Regioselectivity in preparation of unsymmetrically substituted 3-aminoquinoxalin-2(1*H*)-ones

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Regioisomer formation has to be considered in the preparation of quinoxalines having different substituents at the 2- and 3-position. Oxalomonoimidic acid dimethyl ester or oxalomonoimidic acid diethyl ester, chloro(methylimino)acetic acid ethyl ester, chloro[(*Z*)-hydroxyimino]acetic acid ethyl ester and (*Z*)-2-[(*E*)-hydroxyimino]acetohydroximoyl chloride were applied to the synthesis of 3-aminoquinoxalin-2(1*H*)-one derivatives, and the isomer ratio was investigated concerning the reactivity of the ring-closure reagent. The structures of reaction products were identified using ^{1}H, ^{13}C and ^{15}N NMR techniques. A direct synthesis of quinoxaline-2,3(1*H*,4*H*)-dione 3-oximes is described.

Introduction

Quinoxaline chemistry are again in the center of interest because of these compounds' CNS activity. Quinoxaline-2,3-(1*H*,4*H*)-diones are the favorite quinoxalines to have been patented so far. We prepared a series of substituted 3-aminoquinoxalin-2(1*H*)-ones for investigating their biological activity on the *N*-methyl-D-aspartate (NMDA) glycine-binding test. Among these compounds are some which have antagonist character.[1] Our aim was to have in hand all possible isomers.

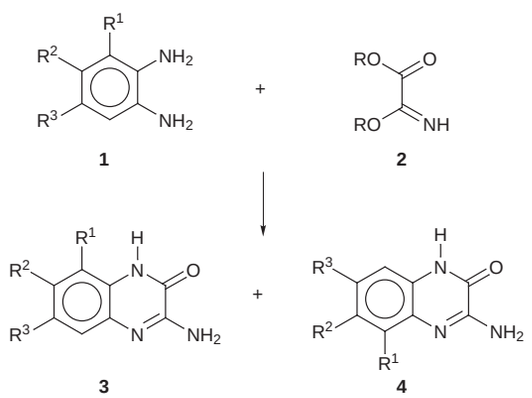
In contrast to quinoxaline-2,3(1*H*,4*H*)-diones in the reaction of a 1,2-disubstituted benzene and an unsymmetrical two-carbon synthon the formation of regioisomers has to be considered. In an analogous example, Alvarez-Builla *et al.* studied the regioselectivity in the Westphal condensation:[2] unsymmetrical 1,2-diketones and α-methylcycloimmonium substrates were allowed to react, and the molar ratio of the product was reported to be highly dependent on the nature of the diketone.

The condensations of methyl[3a] or ethyl[3b] (m)ethoxycarbonylformimidate **2** with 1,2-phenylenediamines gives in an excellent yield 3-aminoquinoxalin-2(1*H*)-ones.[4] McKillop *et al.* suggest some substituent effect of 1,2-phenylenediamines on the formation of regioisomers but, based on these results only, one cannot predict the isomer ratio by using different oxalomonoimidic acid derivatives as a ring-closure agent. We were interested in the impact of the other partner on the reaction; if there is a difference between the two active carbons in the oxalic acid derivatives that makes it possible to influence the reaction not only by the dinucleophile but by the dielectrophile as well. We followed the reactivity of four oxalomonoimidic acid derivatives **2**, **5**, **8**, **11** with 1,2-phenylenediamines **1a** and **1b**.

Results and discussion

In principle 3,5-dichloro-1,2-diaminobenzene **1a** and an oxalomonoimidate **2** can form two isomeric quinoxalines. In spite of this we obtained a uniform product **3a** (Scheme 1).[5] On the other hand, two isomers **3b** and **4b** were formed from trifluoromethyl compound **1b**.

The compounds **3c** and **3d** were used as models to help the identification of the isomers by NMR techniques.



Scheme 1[5] 3-Aminoquinoxalin-2(1*H*)-ones

1,3,4	R^1	R^2	R^3		Ratio[a]	Y (%)[b]
a	Cl	H	Cl	**3a**	100	78
b	H	CF_3	Cl	**3b**	8	80
				4b	92	
c	H	Cl	Cl	**3c**	100	85
d	H	H	H	**3d**	100	82
e	H	CH_3	H	**3e**	71	77
				4e	29	
f	H	Cl	H	**3f**	80	71
				4f	20	

R = Me, Et. [a] Isomer ratio by ^{1}H NMR. [b] Total yield.

^{1}H–^{15}N HMBC[6] and ^{1}H–^{13}C HMQC[7] experiments on **3c** showed that the chemical shifts of C-5 and C-8 are 124.5 and 115.6 ppm, respectively. Thus the chemical shift of the aromatic carbon in an *ortho* position to the amide nitrogen is almost 10 ppm lower than that of the carbon in an *ortho* position to the imino group. This chemical-shift difference was used later to identify quinoxaline isomers.

