Unexpected regioselectivity in nitration of 3-aminoquinoxalin-2(1*H*)-ones †

Csaba Gönczi, Éva Csikós, Benjamin Podányi, Tamás Nusser, Zsolt Böcskei and István Hermecz

Chinoin Pharmaceutical and Chemical Works Ltd., Research Centre, PO Box 110, H-1325 Budapest, Hungary

Received (in Cambridge, UK) 22nd December 1999, Accepted 8th March 2000

Regioselective nitration takes place at position 8 of 6,7-disubstituted-3-aminoquinoxalin-2(1*H*)-ones **3a**–**d**. The orientation is not disturbed by the electronic or steric effects of the substituents on the aromatic ring and on the amino group. The isomeric 5-nitro derivative **9** is formed only in a roundabout way from 3,6,7-trichloroquinoxalin-2(1*H*)-one **7**. When position 8 is occupied, the 5-nitro derivatives appear only as a minor component. The isomers were identified by NMR techniques. Theoretical calculations (AM1, Hartree–Fock, B3LYP) and NMR investigations confirmed the presumed nitronium cation attack on the monoprotonated species **3ap**.

Introduction

An increasing number of publications have appeared in the field of central nervous system (CNS) research, and, in particular, the *N*-methyl-D-aspartate receptor glycine site antagonists have been investigated in detail. Of the quinoxaline derivatives, quinoxaline-2,3(1*H*,4*H*)-diones proved to have excellent activity.[1] However enhanced activity was observed[1b] when a nitro group was introduced into the quinoxaline molecule.

Our research has suggested that a more favourable therapeutic index can be expected in the series of 3-aminoquinoxalin-2(1*H*)-one derivatives,[2] so we decided to prepare its nitro derivatives. A literature search indicated that the area of electrophilic substitution concerned is little studied.

The orientation of aromatic electrophilic substitution has been investigated for several heterocyclic compounds. The site preference was explained by the energy differences between the σ-complexes.[3]

Some preliminary information was also available concerning the substituent directing effects of substituted quinoxalines. Quinoxalin-2(1*H*)-one in mixed acid yields the 6-nitro derivative, presuming attack to be on the diprotonated species,[4] and 2-aminoquinoxaline similarly gives the 6-nitro derivative.[5] Therefore one can only guess the isomer ratio in the nitration reaction of 3-aminoquinoxalin-2(1*H*)-one. We considered it a challenge to find out not only the place of attack, but also the reasons as well.

Results and discussion

In the nitration of 6,7-dichloro-3-aminoquinoxalin-2(1*H*)-one we expected to obtain the 5- and 8-nitro isomers in equal amounts because, considering the substituent effects, there is only a slight difference between the chemical environments of C-5 and C-8. In contrast, nitration of the protected amino derivative 3-acetylamino-6,7-dichloroquinoxalin-2(1*H*)-one **1** furnished the 8-nitro derivative **2** only, so that hydrolysis led to **4a**. The direct nitration of **3a** with potassium nitrate in concentrated sulfuric acid or with nitronium tetrafluoroborate in sulfolane ‡ gave exclusively **4a**.

Evidence concerning the structure of **4a** was obtained by NMR spectroscopy. We reported[6] earlier that the ^{13}C chemical shifts of C-5 and C-8 in **3a** are 124.6 and 115.6 ppm, respectively. The chemical shift of the only aromatic CH carbon in **4a**, easily identified from the DEPT[7] spectrum, was 126.5 ppm, confirming the substitution at C-8 in the reaction. ^{15}N NMR investigations provided further evidence: the signals at 88.7, 144.0, 226.4 and 363.8 ppm were assigned to the amine, the amide, the imine and the nitro moieties, respectively. The only aromatic hydrogen in the compound gave a crosspeak with the imine nitrogen at 226.4 ppm in the ^{1}H–^{15}N HMBC spectrum.

This regioselectivity of the nitration was unexpected and further efforts were made to prepare the other nitro isomer by another synthetic pathway. As we expected, **4a** was again the sole product of the ring closure reaction with oxalomonoimidic acid diethyl ester, as a consequence of the directing effects.[6,8] of the 4,5-dichloro-3-nitro-substituents of the 1,2-phenylenediamine[9] **5** (Scheme 1).

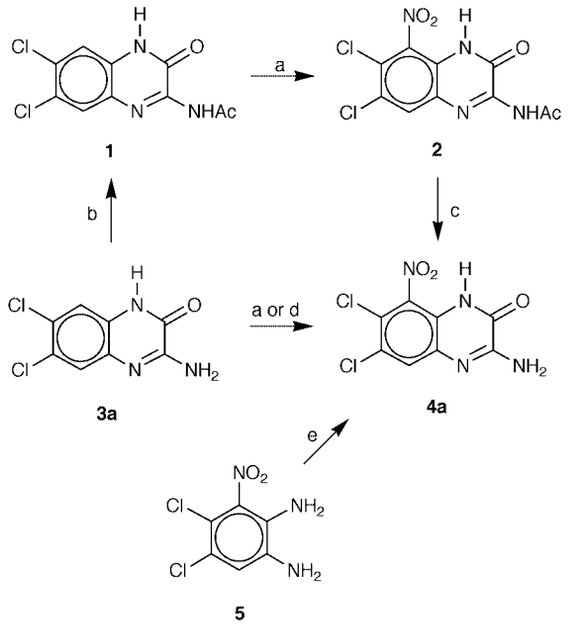
Since none of the direct syntheses of 3-amino-6,7-dichloro-5-nitroquinoxalin-2(1*H*)-one **9** were fruitful, the only possibility remaining was to introduce first the nitro group into the quinoxaline molecule and then the amino group. The electron-withdrawing effect of the nitro group resulted in a regiospecific monochlorination at the more electron-deficient carbon in **6**.[1] The formation of 2,3,6,7-tetrachloroquinoxaline **8** accompanied that of **7**, especially at higher temperatures. The structure of **7** was identified from the X-ray diffraction data. The ^{15}N NMR data were also in agreement with this structure: the aromatic hydrogen gave a crosspeak with the amide nitrogen at 145.1 ppm in the HMBC spectrum. Nucleophilic attack by ammonia on **7** led to the desired 5-nitro derivative **9** (Scheme 2). A crosspeak between the aromatic hydrogen and the amide nitrogen was found at 146.0 ppm in its ^{1}H–^{15}N HMBC spectrum.

