized as previously reported [2].

5-Aryl-2,3-dihydro-1*H*-pyrimido[1,2-a]quinoxalines (**2**).

General Procedure.

A solution of the corresponding pyrimidoquinoxaline 6-oxide 1 (1 mmol) in dry ethanol (10 mL) was treated with sodium borohydride (0.151 g, 4 mmol) and refluxed for 30 minutes. The solvent was then evaporated *in vacuo* and the residue treated with water (10 mL) and extracted with methylene chloride (2 X 20 mL). The organic layers were combined, washed with water (5 mL), dried with sodium sulfate and filtered. The solvent was then evaporated *in vacuo*, affording compounds 2, which were purified by flash chromatography (chloroform:methanol 10:0 to 8:2).

5-Phenyl-2,3-dihydro-1*H*-pyrimido[1,2-a]quinoxaline (**2a**) [9].

This compound was obtained as an oil (62%). ^{1}H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 7.94-7.98 (m, 2 H, aromatics), 7.67 (dd, J_1 = 7.9 Hz, J_2 = 1.5 Hz, 1 H, aromatic), 7.33-7.43 (m, 4 H, aromatics), 7.11 (dt, J_1 = 7.6 Hz, J_2 = 1.0 Hz, 1 H, aromatic), 7.00 (d, J = 8.3 Hz, 1 H, aromatic), 3.87 (t, J = 6.4 Hz, 2 H, CH_2N), 3.62 (t, J = 5.5 Hz, 2 H, CH_2N), 2.03-2.11 (m, 2 H, CH_2-*CH_2*-CH_2) ppm.

5-(4-Chlorophenyl)-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinoxaline (**2b**).

This compound was obtained as an oil (56%). ^{1}H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 7.98 (d, J = 8.2 Hz, 2 H, aromatics), 7.65 (dd, J_1 = 7.9 Hz, J_2 = 1.5 Hz, 1 H, aromatic), 7.30-7.40 (m, 3 H, aromatics), 7.11 (dt, J_1 = 7.6 Hz, J_2 = 1.1 Hz, 1 H, aromatic), 6.99 (dd, J_1 = 8.2 Hz, J_2 = 1.1 Hz, 1 H, aromatic), 3.86 (t, J = 6.4 Hz, 2 H, CH_2N), 3.61 (t, J = 5.5 Hz, 2 H, CH_2N), 2.02-2.10 (m, 2 H, CH_2-*CH_2*-CH_2) ppm. MS: *m/z*= 295 (M^{+}).

Anal. Calcd. for $C_{17}H_{14}ClN_3$: C, 69.03; H, 4.77; N, 14.21. Found: C, 69.18; H, 4.75; N, 14.24.

5-(4-Methoxyphenyl)-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinoxaline (**2c**).

This compound was obtained as an oil (55%). ^{1}H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 8.00 (dd, J_1 = 8.2 Hz, J_2 = 2.0 Hz, 2 H, aromatics), 7.65 (dd, J_1 = 7.9 Hz, J_2 = 1.4 Hz, 1 H, aromatic), 7.33 (dt, J_1 = 7.9 Hz, J_2 = 1.4 Hz, 1 H, aromatic), 7.09 (t, J = 7.6 Hz, 1 H, aromatic), 6.98 (d, J_1 = 7.6 Hz, 1 H, aromatic), 6.94 (dd, J_1 = 8.2 Hz, J_2 = 2.0 Hz, 2 H, aromatic), 3.86 (t, J = 6.4 Hz, 2 H, CH_2N), 3.84 (s, 3 H, C*H_3*O), 3.62 (t, J = 5.5 Hz, 2 H, CH_2N), 2.02-2.12 (m, 2 H, CH_2-*CH_2*-CH_2) ppm. MS: *m/z*= 291 (M^{+}).

Anal. Calcd. for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.43; H, 5.86; N, 14.37.

5-(4-Nitrophenyl)-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinoxaline (**2d**).

This compound was obtained in 64% yield. M.p.: 124-126ºC (ethanol). ^{1}H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 8.18-8.28 (m, 4 H, aromatics), 7.67 (dd, J_1 = 7.9 Hz, J_2 = 1.3 Hz, 1 H, aromatic), 7.38-7.43 (m, 1 H, aromatic), 7.14 (dt, J_1 = 7.6 Hz, J_2 = 1.3 Hz, 1 H, aromatic), 7.02 (d, J_1 = 8.3 Hz, 1 H, aromatic), 3.89 (t, J = 6.4 Hz, 2 H, CH_2N), 3.62 (t, J = 5.5 Hz, 2 H, CH_2N), 2.04-2.09 (m, 2 H, CH_2-*CH_2*-CH_2) ppm. MS: *m/z*= 306 (M^{+}).

Anal. Calcd. for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.82; H, 4.59; N, 18.31.

5-Aryl-4-methyl-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinoxalinium iodide 6-oxides (**3**). General Procedure.