Starting from the ^{13}C chemical shifts of compound **3d** the shift values of compound **3a** and its possible isomer **4a** were calculated using substituent chemical-shift increments of the chlorine atom.[8] The crucial shifts of benzene-ring carbons are shown in Table 1. The aromatic C–H carbons were differ-

Table 1 ^{13}C Chemical shifts (ppm) for **3a** and **4a**

	CH	CH	CCl
Calc. **3a**	122.2 C-5	124.4 C-7	122.4 C-8
Calc. **4a**	113.2 C-8	124.4 C-6	131.4 C-5
Measured	122.5	122.6	119.0 C-8

entiated from all others using the DEPT pulse sequence.[9] The measured chemical shifts of the two C–H carbons indicate that the product is **3a**. A further argument is the chemical shift of C-8.

In the ^{13}C NMR spectrum of **3b** and **4b** one of the aromatic CH carbons in each signal set showed a small quartet splitting due to the spin–spin interaction with the CF_3 group in an *ortho* position. The chemical shift of this carbon is 123.0 ppm in the major and 114.3 ppm in the minor set of signals. The chemical shift of the other CH carbon is 117.2 ppm in the major and 125.8 ppm in the minor set of signals. These chemical-shift differences show that the major component corresponds to **4b** and the minor to the isomeric structure **3b**.

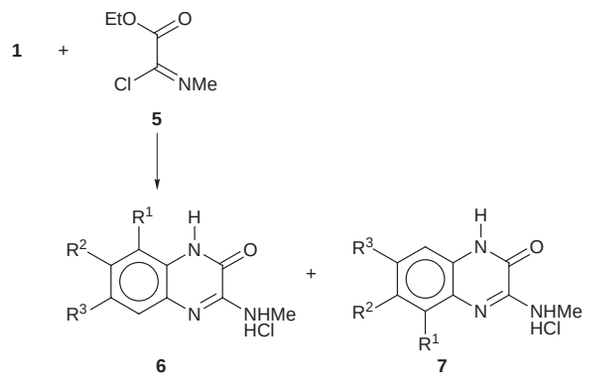
Earlier work reported 100% chemoselectivity in the case of 4-nitro-1,2-phenylenediamine, where due to the electron-withdrawing effect of the nitro group 3-amino-6-nitroquinoxalin-2-(1*H*)-one was formed, exclusively. Surprisingly no effect was found in the case of 4-methyl-1,2-phenylenediamine **1e** (1 : 1 mixture of the two possible isomers was reported).[4] In our experiments oxalomonoimidic acid esters **2** and diamine **1e** gave the condensation product with excellent yield. The intensity ratio of **3e** and **4e** was 71 : 29 by ^{1}H NMR, which was confirmed by HPLC results as well. The ^{13}C data on **3a**–**d** and **4b** reveal that one of the aromatic CH carbons from the major set of signals at 115.1 ppm, and one from the minor set of signals at 114.9 ppm, are in an *ortho* position to the amide group. The HMQC chemical-shift-correlation experiment indicated that the former carbon is in *ortho* position with the methyl group, while the latter is in *meta* position with the methyl group.

In the case of **3f** and **4f** the isomer ratio is very close to that of **4b** and **3b**. The electron-withdrawing effect of the 4-trifluoromethyl group on the amino group *para* in **1b** is reflected by the product isomer ratio. The effect of 3- and 5-chloro substituents in **1a** is opposite to that of the 4-chloro in **1f**. The substituent at position 3 in 1,2-phenylenediamine **1a** has a remarkable steric effect, so that we obtained **3a** exclusively.

Chloro(methylimino)acetic acid ethyl ester[10] **5** is also suitable to give quinoxalines; the unsubstituted 3-(methylamino)-quinoxalin-2(1*H*)-one is described.[11] Imidoyl chloride **5** behaves similarly to **2**, so it reacts readily with diamines **1a** and **1b**, giving the hydrochloride salts of 6,8-dichloro-3-(methylamino)quinoxalin-2(1*H*)-one **6a**, and a regioisomeric mixture of **6b** and **7b** (Scheme 2). The NMR chemical shifts are close to the values measured for **3a**, confirming that only **6a** was formed in this reaction from the two possible isomers. The data are comparable, because the salt is dissociated into the free base to a large extent in the DMSO solution at 70 °C. For the structure identification of **6b** and **7b** their base was used. The chemical shifts of **7b** base is similar to the values measured for **4b**, confirming that the major and the minor component correspond to structures **7b** and **6b**, respectively.