In order to study the scope and limitations of observed regioselectivity we nitrated further 3-aminoquinoxalin-2(1*H*)-

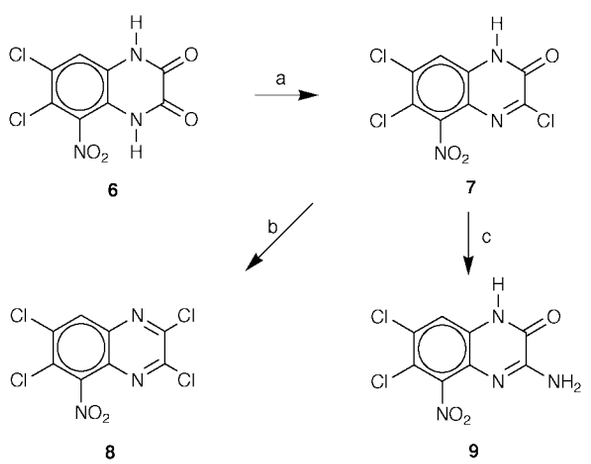
† Optimized geometries of the σ-complexes $\mathbf{3a_1}$, $\mathbf{3a_2}$, $\mathbf{3ap_1}$ and $\mathbf{3ap_2}$ with the AM1, HF and B3LYP methods together with the X-ray crystal structure of **7**, are available as supplementary data from BLDSC (SUPPL. NO. 57698, 5 pp.) or the RSC Library. See Instructions for Authors available *via* the RSC web page (http://www.rsc.org/authors).

‡ IUPAC name for sulfolane is 2,3,4,5-tetrahydrothiophene 1,1-dioxide.

DOI: 10.1039/a910234p



Scheme 1 Synthesis of 3-amino-6,7-dichloro-8-nitroquinoxalin-2(1*H*)-one **4a**. *Reagents*: (a) KNO_3, conc. H_2SO_4; (b) Ac_2O; (c) ethanol, 5 M NaOH; (d) BF_4NO_2, sulfolane; (e) oxalomonoimidic acid diethyl ester, ethanol.



Scheme 2 Synthesis of 3-amino-6,7-dichloro-5-nitroquinoxalin-2(1*H*)-one **9**. *Reagents and conditions*: (a) $POCl_3$, DMF, rt; (b) $POCl_3$, DMF, 50 °C; (c) NH_3, ethanol.

ones (Scheme 3). The 3-amino-6,7-dihalogenoquinoxalin-2(1*H*)-ones **3b**,**c** behaved in a similar manner to **3a**, giving 3-amino-6,7-dihalogeno-8-nitroquinoxalin-2(1*H*)-ones **4b**,**c**. The directing effect was not even perturbed by the methyl groups in **3d**: only **4d** was obtained.

We also investigated other substituent patterns for further characterization of the title compound. The methyl group on the 3-amino moiety in **10** did not disturb the regioselectivity of the reaction: only the 8-nitro derivative **11** was formed.

The question then arose as to whether it is possible to introduce a nitro group at position 5 at all. When position 8 was occupied, as in 3-amino-6,8-dichloroquinoxalin-2(1*H*)-one **12**, the nitration started at position 7 rather than at position 5, giving **13** and a trace (5%) of 3-amino-6,8-dichloro-5,7-dinitroquinoxalin-2(1*H*)-one **14**, formed as a consequence of the forced nitration (Scheme 3). In contrast with the situation for **10**, we observed a slight effect of the methyl group during the nitration of **15**, which gave a mixture of **16a** and **16b**, in an isomer ratio of 88 : 12 according to ^{1}H NMR.

In order to acquire a more complete picture, we investigated derivatives with one substituent on the benzenoid ring. Nitration of a mixture of isomers **17a** and **17b** yielded a mixture of **18a** and **18b** with an unchanged isomer ratio of 82 : 18, as indicated by the two aromatic singlets of each set of signals in the ^{1}H NMR spectrum.

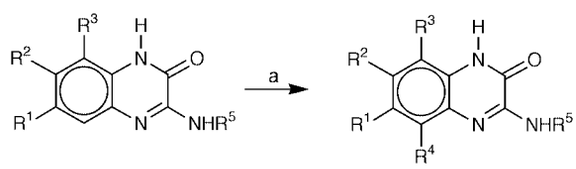
The nitration of 3-aminoquinoxalin-2(1*H*)-one **19** regiospecifically afforded the 6-nitro derivative **20**, which is identical to the derivative obtained by ring closure.[8] Under the forcing reaction conditions, a small amount (13%) of 6,8-dinitro-3-aminoquinoxalin-2(1*H*)-one **21** was identified.