A mixture of the corresponding 5-aryl-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinoxaline 6-oxide 1 (1 mmol) and methyl iodide (0.426 g, 3 mmol) in anhydrous methylene chloride (10 mL) was refluxed protected from moisture. The reaction was monitored by TLC (chloroform:methanol 9:1) until disappearance of the starting material. The solution was evaporated *in vacuo* and the residue purified by recrystalization to yield compounds **3a-d**.

5-Phenyl-4-methyl-2,3-dihydro-1*H*-pyrimido[1,2-*a*]quinoxalinium iodide 6-oxide (**3a**).

This compound was obtained in 60% yield. M.p.: 253-254ºC (isopropanol). ^{1}H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 8.54 (dd, J = 8.2 Hz, 1 H, aromatic), 7.68-7.78 (m, 3 H, aromatics), 7.38-7.57 (m, 5 H, aromatics), 4.79 (t, J = 6.4 Hz, 2 H, CH_2N), 3.92 (t, J = 5.5 Hz, 2 H, CH_2N), 2.78 (s, 3 H, CH_3N), 2.60-2.78 (m, 2 H, CH_2-*CH_2*-CH_2) ppm. MS: *m/z*= 277 (M^{+}-ICH_3) [10].

Anal. Calcd. for $C_{18}H_{18}IN_3O$: C, 51.57; H, 4.33; N, 10.02. Found: C, 51.75; H, 4.32; N, 9.99.

5-(4-Chlorophenyl)-4-methyl-2,3-dihydro-1*H*-pyrimido[1,2-*a*]-quinoxalinium iodide 6-oxide (**3b**).

This compound was obtained in 65% yield. M.p.: 238-239ºC (isopropanol). ^{1}H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 8.48 (d, J = 7.2 Hz, 1 H, aromatic), 7.76-7.83 (m, 2 H, aromatics), 7.61-7.66 (m, 3 H, aromatics), 7.56 (dd, J_1 = 6.7 Hz, J_2 = 2.3 Hz, 2 H,

aromatics), 4.74 (t, J = 6.4 Hz, 2 H, CH_2N), 3.78 (t, J = 5.5 Hz, 2 H, CH_2N), 2.82 (s, 3 H, CH_3N), 2.59-2.63 (m, 2 H, CH_2-*CH_2*-CH_2) ppm. MS: *m/z*= 311 (M^{+}-ICH_3).

Anal. Calcd. for $C_{18}H_{17}ClIN_3O$: C, 47.65; H, 3.78; N, 9.26. Found: C, 47.59; H, 3.79; N, 9.23.

5-(4-Methoxyphenyl)-4-methyl-2,3-dihydro-1*H*-pyrimido[1,2-*a*]-quinoxalinium iodide 6-oxide (**3c**).

This compound was obtained in 68% yield. M.p.: 242-244ºC (isopropanol). ^{1}H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 8.44 (d, J = 8.1 Hz, 1 H, aromatic), 7.86 (d, J = 7.6 Hz, 2 H, aromatics), 7.56-7.65 (m, 3 H, aromatics), 7.03 (d, J = 7.6 Hz, 2 H, aromatic), 4.72 (t, J = 5.5 Hz, 2 H, CH_2N), 3.80-3.91 (m, 5 H, CH_3O-CH_2N), 2.78 (s, 3 H, CH_3N), 2.58-2.64 (m, 2 H, CH_2-*CH_2*-CH_2) ppm. MS: *m/z*= 307 (M^{+}-ICH_3).

Anal. Calcd. for $C_{19}H_{20}IN_3O_2$: C, 50.79; H, 4.49; N, 9.35. Found: C, 50.85; H, 4.50; N, 9.32.

5-(4-Nitrophenyl)-4-methyl-2,3-dihydro-1*H*-pyrimido[1,2-*a*]-quinoxalinium iodide 6-oxide (**3d**).

This compound was obtained in 63% yield. M.p.: 240-242ºC (isopropanol). ^{1}H NMR (300 MHz, CD_3OD, 25ºC): δ = 8.56 (d, J = 8.2, 1 H, aromatic), 8.52 (dd, J_1 = 7.9 Hz, J_2 = 2.2 Hz, 2 H, aromatic), 8.00-8.09 (m, 2 H, aromatics), 7.97 (dd, J_1 = 7.9 Hz, J_2 = 2.2 Hz, 2 H, aromatics), 7.77 (d, J_1 = 8.3 Hz, 1 H, aromatic), 4.58 (t, J = 6.4 Hz, 2 H, CH_2N), 3.56 (t, J = 4.4 Hz, 2 H, CH_2N), 2.73 (s, 3 H, CH_3N), 2.52-2.56 (m, 2 H, CH_2-*CH_2*-CH_2) ppm. MS: *m/z*= 322 (M^{+}-ICH_3).

Anal. Calcd. for $C_{18}H_{17}IN_4O_3$: C, 46.57; H, 3.69; N, 12.07. Found: C, 43.47; H, 3.68; N, 12.10.

4-(3-Aminopropyl)-2-arylquinoxaline-3-one 1-oxides (**4**).

General Procedure.