(*Z*)-Chloro-(hydroxyimino)acetic acid ethyl ester[12] **8** reacts readily in the presence of base in ethanol–water media with 1,2-phenylenediamines to give quinoxaline-2,3(1*H*,4*H*)-dione 3-oximes (Scheme 3). Compound **1a** gave with **8** the two possible quinoxaline isomers **9a** and **10a**. The isomer ratio was confirmed by HPLC. The structure of the major component was confirmed by a ^{1}H–^{15}N HMBC spectrum.

The ^{1}H NMR isomer ratio of **10b** and **9b** was supported by

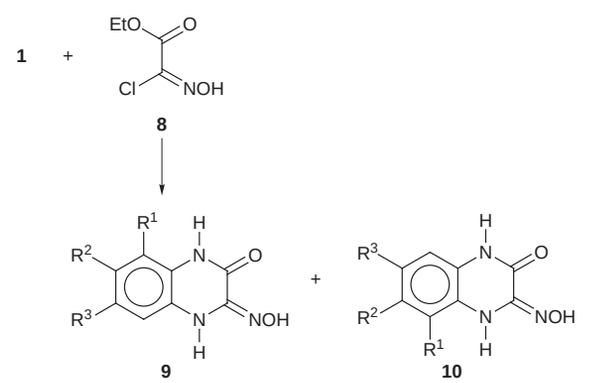


Scheme 2[5] 3-(*N*-Methylamino)quinoxalin-2(1*H*)-ones

a; $R^1 = R^3 = Cl$, $R^2 = H$; **b**; $R^1 = H$, $R^2 = CF_3$, $R^3 = Cl$

	Ratio[a]	Y (%)[b]
6a	100	61
6b	10	75
7b	90	

[a] Isomer ratio by ^{1}H NMR. [b] Total yield.



Scheme 3[5] Quinoxaline-2,3(1*H*,4*H*)-dione 3-oximes

a; $R^1 = R^3 = Cl$, $R^2 = H$; **b**; $R^1 = H$, $R^2 = CF_3$, $R^3 = Cl$

	Ratio[a]	Y (%)[b]
9a	76	80
10a	24	
9b	21	81
10b	79	

[a] Isomer ratio by ^{1}H NMR. [b] Total yield.

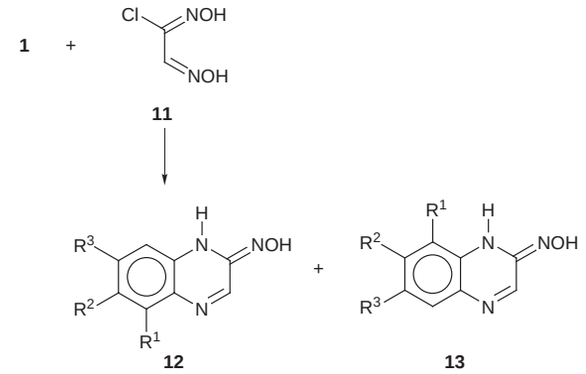
HPLC as well. The structure of the isomers was confirmed by ^{13}C NMR, ^{1}H–^{13}C HMBC and ^{1}H–^{15}N HMBC spectra.

Chloroglyoxime with two mol equiv. of 1,2-phenylenediamine was reported to form quinoxaline oxime.[13] More precisely, (*Z*)-2-[(*E*)-hydroxyimino]acetohydroximoyl chloride[14] **11** reacts readily only (the *E*,*E* isomer failed) with **1a** and **1b** in the presence of base in ethanol–water media, giving mixtures of isomers **12a** and **13a**, **12b** and **13b**, respectively (Scheme 4).

Isomers **12a** and **13a** were separated by chromatography.[15] In the 2-quinoxalinone oxime structure the C-5 and the C-8 carbons show the expected characteristic chemical-shift differences: 13.8 and 14.9 ppm between C-5 in **13a** and C-8 in **12a** and between C-5 in **12a** and C-8 in **13a**, respectively.

The structure of **12b** and **13b** was confirmed by ^{13}C NMR spectrum. The aromatic CH carbons' chemical shifts show the characteristic differences observed between the same carbons' of the isomers **12a** and **13a**.

The decreased selectivity of the ring closure using **8** com-



Scheme 4[5] Quinoxalin-2(1*H*)-one oximes

a; $R^1 = R^3 = Cl$, $R^2 = H$; **b**; $R^1 = H$, $R^2 = CF_3$, $R^3 = Cl$

	Ratio[a]	Y (%)[b]
12a	84	84
13a	16	
12b	23	78
13b	77	

[a] Isomer ratio by ^{1}H NMR. [b] Total yield.

pared to the two other oxalomono imidic acid derivatives **2** and **5** permit compound **10a** to appear as a minor component, and the **9b**:**10b** ratio is also higher than **4b**:**3b** or **6b**:**7b**. The ring-closure reagent **11** behaves in a similar manner to **8**, giving isomer mixtures. There is no significant difference in the isomer ratios in all four mixtures. The more reactive chloroxime eliminates the fine difference between amino groups in 1,2-phenylenediamines **1a** and **1b**, resulting in a ≈3:1–4:1 isomer ratio.