Table 1 Calculated energies (E_h) of optimized σ-complexes

	Energy/E_h		
σ-complex	AM1	RHF	B3LYP
3a$_1$	0.3347354	−1666.46566	−1672.36746
3a$_2$	0.3228892	−1666.48085	−1672.37693
3ap$_1$	0.17181325	−1666.67657	−1672.58383
3ap$_2$	0.7255667	−1666.66864	−1672.57781

Table 2 Energy differences between 8-nitro- and 5-nitro-σ-complexes obtained by different methods

Method	E(**3a**$_1$) − E(**3a**$_2$)/ kcal mol^{-1}	E(**3ap**$_1$) − E(**3ap**$_2$)/ kcal mol^{-1}
AM1	7.43	−4.67
RHF	9.53	−4.98
B3LYP	5.94	−3.78



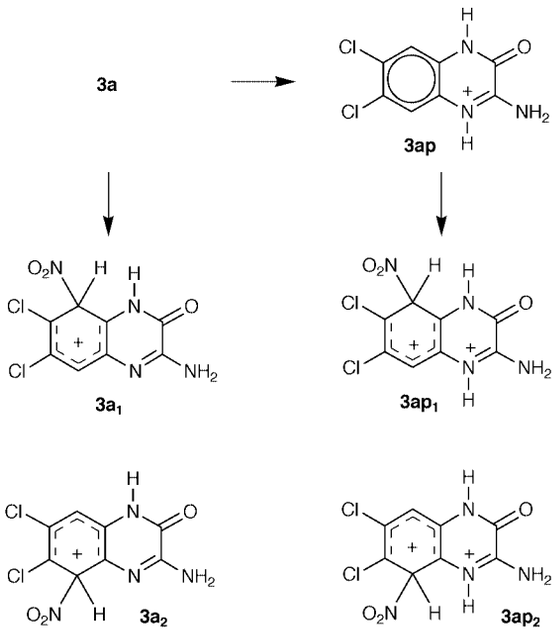
	R^1	R^2	R^3		R^1	R^2	R^3	R^4
3b	Br	Br	H	**4b**	Br	Br	NO_2	H
3c	F	F	H	**4c**	F	F	NO_2	H
3d	CH_3	CH_3	H	**4d**	CH_2	CH_3	NO_2	H
10[a]	Cl	Cl	H	**11**[a]	Cl	Cl	NO_2	H
12	Cl	H	Cl	**13**	Cl	NO_3	Cl	H
				14	Cl	NO_2	Cl	NO_2
15[a]	Cl	H	Cl	**16a**[a]	Cl	NO_2	Cl	H
				16b[a]	Cl	H	Cl	NO_2
17a	H	Cl	H	**18a**	NO_2	Cl	H	H
17b	Cl	H	H	**18b**	Cl	NO_2	H	H
19	H	H	H	**20**	NO_2	H	H	H
				21	NO_2	H	NO_2	H

[a] $R^5 = CH_3$.

Scheme 3 Preparation of 3-aminoquinoxalin-2(1*H*)-ones. *Reagents*: (a) KNO_3, conc. H_2SO_4.

Reaction mechanism aspects

The unambiguous direction of nitration was presumed to be due to the presence of a strong directing group in the quinoxaline ring, *i.e.* an ammonium type structure. We investigated the protonation of **3a** by NMR spectroscopy. There were two NH signals at 8.15 and 7.77 ppm, each with 1H intensity, in the ^{1}H NMR spectrum recorded in concentrated H_2SO_4. This suggested that protonation took place on N(4). This was confirmed by ^{15}N NMR investigations. We reported earlier[6] that the chemical shifts of N(1), N(4) and the amino nitrogens in DMSO are 144.4, 227.2 and 85.0 ppm, respectively. The chemical shifts of these nitrogens in concentrated D_2SO_4 were 147.1, 134.7 and 98.5 ppm. The first two displayed long-range couplings with the aromatic hydrogens in the ^{1}H–^{15}N HMBC spectrum, and they were therefore assigned to N(1) and N(4), respectively. The



Scheme 4 The 8-nitro- and 5-nitro-σ-complexes of **3a** and the monoprotonated **3ap**.

large chemical shift decrease of N(4) is in agreement with the protonated structure **3ap** (Scheme 4). Similar chemical shift decreases for N(3) in 2-aminothiazole,[10] and for N(1) in adenine and adenosine derivatives,[11] were reported upon protonation of the ring nitrogens of *amidine* moieties.

The calculated energy difference between the two σ-complexes $\mathbf{3a_1}$ and $\mathbf{3a_2}$ (Tables 1 and 2) suggested that nitronium cation attack on the neutral 6,7-dichloroquinoxaline would give the 5-nitro derivative. On the other hand, the calculated energy of $\mathbf{3ap_1}$ is lower than that of $\mathbf{3ap_2}$, in agreement with the experimental findings, *e.g.* formation of the 8-nitro derivative. These σ-complexes are formed from the monoprotonated species, indicating nitronium cation attack on this, rather than on a neutral or on a diprotonated species as described in the literature.[4]

Conclusions

The nitration of 6,7-disubstituted-3-aminoquinoxalin-2(1*H*)-ones takes place at position 8 rather than at position 5. The reaction is selective in the presence of electron-withdrawing halogeno groups. The electron-donating methyl group does not decrease the regioselectivity, either when it is present at positions 6 and 7 or when it is on the amino moiety. An electron-withdrawing group, such as acetyl in **1**, does not influence the selectivity of the electrophilic substitution reaction. The electrophilic nitronium ion seems to be unable to attack at position 5. There is a slight departure from this rule when positions 6 and 8 are occupied, so that a small amount of the 5,7-dinitro derivative **14** is produced. The 5-nitro derivative **16b** is formed as a minor component from **15**. The reactivity sequence is C6 > C7 > C8 ⩾ C5 when *ortho*, *para* directing substituents are present on the benzenoid ring. In the case of *meta* directing substituents the *meta* directing prevails.