The corresponding pyrimidoquinoxaline 6-oxide **1** (1 mmol) was dissolved in a minimum volume of methanol and diluted with water (final volume: 10 mL). The solution was treated with aqueous 10% sodium hydroxide (10 mL), and refluxed until disappearance of the strarting material, as disclosed by TLC (chloroform:methanol 8:2). The reaction mixture was then extracted with methylene chloride (2 X 20 mL). The organic phases were pooled, washed with water, dried over sodium sulfate and filtered. The solvent was then eliminated *in vacuo* at rt. Compounds **4** were purified by flash chromatography employing mixtures of methylene chloride: isopropylamine 100:0 to 20:1).

4-(3-Aminopropyl)- 2-phenylquinoxaline-3-one 1-oxide (**4a**).

This compound was obtained as an oil (89%). ^{1}H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 8.52 (d, J = 8.3 Hz, 1 H, aromatic), 7.53-7.76 (m, 3 H, aromatics), 7.31-7.50 (m, 5 H, aromatics), 4.40 (t, J = 6.6 Hz, 2 H, CH_2N), 2.83 (t, J = 6.4 Hz, 2 H, CH_2N), 2.5 (b.s., ex., 2 H, NH_2), 1.94-2.01 (m, 2 H, CH_2-*CH_2*-CH_2) ppm. MS: *m/z*= 295 (M^{+}).

Anal. Calcd. for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 68.95; H, 5.78; N, 14.27.

4-(3-Aminopropyl)-2-(4-chlorophenyl)quinoxaline-3-one 1-oxide (**4b**).

This compound was obtained as an oil (75%). ^{1}H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 8.53 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1 H, aromatic), 7.79 (dd, J_1 = 8.7 Hz, J_2 = 2.3 Hz, 2 H, aromatics), 7.70 (dt, J_1 = 7.0 Hz, J_2 = 1.5 Hz, 1 H, aromatic), 7.55 (dd, J_1 = 7.0 Hz, J_2 = 2.8 Hz, 1 H, aromatic), 7.38-7.49 (m, 3 H, aromatics), 4.42 (t, J = 7.1 Hz, 2 H, CH_2N), 2.83 (t, J = 6.4 Hz, 2 H, CH_2N), 1.90-1.99 (m, 2 H, CH_2-*CH_2*-CH_2), 1.6 (b.s., ex., 2 H, NH_2) ppm. MS: *m/z*= 329 (M^{+}).

Anal. Calcd. for $C_{17}H_{16}ClN_3O_2$: C, 61.91; H, 4.89; N, 12.74. Found: C, 62.01; H, 4.91; N, 12.69.

4-(3-Aminopropyl)-2-(4-methoxyphenyl)quinoxaline-3-one 1-oxide (**4c**).

This compound was obtained as an oil (81%). ^{1}H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 8.55 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1 H, aromatic), 7.85 (dd, J_1 = 8.7 Hz, J_2 = 1.0 Hz, 2 H, aromatics), 7.66-7.74 (m, 1 H, aromatic), 7.53 (d, J = 7.9, 1 H, aromatic), 7.40 (dt, J_1 = 7.4 Hz, J_2 = 1.0 Hz, 1 H, aromatic), 7.01 (d, J = 8.7 Hz, 2 H, aromatics), 4.43 (t, J = 7.1 Hz, 2 H, CH_2N), 3.87 (s, 3 H, CH_3O), 2.83 (t, J = 6.4 Hz, 2 H, CH_2N), 1.92-1.97 (m, 2 H, CH_2-*CH_2*-CH_2), 1.6 (b.s., ex., 2 H, NH_2) ppm. MS: *m/z*= 325 (M^{+}).

Anal. Calcd. for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.89; N, 12.91. Found: C, 66.24; H, 5.86; N, 12.95.

4-(3-Aminopropyl)-2-(4-nitrophenyl)quinoxaline-3-one 1-oxide (**4d**).

This compound was obtained in 60% yield. M.p.: 149-151ºC (ethanol). ^{1}H NMR (300 MHz, $CDCl_3$, 25ºC): δ = 8.52 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1 H, aromatic), 8.34 (dd, J_1 = 8.9 Hz, J_2 = 2.0 Hz, 2 H, aromatics), 8.02 (dd, J_1 = 8.9 Hz, J_2 = 2.0 Hz, 2 H, aromatics), 7.75 (dt, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1 H, aromatic), 7.61 (dd, J_1 = 8.6 Hz, J_2 = 1.0 Hz, 1 H, aromatic), 7.44 (dt, J_1 = 7.2 Hz, J_2 = 1.0 Hz, 1 H, aromatic), 4.45 (t, J = 7.2 Hz, 2 H, CH_2N), 2.85 (t, J = 6.4 Hz, 2 H, CH_2N), 1.87-1.98 (m, 2 H, CH_2-*CH_2*-CH_2), 1.5 (b.s., ex., 2 H, NH_2) ppm. MS: *m/z*= 340 (M^{+}).

Anal. Calcd. for $C_{17}H_{16}N_4O_4$: C, 59.99; H, 4.74; N, 16.46. Found: C, 60.15; H, 4.76; N, 16.50.

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