In the first approach[4] the obtained isomeric ratios in the ring-closure reactions can be interpreted as the electronic effect of the substituent of the 1,2-phenylenediamines, because the first step is the nucleophilic attack at the imino carbon atom of the more electron rich nitrogen. Examining the question more deeply we can draw the conclusion that the isomer ratios in the product do not depend only on this. Our examples clearly reveal the essential impact of the ring-closure agent's reactivity as well. Namely, the more reactive chloro(hydroxyimino) derivatives decrease the selectivity, raising the probability of the appearance of a minor isomer. This way we can obtain the missing aminoquinoxalinone isomer by simple chemical reactions (*e.g.*, from oxime). The steric effect also has to be considered in the case of 1,2-phenylenediamines having a substituent at position 3.

Our results reveal that by choosing the appropriate tool one can influence the isomer ratio of quinoxalines more or less independently from the effects of the substituents of the 1,2-phenylenediamine.

Experimental

Mps were determined in open capillary tubes on a Büchi 535 apparatus and are uncorrected. The yields were not maximised. The NMR spectra were measured on a Bruker DRX-400 instrument at 400.13 (^{1}H), 100.6 (^{13}C) and 40.5 (^{15}N) MHz respectively, or on a Bruker AC-200 instrument at 200.13 (^{1}H) and 50.6 (^{13}C) MHz, respectively, for solutions in DMSO-d_6. The DEPT, HMQC and HMBC spectra were measured using the standard pulse programs of the XWINNMR software. We applied a 40 ms delay for polarisation transfer and a 1 ms purging pulse in the long-range HSQC experiment.[16] The ^{1}H–^{15}N HMBC spectra were measured on a Bruker DRX-500 instrument using gradient coherence[17] selection. ^{1}H and ^{13}C chemical shifts are referenced to internal tetramethylsilane; ^{15}N chemical shifts are referenced to external liq. NH_3. *J*-Values are given in Hz. The ratio of isomers was determined by NMR and HPLC (Waters 991 system with Chiracel OD, 10 μm, 250 × 4.6 mm column; Waters Maxima 820 system Purospher RP-18, 5 μm, 250 × 4.0 mm column, flow rate 1.0 ml min^{-1}). IR spectra were measured on Bruker IFS-28 (KBr). MS spectra were measured on a VG-TS 250. Flash chromatography was carried out on silica gel 60H (5–40 μm), Merck, for TLC.

Oxalomonoimidic acid dimethyl ester 2, R = Me

Methyl cyanoformate (24.3 g, 0.285 mol) and MeOH (9.13 g, 0.285 mol) in petroleum ether (distillation range 40–70 °C; 30 ml) were cooled to −10 °C. Anhydrous HCl gas was bubbled through the mixture for one and a half hours; temperature was maintained between −10 and 0 °C. The precipitated hydrochloride salt was collected by filtration (wet weight 41.8 g). It was suspended in Et_2O (200 ml) and the mixture was stirred while triethylamine (35 ml, 0.25 mol) was added dropwise, while the temperature was maintained between 8 and 15 °C, and was then stirred for another hour. The precipitate was filtered off, and washed with Et_2O. The solvent was evaporated *in vacuo*. The residue (yellow oil, 16.6 g) was distilled *in vacuo* to afford a liquid (11.6 g, 34.5%; bp 60 °C/28 mmHg; n_D^{20} 1.4245).

3-Aminoquinoxalin-2(1*H*)-ones 3 and 4. General procedure

To a solution or suspension of 1,2-diaminobenzene derivative **1a**–**e** (10 mmol) in absolute EtOH (15 ml) was added oxalomonoimidic acid diethyl ester[3b] (**2**; R = Et) (1.60 g, 11 mmol) or oxalomonoimidic acid dimethyl ester (**2**; R = Me) (1.29 g, 11 mmol). The reaction mixture was kept at 25 °C for 8–48 h. The precipitate was filtered off, washed with EtOH (3 × 5 ml) and dried. The crude material was analyzed.