Our results show that the main mechanism of the nitration involves nitronium cation attack on a monoprotonated species. The protonated *amidine* moiety plays the key role in the orientation of the aromatic electrophilic substitution.

Experimental

Melting points were determined in open capillary tubes on a Büchi 535 apparatus and are uncorrected. The yields were not maximized. Elemental analyses for C, H, N were performed on a Carlo Erba Mod 1106 instrument; halogen was determined by titration after Schöniger oxidation. The NMR spectra were recorded on a Bruker DRX-400 instrument at 400.13 (^{1}H), 100.6 (^{13}C) and 40.5 (^{15}N) MHz. The ^{1}H–^{15}N HMBC spectra were measured on a Bruker DRX-500 instrument, using gradient coherence[12] selection. ^{1}H and ^{13}C chemical shifts are referred to internal tetramethylsilane; ^{15}N chemical shifts are referred to external liquid NH_3. In DMSO, the ^{15}N chemical shifts referencing was solved by means of the XWINNMR program, utilizing the frequency of the lock signal. In D_2SO_4, a coaxial tube containing $Na^{15}NO_3$ in D_2O was used (376.6 ppm). All *J* values are quoted in Hz. The ratio of isomers was determined by NMR. MS spectra were measured on a VG-TS 250 instrument. Flash chromatography was carried out on silica gel 60H (5–40 μm, Merck, for thin-layer chromatography).

3-Acetylamino-6,7-dichloroquinoxalin-2(1*H*)-one (1)

A mixture of 3-amino-6,7-dichloroquinoxalin-2(1*H*)-one[8] (**3a**, 1.15 g, 5 mmol) and acetic anhydride (5 mL) was heated at reflux for 20 min and was then cooled down to 25 °C. Methanol (10 mL) was added and the mixture was refluxed for 30 min. It was then cooled down to 25 °C and the precipitated crystals were filtered off and washed with methanol. White crystals (1.03 g, 76%), mp 306 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.34 (s, 3H, CH_3), 7.38 (s, 1H, 8-H), 7.78 (s, 1H, 5-H), 9.83 (br s, 1H, 3-NH), 12.77 (br s, 1H, N(1)-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.2 (q, CH_3), 116.4 (d, C-8), 127.9 (d, C-5), 125.4, 129.3, 130.0, 131.1 (each s, C-8a, C-7, C-6, C-4a), 147.0 (s, C-3), 150.8 (s, C-2), 169.4 (s, CO). Anal. calcd for $C_{10}H_7Cl_2N_3O_2$: C, 44.13; H, 2.59; N, 15.44. Found: C, 43.94; H, 2.78; N, 15.35%.

3-Amino-6,7-dichloro-8-nitroquinoxalin-2(1*H*)-one (4a)

By hydrolysis from 2. 3-Acetylamino-6,7-dichloro-8-nitroquinoxalin-2(1*H*)-one (**2**, 1.54 g, 4.9 mmol) was dissolved in ethanol (96%, 16 mL) and sodium hydroxide solution (5 M, 2.5 mL) at pH 9, and the solution was heated to 80 °C. It was then treated with charcoal, which was subsequently filtered off. The solution was acidified with hydrochloric acid (5 M, 2 mL) to pH 4.5–5 and crystals of **4a** were obtained. Yellow crystals (1.13 g, 85%), mp 295 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (s, 1H, 5-H), 7.61, 7.98 (each br s, each 1H, 3-NH_2), 12.67 (br s, 1H, N(1)-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 116.4 (d, $J_{C8a,5H}$ = 9.4, C-8a), 121.4 (d, $J_{C7,5H}$ = 9.7, C-7), 126.0 (d, $J_{C6,5H}$ = 4.4, C-6), 126.5 (d, $J_{C5,5H}$ = 69.8, C-5), 135.3, 137.3 (each s, C-8,4a), 151.6, 153.1 (each s, C-2,3); ^{15}N NMR (40.5 MHz, DMSO-d_6) δ 88.7 (3-NH_2), 144.0 (N(1), 226.4 (N(4), 363.8 (8-NO_2); MS (EI): *m*/*z* 274 (M^+); ν_{max} (KBr)/cm^{-1} 3535, 3433, 3321, 1708. Anal. calcd for $C_8H_4Cl_2N_4O_3$: C, 34.93; H, 1.47; N, 20.37. Found: C, 34.70; H, 1.55; N, 20.33%.

Compound 4a by ring closure from 5. 4,5-Dichloro-3-nitro-1,2-diaminobenzene[9] (**5**, 0.51 g, 2.3 mmol) was dissolved in absolute EtOH (15 mL), and oxalomonoimidic acid diethyl ester (0.36 g, 2.5 mmol) was added. The reaction mixture was kept at 25 °C for 24 h. The precipitate was then filtered off, washed with EtOH (3 × 5 mL) and dried. The crude material was analysed, and proved to be identical to the hydrolysis product of **2**. Yellow crystals (0.61 g, 96%), mp 295 °C.

Compound 4a from by nitronium tetrafluoroborate with 3a. 3-Amino-6,7-dichloroquinoxalin-2(1*H*)-one (**3a**, 0.46 g, 2 mmol) was suspended in sulfolane (1.5 mL), NO_2BF_4 (0.53 g, 4 mmol) was added, and the mixture was stirred at 10 °C for 1 h, followed by ageing at room temperature for 4 h. It was next quenched into ice (5 g), and the precipitate was filtered off and washed with water. Yellow crystals (0.16 g, 29%), mp 295 °C. The material was identical to the hydrolysis product of **2**.

Nitration of 3-aminoquinoxalin-2(1*H*)-ones (1, 3a–d, 10, 12, 15, 17ab, 19). General procedure

3-Aminoquinoxalin-2(1*H*)-one (5 mmol) was dissolved in conc. H_2SO_4 (10 mL), and the solution was cooled down to 10 °C. KNO_3 (1.01 g, 10 mmol) was added slowly to the solution, which was then stirred at 10 °C for 1 h and aged at room temperature for 4 h. It was next quenched into ice (25 g), and the precipitate was filtered off and washed with water.

3-Acetylamino-6,7-dichloro-8-nitroquinoxalin-2(1*H*)-one (2). White crystals (0.95 g, 60%), mp 237–241 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.34 (s, 3H, CH_3), 8.03 (s, 1H, 5-H), 10.07 (s, 1H, 3-NH), 13.3 (br s, 1H, N(1)-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.3 (CH_3), 120.8 (C-8a), 123.7, 125.9 (C-6,7), 129.3 (C-5), 132.6, 137.6 (C-8,4a), 147.3, 151.5 (C-2,3), 169.5 (CO); ν_{max} (KBr)/cm^{-1} 3481, 3262, 1694. Anal. calcd for $C_{10}H_6Cl_2N_4O_4\cdot H_2O$: C, 35.83; H, 2.40; N, 16.72. Found: C, 35.98; H, 2.56; N, 16.88%.

3-Amino-6,7-dichloro-8-nitroquinoxalin-2(1*H*)-one (4a). Yellow crystals (1.18 g, 86%), mp 295 °C. The material was identical to the hydrolysis product of **2**, to the ring-closure product of **5**, and to the product obtained by nitration with nitronium fluoroborate.

3-Amino-6,7-dibromo-8-nitroquinoxalin-2(1*H*)-one (4b). Yellow crystals (1.24 g, 68%), mp 301–303 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (s, 5-H), 7.64, 8.00 (each br s, each 1H, 3-NH_2), 12.6 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 108.1 (C-7), 117.4 (C-6), 121.3 (C-8a), 128.5 (C-5), 135.5 (C-4a), 139.0 (C-8), 151.3, 152.6 (C-2,3); MS (EI): *m*/*z* 362 (M^+); ν_{max} (KBr)/cm^{-1} 3429, 3323, 1705. Anal. calcd for $C_8H_4Br_2N_4O_3\cdot H_2O$: C, 25.14; H, 1.58; N, 14.66; Br, 41.84. Found: C, 25.09; H, 1.62; N, 14.48; Br, 42.02%.

3-Amino-6,7-difluoro-8-nitroquinoxalin-2(1*H*)-one (4c). Yellow crystals (0.29 g, 24%), mp 288–290 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (dd, 1H, $J_{5H,6F}$ = 11.4, $J_{5H,7F}$ = 7.9, 5-H), 7.45, 7.78 (each br s, each 1H, NH_2), 12.06 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 115.0 (d, $J_{C5,6F}$ = 18.6, C-5), 119.3 (s, C-8a), 126.9 (d, $J_{C8,7F}$ = 12.1, C-8), 131.2 (d, $J_{C4a,6F}$ = 8.6, C-4a), 139.4 (dd, $J_{C7,7F}$ = 254.4, $J_{C7,6F}$ = 17.6, C-7), 145.0 (dd, $J_{C6,6F}$ = 242.0, $J_{C6,7F}$ = 12.4, C-6), 151.4, 152.4 (each s, C-2,3); MS (EI): *m*/*z* 242 (M^+); ν_{max} (KBr)/cm^{-1} 3435, 3313, 1683. Anal. calcd for $C_8H_4F_2N_4O_3$: C, 39.68; H, 1.67; N, 23.14. Found: C, 39.60; H, 1.56; N, 22.97%.

3-Amino-6,7-dimethyl-8-nitroquinoxalin-2(1*H*)-one (4d). Yellow crystals (0.59 g, 50%), mp 283 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.13 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 7.2 (br s, 2H, NH_2), 7.29 (s, 1H, 5-H), 11.98 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.2 (q, CH_3), 19.6 (q, CH_3), 122.9 (s, C-8a), 125.6 (s, C-7), 126.9 (d, C-5), 131.9, 132.7 (each s, C-4a, C-6), 139.2 (s, C-8), 151.9, 152.1 (each s, C-2,3); MS (EI): *m*/*z* 234 (M^+). Anal. calcd for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.18; H, 4.43; N, 23.77%.

6,7-Dichloro-3-methylamino-8-nitroquinoxalin-2(1*H*)-one (11). Yellow crystals (from 0.5 mmol of **10**: 0.13 g, 90%), mp 276–279 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.90 (d, 3H, J_{NH,CH_3} = 4.8, CH_3), 7.68 (s, 1H, 5-H), 8.25 (br d, 1H, NH), 12.62 (br s, 1H, N(1)-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.7 (q, NCH_3), 115.6 (d, $J_{C8a,\ 5H}$ = 9.5, C-8a), 121.0 (d, $J_{C7,5H}$ = 8, C-7), 125.5 (s, C-6), 126.3 (d, $J_{C5,5H}$ = 169.9, C-5), 135.3 (s, C-8), 137.2 (s, C-4a), 151.3, 151.6 (each s, C-2,3); MS (EI): *m*/*z* 288 (M^+); ν_{max} (KBr)/cm^{-1} 3360, 3316, 1722. Anal. calcd for $C_9H_6Cl_2N_4O_3$: C, 37.39; H, 2.09; N, 19.38. Found: C, 37.28; H, 2.15; N, 19.17%.