3-Amino-6,8-dichloroquinoxalin-2(1*H*)-one 3a. (1.79 g, 78%) as off-white crystals, mp > 316 °C (Found: C, 41.7; H, 2.1; N, 18.5; Cl, 30.9. Calc. for $C_8H_5Cl_2N_3O$: C, 41.8; H, 2.2; N, 18.3; Cl, 30.8%); δ_H (400 MHz) 7.23 (d, 1H, $J_{5,7}$ 2.3, 5-H), 7.32 (d, 1H, 7-H) 7.40 and 7.75 (each br, each 1H, NH_2), 11.90 (br s, 1H, NH); δ_C (100 MHz) 119.0 (dd, $J_{C8,7H}$ 4.2, $J_{C8,5H}$ 0.9, C-8), 122.5 (dd, $J_{C5,5H}$ 167.4, $J_{C5,7H}$ 5.3, C-5), 122.6 (dd, $J_{C7,7H}$ 172.8, $J_{C7,5H}$ 5.9, C-7), 125.0 (t, $J_{C8a,7H} = J_{C8a,5H} = 6.9$, C-8a), 126.9 (t, $J_{C6,5H} = J_{C6,7H} = 4.2$, C-6), 135.9 (d, $J_{C4a,5H}$ 1.8, C-4a), 151.9 and 153.3 (each s, C-2, -3); MS (EI) *m*/*z* 229 (M^+).

3-Amino-7-chloro-6-(trifluoromethyl)quinoxalin-2(1*H*)-one 4b and 3-amino-6-chloro-7-(trifluoromethyl)quinoxalin-2(1*H*)-one 3b. (2.11 g, 80%) as off-white crystals, mp 315 °C (Found: C, 41.1; H, 2.0; N, 16.05. Calc. for $C_9H_5ClF_3N_3O$: C, 41.2; H, 1.9; N, 15.9%); δ_H (400 MHz) 7.3 and 7.65 (each br, each 1H, NH_2); 12.42 (br, 1H, NH); **4b**: 7.26 (s, 0.92H, 8-H), 7.54 (s, 0.92H, 5-H); **3b**: 7.42 and 7.47 (each s, each 0.08H, 5-, 8-H); δ_C (100 MHz) **4b**: 117.2 (s, C-8), 121.0 (q, $J_{C6,F}$ 31.2, C-6), 123.0 (q, $J_{C5,F}$ 4.9, C-5), 123.2 (q, $J_{C,F}$ 272, CF_3), 123.5 (s, C-7), 132.4 and 132.3 (each s, C-4a, -8a), 151.6 and 153.2 (each s, C-2, -3), **3b**: 114.3 (q, $J_{C8,F}$ 4, C-8), 124.0 (s, C-6), 125.8 (s, C-5), 127.4 (C-8a), 137.7 (s, C-4a), 151.3 and 154.4 (each s, C-2, -3).

3-Amino-6,7-dichloroquinoxalin-2(1*H*)-one 3c. (1.96 g, 85%) as off-white crystals, mp > 316 °C (lit.,[4] > 320 °C) (Found: C, 41.85; H, 2.2; N, 18.3; Cl, 31.0. Calc. for $C_8H_5Cl_2N_3O$: C, 41.8; H, 2.2; N, 18.3; Cl, 30.9%); δ_H (400 MHz) 7.25 and 7.65 (each br, each 1H, NH_2), 7.26 (s, 1H, 8-H), 7.43 (s, 1H, 5-H), 12.27 (br, 1H, NH); δ_C (100 MHz) 115.6 (C-8), 124.4, 124.5 and 128.4 (C-6, -7, -8a), 124.6 (C-5), 133.5 (C-4a), 150.9 and 152.6 (C-2, -3); δ_N (40.5 MHz) 85.0 (NH_2), 144.4 (N-1), 227.2 (N-4).

3-Aminoquinoxalin-2(1*H*)-one 3d. (1.32 g, 82%) as off-white crystals, mp > 316 °C (lit.,[4] > 350 °C) (Found: C, 59.6; H, 4.5; N, 26.25. Calc. for $C_8H_7N_3O$: C, 59.6; H, 4.4; N, 26.1%); δ_H (400 MHz) 7.05 (br, 2H, NH_2), 7.15–7.05 (m, 3H, 6, -7, -8-H), 7.27

(m, 1H, 5-H), 12.11 (br, 1H, NH); δ_C (100 MHz) 115.0 (C-8), 123.2, 123.4 and 124.3 (C-5, -6, -7), 128.7 (C-8a), 133.6 (C-4a), 151.6 and 152.2 (C-2, -3).