6,8-Dichloro-3-methylamino-7-nitroquinoxalin-2(1*H*)-one (16a) and 6,8-dichloro-3-methylamino-5-nitroquinoxalin-2(1*H*)-one (16b). Yellow crystals (from 0.5 mmol of **15**: 0.14 g, 97%), isomer ratio: **16a**:**16b** = 88:12 by ^{1}H NMR; ^{1}H NMR (400 MHz, DMSO-d_6) δ **16a**: 2.92 (d, 3H, J_{NH,CH_3} = 4.8, CH_3), 7.51 (s, 1H, 5-H), 8.44 (br d, 1H, NH), 12.22 (br s, 1H, N(1)-H); **16b**: 2.83 (d, 3H, $J_{NH,CH3}$ = 5.2, CH_3), 7.55 (s, 1H, 7-H), 8.56 (br d, 1H, NH), 12.20 (br s, 1H, N(1)-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ **16a**: 28.1 (q, NCH_3), 111.2 (s, C-8), 118.2 (d, $J_{C6,5H}$ = 3.8, C-6), 123.7 (d, $J_{C5,5H}$ = 171.2, C-5), 125.6 (d, $J_{C8a,5H}$ = 7.1, C-8a), 136.9 (s, C-4a), 142.2 (d, $J_{C7,5H}$ = 8.5, C-7), 152.2, 152.4 (each s, C-2,3); **16b**: 27.9 (q, NCH_3), 117.1 (d, $J_{C6,7H}$ = 3.9, C-6), 120.4 (d, $J_{C8,7H}$ = 3.9, C-8), 122.3 (d, $J_{C7,7H}$ = 176.4, C-7), 126.3 (d, $J_{C8a,7H}$ = 7.8, C-8a), 128.8 (s, C-4a), 142.4 (d, $J_{C5,7H}$ = 7.8, C-5), 151.9, 152.3 (each s, C-2,3); MS (EI): *m*/*z* 288 (M^+). Anal. calcd for $C_9H_6Cl_2N_4O_3$: C, 37.39; H, 2.09; N, 19.38. Found: C, 37.45; H, 2.27; N, 19.24%.

7-Chloro-3-amino-6-nitroquinoxalin-2(1*H*)-one (18a) and 6-chloro-3-amino-7-nitroquinoxalin-2(1*H*)-one (18b). Yellow crystals (from 0.5 mmol of **17a** and **17b**[6]: 0.11 g, 88%), isomer ratio: **18a**:**18b** = 82:18 by ^{1}H NMR; ^{1}H NMR (400 MHz, DMSO-d_6) δ **18a**: 7.23 (s, 1H, 8-H), 7.57, 7.94 (each br s, each 1H, NH), 7.87 (s, 1H, 5-H), 12.55 (br s, 1H, N(1)-H); **18b**: 7.39 (s, 1H, 5-H), 7.80 (s, 1H, 8-H), 7.9, 8.22 (each br s, 1H, NH), 12.44 (br s, 1H, N(1)-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ **18a**: 116.7 (d, C-8), 119.2 (C-7), 120.8 (d, C-5), 132.2, 133.0 (C-4a,8a), 142.1 (C-6), 151.6, 153.3 (C-2,3); **18b**: 113.0 (d, C-8), 120.3 (C-6), 125.3 (d, C-5), 127.5 (C-8a), 138.6 (C-4a), 140.5 (C-7), 151.3, 154.6 (C-2,3). Anal. calcd for $C_8H_5ClN_4O_3\cdot\frac{1}{2}H_2O$: C, 38.49; H, 2.42; N, 22.45. Found: C, 38.72; H, 2.13; N, 22.53%.

Nitration of 3-amino-6,8-dichloroquinoxalin-2(1*H*)-one.[6]

From **12** (1.00 g, 4.3 mmol); the crude yellow crystals (1.00 g, 83%) were purified by flash chromatography, giving **13** and **14**.

3-amino-6,8-dichloro-7-nitroquinoxalin-2(1*H*)-one (13). Yellow crystals (0.72 g, 72%), mp >300 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (s, 1H, 5-H), 7.77, 8.12 (each br s, each 1H, 3-NH_2), 12.24 (br s, 1H, N(1)-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 111.3 (C-8), 118.3 (C-6), 123.6 (C-5), 126.1 (C-8a) 136.7 (C-4a), 142.6 (C-7), 152.1, 154.2 (C-2,3); MS (EI): *m*/*z* 274 (M^+); ν_{max} (KBr)/cm^{-1} 3499, 3382, 1701. Anal. calcd for $C_8H_4Cl_2N_4O_3$: C, 34.93; H, 1.57; N, 20.37. Found: C 34.77; H, 1.62; N, 20.29%.

3-Amino-6,8-dichloro-5,7-dinitroquinoxalin-2(1*H*)-one (14). Yellow crystals (50 mg, 5%), mp >300 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34, 8.71 (each br s, each 1H, 3-NH_2), 12.65 (br s, 1H, N(1)-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 109.7 (C-6), 112.4 (C-8), 128.2 (C-8a), 130.2 (C-4a), 140.7, 140.9 (C-5,7), 151.9, 154.9 (C-2,3); MS (EI): *m*/*z* 319 (M^+); ν_{max} (KBr)/cm^{-1} 3491, 3379, 1691. Anal. calcd for $C_8H_3Cl_2N_5O_5$: C, 30.02; H, 0.94; N, 21.88. Found: C 30.12; H, 1.13; N, 21.64%.

Nitration of 3-aminoquinoxalin-2(1*H*)-one:[8] from 19 (240 mg, 1.5 mmol)

3-Amino-6-nitroquinoxalin-2(1*H*)-one (20). Yellow crystals (180 mg, 59%), mp 293–296 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29 (d, $J_{8H,7H}$ = 8.9, 1H, 8-H), 8.00 (dd, $J_{7H,5H}$ = 2.5, 1H, 7-H), 8.05 (d, 1H, 5-H), 8.2, 8.4 (each br, each 1H, NH), 12.76 (br s, 1H, N(1)-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 116.0 (C-8), 117.1 (C-5), 119.3 (C-7), 130.3, (C-8a), 133.7 (C-4a), 143.0 (C-6), 151.8, 152.6 (C-2,3); MS (EI): *m*/*z* 206 (M^+). Anal. calcd for $C_8H_6N_4O_3$: C, 46.61; H, 2.93; N, 27.18. Found: C 46.42; H, 3.12; N, 27.29%.

3-Amino-6,8-dinitroquinoxalin-2(1*H*)-one (21). The mother liquor was extracted with ethyl acetate, and was then purified by flash chromatography, giving yellow crystals (50 mg, 13%), mp 247–250 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79, 8.11 (each br s, each 1H, NH), 8.22 (d, $J_{5H,7H}$ = 2.6, 1H, 7-H), 8.56 (d, 1H, 5-H), 11.80 (br s, 1H, N(1)-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 114.3 (C-7), 123.0 (C-5), 128.8 (C-8a), 134.2, 136.2 (C-8,4a), 141.2 (C-6), 151.4, 153.0 (C-2,3); MS (EI): *m*/*z* 251 (M^+). Anal. calcd for $C_8H_5N_5O_5$: C, 38.26; H, 2.01; N, 27.88. Found: C 38.15; H, 2.12; N, 27.73%.

3,6,7-Trichloro-5-nitroquinoxalin-2(1*H*)-one (7)

Phosphoryl chloride (0.58 g, 0.35 mL, 3.8 mmol) was added slowly to a suspension of **6**[1] (1.00 g, 3.6 mmol) in DMF (2 mL). The mixture was aged at room temperature for 24 h and was then quenched into water (20 mL). The precipitate was filtered off and the crude material (1.1 g) was purified by flash chromatography. Pale yellow crystals (0.80 g, 75%), mp >300 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (s, 1H, 8-H), 13.33 (br s, 1H, N(1)-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 116.5 (C-4a), 118.1 (C-8), 122.3 (C-6), 133.3 (C-8a), 133.6 (C-7), 145.6 (C-5), 151.0, 154.3 (C-2,3); MS (EI): *m*/*z* 293 (M^+). Anal. calcd for $C_8H_2Cl_3N_3O_3$: C, 32.62; H, 0.68; N, 14.27. Found: C, 32.65; H, 0.78; N, 14.06%.

2,3,6,7-Tetrachloro-5-nitroquinoxaline (8)

Phosphoryl chloride (1.34 g, 0.81 mL, 8.6 mmol) was added slowly to a suspension of **6** (1.00 g, 3.6 mmol) in DMF (2 mL). The mixture was heated at 50 °C for 4 h, aged at room temperature for 24 h, and then quenched into water (20 mL). The precipitate was filtered off and the crude material (0.98 g) was purified by flash chromatography. Off-white crystals (0.62 g, 55%), mp 118–120 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (s, 1H, 8-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 125.9 (C-6), 130.9 (C-8), 131.2 (C-7), 134.5 (C-4a), 138.8 (C-8a), 145.0 (C-5), 148.8, 149.0 (C-2,3); MS (EI): *m*/*z* 311 (M^+). Anal. calcd for $C_8HCl_4N_3O_2$: C, 30.71; H, 0.32; N, 13.43. Found: C, 30.70; H, 0.45; N, 13.25%.

3-Amino-6,7-dichloro-5-nitroquinoxalin-2(1*H*)-one (9)

3,6,7-Trichloro-5-nitroquinoxalin-2(1*H*)-one (**7**, 0.30 g, 1 mmol) was dissolved in ethanol (20 mL) saturated with ammonia. The solution was heated at 70 °C for 8 h in a sealed tube. The solvent was then removed, and the residue was washed with chloroform, ethyl acetate and ethanol. Yellow crystals (0.20 g, 71%), mp > 300 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37 (s, 1H, 8-H), 7.77, 8.25 (each br s, each 1H, 3-NH_2), 12.58 (br s, 1H, N(1)-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 115.4 (d, $J_{C4a,8H}$ = 9.4, C-4a), 116.4 (d, $J_{C8,8H}$ = 169.3, C-8), 124.2 (d, $J_{C7,8H}$ = 4.6, C-7), 126.9 (d, $J_{C6,8H}$ = 7.3, C-6), 129.8 (d, $J_{C8a,8H}$ = 2.6, C-8a), 143.4 (d, $J_{C5,8H}$ = 1.5, C-5), 151.1, 154.0 (each s, C-2,3); MS (EI): *m*/*z* 274 (M^+); ν_{max} (KBr)/cm^{-1} 3483, 3367, 1693. Anal. calcd for $C_8H_4Cl_2N_4O_3$: C, 34.93; H, 1.47; N, 20.37. Found: C 35.25; H, 1.57; N, 20.13%.