3-Amino-7-methylquinoxalin-2(1*H*)-one 3e and 3-amino-6-methylquinoxalin-2(1*H*)-one 4e. (1.35 g, 77%) as off-white crystals, mp > 316 °C (lit.,[4] > 320 °C) (Found: C, 61.5; H, 5.3; N, 24.2. Calc. for $C_9H_9N_3O$: C, 61.7; H, 5.2; N, 24.0%); δ_H (400 MHz) 2.30 (s, 3H, CH_3), 6.9 (br, 2H, NH_2), 12.02 (br, 1H, NH); **3e**: 6.93 (dd, 0.71H, $J_{5,6}$ 8.1, $J_{6,8}$ 1.9, 6-H), 6.98 (d, 0.71H, 5-H), 7.20 (d, 0.71H, 8-H), **4e**; 6.92 (dd, 0.29H, $J_{7,8}$ 8.1, $J_{5,7}$ 2.1, 7-H), 7.06 (d, 0.29H, 8-H), 7.12 (d, 0.29H, 5-H); δ_C (100 MHz) **3e**: 21.0 (CH_3), 115.1 (C-8), 124.2–124.5 (C-5, -6), 128.6 (C-8a), 131.5 and 132.9 (C-4a, -7), 151.7 and 151.8 (C-2, -3); **4e**: 20.9 (CH_3), 114.9 (C-8), 124.2–124.5 (C-5, -7), 126.5 (C-8a), 132.4 and 133.6 (C-4a, -6), 151.6 and 152.3 (C-2, -3); MS (EI) *m*/*z* 175 (M^+); HPLC (Waters 991, eluent: n-hexane–ethanol–propan-2-ol, 800 : 150 : 50; analysis time: 50 min, detection: 222 nm) [t_R(major) 17.84 min, t_R(minor) 15.86 min]. Ratio of integration major : minor = 72 : 28.

3-Amino-7-chloroquinoxalin-2(1*H*)-one 3f and 3-amino-6-chloroquinoxalin-2(1*H*)-one 4f. (1.39 g, 71%) as off-white crystals, mp > 315 °C (Found: C, 49.1; H, 3.3; N, 21.35. Calc. for $C_8H_6ClN_3O$: C, 49.1; H, 3.1; N, 21.5%); δ_H (200 MHz) 7.19 (br, 2H, NH_2), 12.13 (br, 1H, NH); **3f**: 7.11 (dd, 0.80 H, $J_{5,6}$ 11.5, $J_{6,8}$ 2.4, 6-H), 7.12 (d, 0.80H, 8-H), 7.26 (d, 0.80H, 5-H); **4f**: 7.11 (dd, 0.20H, 8-H), 7.14 (d, 0.20H, 7-H), 7.28 (d, 0.20H, 5-H); δ_C (50 MHz) **3f**: 114.2 (C-8), 123.1 (C-6), 125.6 (C-5), 126.8, 129.6 and 132.5 (C-7, -4a, -8a), 151.4 and 152.2 (C-2, -3), **4f**: 116.4 (C-8), 123.0 (C-5), 127.0, 127.6 and 134.8 (C-6, -8a, -4a), 152.2 and 152.8 (C-2, -3).

3-(*N*-Methylamino)quinoxalin-2(1*H*)-ones 6 and 7. General procedure

A 1,2-diaminobenzene derivative **1a** or **1b** (5 mmol) was dissolved or suspended in absolute THF (8 ml). Keeping the temperature of the mixture at 10 °C, chloro(methylimino)acetic acid ethyl ester **5** (0.90 g, 6 mmol) was added. After storage at room temperature for 1 day the precipitate was filtered off, and washed with EtOH.

6,8-Dichloro-3-(methylamino)quinoxalin-2(1*H*)-one hydrochloride 6a. (0.86 g, 61%) as off-white crystals, mp 262–265 °C (Found: C, 38.5; H, 2.9; N, 15.2; Cl, 30.9. Calc. for $C_9H_7Cl_2N_3O{\cdot}HCl$: C, 38.5; H, 2.9; N, 15.0; Cl, 30.8%); δ_H (400 MHz) 2.95 [d, 3H, J(NH,CH_3) 4.8, CH_3] 7.37 and 7.44 (each s, each 1H, 5-, -7-H), 8.47 (br, 1H, N*H*Me), 11.92 (br s, 1H, N^1-H); δ_C (100 MHz, 70 °C) 28.1 (NCH_3), 119.1 (C-8), 121.1 and 122.8 (C-5, -7), 123.8 (C-8a), 126.9 (C-6), 133.2 (C-4a), 150.6 and 151.3 (C-2, -3).