Computational methods

All calculations were carried out with the Gaussian 98W program.[13] The geometries of the σ-complexes **3a$_1$**, **3ap$_1$**, **3a$_2$** and **3ap$_2$** were optimized at the semi-empirical AM1,[14] *ab initio* Hartree–Fock[15] and B3LYP[16] level. For the *ab initio* and the density functional methods, Dunning–Huzinaga full double zeta basis sets[17] were used. The energies of optimized σ-complexes are given in Table 2. The energy differences between 8-nitro- and 5-nitro-σ-complexes are listed in Table 3.

X-ray crystallographic study

The structure was solved by direct methods and refined by full matrix least squares method on F^2 using SHELXL97.[18] Hydrogen atoms were included in calculated positions and refined in riding mode. Refinement converged at R = 0.137 (wR = 0.3673 for 2892 data and 193 parameters).

X-ray data for 7.§ $C_{10}H_8Cl_3N_3O_4S$; M = 372.60, triclinic, a = 9.170(17), b = 9.477(7), c = 8.883(6) Å, α = 91.52(6), β = 104.20(12), γ = 101.15(14)°, V = 732.0(15) Å^3, Z = 2, D_c = 1.691 g cm^{-3}, space group $P\bar{1}$, Cu-Kα radiation (λ = 1.5418 Å), μ (Cu-Kα) = 7.194 mm^{-1}, F(000) = 376.

Crystals grown in an NMR tube from DMSO were mounted in a capillary and X-ray data were collected at room temperature on a Rigaku AFC6S diffractometer (out of 3085 collected reflections 2899 were independent, R_{int} = 0.1588, $wR2$ = 0.4196). The crystals available were of inferior quality, therefore the collected data are also of low quality, but do give unambiguous proof of the structure of **7**.

§ CCDC reference number 207/410. See http://www.rsc.org/suppdata/p1/a9/a910234p/ for crystallographic files in .cif format.

References

1 (*a*) S. M. Kher, S. X. Cai, E. Weber and J. F. W. Keana, *J. Org. Chem.*, 1995, **60**, 5838 and references therein; (*b*) S. X. Cai, S. M. Kher, Z. L. Zhou, V. Ilyn, S. A. Espitia, M. Tran, J. E. Hawkinson, R. M. Woodward, E. Weber and J. F. W. Keana, *J. Med. Chem.*, 1997, **40**, 730.

2 Cs. Gönczi, É. Csikós, S. Erdö, J. Bencze, V. Lakics, P. Molnár, A. Szappanos, B. Podányi, I. Hermecz, G. Héja, S. Báthori, I. Bata, A. Csutor, I. Szvoboda, Zs. Böcskei and I. Ritz, WO9719934, 1997; *Chem. Abstr.*, 1997, **127**, 95295c.

3 (*a*) K. J. Szabó, G. Timári and S. Gronowitz, *Chem. Scr.*, 1989, **29**, 313; (*b*) K. J. Szabó, A. B. Hörnfeldt and S. Gronowitz, *J. Org. Chem.*, 1991, **56**, 1590.

4 A. E. A. Porter, in *Comprehensive Heterocyclic Chemistry*, eds. A. R. Katritzky, C. W. Rees, A. J. Boulton and E. McKillop, Pergamon Press, Oxford, 1984, vol. 3, p. 163.

5 H. Poradowska, *Zesz. Nauk. Uniw. Jagiellon. Pr. Chem.*, 1987, **30**, 97; *Chem. Abstr.*, 1988, **109**, 92044n.

6 É. Csikós, Cs. Gönczi, B. Podányi, G. Tóth and I. Hermecz, *J. Chem. Soc., Perkin Trans. 1.*, 1999, 1789.

7 D. M. Doddrell, D. T. Pegg and M. R. Bendall, *J. Magn. Reson.*, 1982, **48**, 323.

8 (*a*) A. McKillop, A. Henderson, P. S. D. Ray, *Tetrahedron Lett.*, 1982, **23**, 3357; (*b*) A. McKillop, S. K. Chattopadhyay, A. Henderson and C. Avendano, *Synthesis*, 1997, 301.

9 W. Tian, S. Grivas and K. Olsson, *J. Chem. Soc., Perkin Trans. 1.*, 1993, 257.

10 G. Tóth and B. Podányi, *J. Chem. Soc., Perkin Trans. 2*, 1984, 91.

11 (*a*) V. Markowski, G. R. Sullivan and J. D. Roberts, *J. Am. Chem. Soc.*, 1977, **99**, 714; (*b*) N. C. Gonella, H. Nakanishi, J. B. Holtwick, D. S. Horowitz, K. Kanamori, N. J. Leonard and J. D. Roberts, *J. Am. Chem. Soc.*, 1983, **105**, 2050.

12 W. Wieker, D. Leibfritz, R. Kerssebaum and W. Bermel, *Magn. Reson. Chem.*, 1993, **31**, 287.

13 Gaussian 98 (Revision A.1), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, Ö. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1998.

14 M. Dewar and W. Thiel, *J. Am. Chem. Soc.*, 1977, **99**, 4499.

15 C. C. J. Roothan, *Rev. Mod. Phys.*, 1951, **23**, 69.

16 A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648.

17 T. H. Dunning Jr. and P. J. Hay, *Modern Theoretical Chemistry III*, ed. H. F. Schaefer, Plenum, New York, 1976, vol. 3, p. 1.

18 G. M. Sheldrick, SHELXL97, Program for the Refinement of Crystal Structures, University of Göttingen, Göttingen, Germany, 1997.