7-Chloro-3-methylamino-6-(trifluoromethyl)quinoxalin-2(1*H*)-one hydrochloride 7b and 6-chloro-3-methylamino-7-(trifluoromethyl)quinoxalin-2(1*H*)-one hydrochloride 6b. (1.18 g, 75%) as off-white crystals, mp > 316 °C (Found: C, 38.0; H, 2.8; N, 13.3; Cl, 22.6. Calc. for $C_{10}H_7ClF_3N_3O{\cdot}HCl$: C, 38.2; H, 2.6; N, 13.4; Cl, 22.6%); δ_H (400 MHz) **7b**: 3.06 [d, 2.7H, J(NH,CH_3) 4.7, CH_3], 7.47 (s, 0.9H, 8-H), 8.14 (br s, 0.9H, 5-H), 9.20 (br, 0.9H, N*H*Me), 12.87 (br s, 0.9H, N^1H); **6b**: 3.04 [d, 0.3H, J(NH,CH_3) 4.7, CH_3], 7.64 (s, 0.1H, 5-H), 7.84 (br s, 0.1H, 8-H), 9.10 (br, 0.1H, N*H*Me), 12.67 (br s, 0.1H, N^1H); δ_C (100 MHz) **7b**: 30.1 (s, CH_3), 118.0 (s, C-8), 119.0 (q, $J_{C5,F}$ 5, C-5), 121.3 (q, $J_{C6,F}$ 31.5, C-6), 122.9 (q, $J_{C,F}$ 272, CF_3), 125.3 (s, C-7), 125.7 (s, C-4a), 131.1 (s, C-8a), 149.7 and 151.5 (each s, C-2, -3); **6b**: 29.8 (s, CH_3), 115.1 (q, $J_{C8,F}$ 5, C-8), 122.4 (s, C-5), 126.2 (s, C-6), 150.7 and 151.2 (each s, C-2, -3).

7-Chloro-3-methylamino-6-(trifluoromethyl)quinoxalin-2(1*H*)-one 7b free base and 6-chloro-3-methylamino-7-(trifluoromethyl)quinoxalin-2(1*H*)-one 6b free base. 0.15 g (0.48 mmol) of a mixture of **7b** and **6b** was dissolved in EtOH (15 ml) and 1 M NaOH (0.48 ml) was added. The solvent was evaporated *in vacuo*; the residue was washed with water, to afford free bases **7b** and **6b** (0.12 g, 97%) as off-white crystals, mp 284–290 °C; δ_H (200 MHz) **7b base**: 2.92 [d, 2.79H, J(NH,CH_3) 4.9, NCH_3], 7.28 (s, 0.93H, 8-H), 7.62 (s, 0.93H, 5-H), 7.99 (q, 0.93H, N*H*Me), 12.4 (br, 1H, N^1-H); **6b base**: 2.94 [d, 0.21H, J(NH,CH_3) 4.9, NCH_3], 7.49 (s, 0.14H, 5-, 8-H), 8.24 (q, 0.07H, N*H*Me), 12.4 (br, 1H, N^1-H); δ_C (50 MHz) **7b base**: 27.6 (s, NCH_3), 117.2 (s, C-8), 121.0 (q, $J_{C6,F}$ 30.9, C-6), 123.2 (q, $J_{C,F}$ 270.3, CF_3), 123.3 (s, C-7), 123.4 (q, $J_{C5,F}$ 5.2, C-5), 131.7 and 132.5 (each s, C-4a, 8a), 151.5 and 151.6 (each s, C-2, -3); **6b base**: 27.6 (s, NCH_3), 126.1 and 126.7 (each s, C-5, -6), 151.3 and 152.6 (each s, C-2, -3).

Quinoxaline-2,3(1*H*,4*H*)-dione 3-oximes 9 and 10. General procedure

A 1,2-diaminobenzene derivative **1a** or **1b** (5 mmol) was dissolved or suspended in 96% EtOH (4 ml) at room temperature, chloro-[(*Z*)-hydroxyimino]acetic acid ethyl ester **8** (0.83 g, 5.5 mmol) was added, and then a solution of $NaHCO_3$ (0.63 g, 7.5 mmol) in water (12 ml) was added to the mixture dropwise. After storage at room temperature for 1 day the precipitate was filtered off, and washed with water.

6,8-Dichloroquinoxaline-2,3(1*H*,4*H*)-dione 3-oxime 9a and 5,7-dichloroquinoxaline-2,3(1*H*,4*H*)-dione 3-oxime 10a. (1.06 g, 80%) as beige crystals, mp 240 °C (decomp.) (Found: C, 36.25; H, 2.8; N, 16.15; Cl, 26.7. Calc. for $C_8H_5Cl_2N_3O_2{\cdot}H_2O$: C, 36.4; H, 2.7; N, 15.9; Cl, 26.85%); ν_{max} (KBr)/cm^{-1} 3188, 1682, 1626; δ_H (400 MHz) 10.3, 10.8 and 11.15 (each br, each 1H, NH, OH); **9a**: 7.06 (d, 0.76H, $J_{5,7}$ 2.0, 7-H), 7.31 (d, 0.76H, 5-H); **10a**: 6.97 (d, 0.24H, $J_{6,8}$ 2.0, 6-H), 7.29 (d, 0.24H, 8-H); δ_C (100 MHz) **9a**: 112.7 (dd, $J_{C5,H}$ 169.5, $J_{C5,7H}$ 5.6, C-5), 119.1 (s, C-8), 120.0 (dd, $J_{C7,H}$ 173.2, $J_{C7,5H}$ 5.6, C-7), 121.3 (dd, $J_{C8a,5H} = J_{C8a,7H}$ = 6.7, C-8a), 126.9 (dd, $J_{C6,7H} = J_{C6,5H}$ = 4.4, C-6), 129.5 (d, $J_{C4a,5H}$ 1.9, C-4a), 139.3 (s, C-3), 154.6 (s, C-2); **10a**: 113.8 (dd, $J_{C8,H}$ 167.8, $J_{C8,6H}$ 5.8, C-8), 122.2 (dd, $J_{C6,H}$ 170.3, $J_{C6,8H}$ 5.4, C-6), 124.8 (dd, $J_{C7,6H} = J_{C7,8H}$ = 4.4, C-7), 127.3 (d, $J_{C8a,8H}$ 2.0, C-8a), 154.0 (s, C-2); δ_N (50.7 MHz, DMSO-d_6) **9a**: 104.4 (N-4); MS (EI) *m*/*z* 245 (M^+); HPLC (Waters Maxima 820, eluent: 25 mM phosphate buffer–CH_3CN 675–325, analysis time: 30 min, detection: 222 nm) [t_R(major) 6.50, t_R(minor) 9.10 min]. Ratio of integration major : minor = 75 : 25.

7-Chloro-6-(trifluoromethyl)quinoxaline-2,3(1*H*,4*H*)-dione 3-oxime 10b and 6-chloro-7-(trifluoromethyl)quinoxaline-2,3-(1*H*,4*H*)-dione 3-oxime 9b. (1.13 g, 81%) as beige crystals, mp 277–280 °C (Found: C, 38.6; H, 1.9; N, 15.1; Cl, 13.0. Calc. for $C_9H_5ClF_3N_3O_2$: C, 38.7; H, 1.8; N, 15.0; Cl, 12.7%); ν_{max} (KBr)/cm^{-1} 3410, 3067, 1703; δ_H (400 MHz) **10b**: 7.09 (s, 0.79H, 8-H), 7.73 (s, 0.79H, 5-H), 10.3 (br s, 0.79H, N^4-H), 11.11 (s, 0.79H, OH), 11.51 (br s, 0.79H, N^1-H); **9b**: 7.29 (s, 0.21H, 8-H), 7.48 (s, 0.21H, 5-H), 10.46 (br s, 0.21H, N^4-H), 11.24 (br s, 0.21H, OH), 11.40 (br s, 0.21H, N^1-H); δ_C (100 MHz) **10b**: 113.2 (q, $J_{C5,F}$ 5.2, C-5), 116.8 (s, C-8), 120.4 (q, $J_{C6,F}$ 31.4, C-6), 121.3 (s, C-7), 123.2 (q, $J_{C,F}$ 270, CF_3), 126.3 (s, C-4a), 129.1 (s, C-8a), 139.4 (s, C-3), 154.6 (s, C-2); **9a**: 113.8 (q, $J_{C8,F}$ 5.2, C-8), 116.0 (s, C-5), 117.8 (q, $J_{C7,F}$ 31.4, C-7), 123.3 (q, $J_{C,F}$ 270, CF_3), 124.0 (s, C-6), 124.3 (s, C-8a), 131.3 (s, C-4a), 139.2 (s, C-3), 154.1 (s, C-2); Carbon–proton spin–spin interactions detected in ^{1}H–^{13}C HMBC experiment: **10b**: N(1)H (C-2, C-3, C-4a, C-8a, C-8), OH (C-3), N(4)-H (C-2, C-8a, C-3, C-4a), 5-H (C-4a, C-5, C-6, C-7), 8-H (C-4a, C-6, C-7, C-8, C-8a); **9b:** N(1)-H (C-3, C-4a, C-8), OH (C-3), N(4)-H (C-2, C-5, C-8a), 5-H (C-4a, C-5, C-8a, C-7, C-6), 8-H (C-4a, C-6, C-8); δ_N (50.7 MHz, DMSO-d_6) **10b**: 103.3 (N-4), 139.2 (N-1), 308.3 (C^3=N); **9b**: 105.7 (N-4), 137.8 (N-1), 310.7 (C^3=N); Nitrogen–proton spin–spin interactions detected in ^{1}H–^{15}N HMBC experiment: **10b**: N(1)-H

(N-1), OH (C^3=N), N(4)-H (N-4), 5-H (N-4), 8-H (N-1); **9b**: N(1)-H (N-1), OH (C^3=N), N(4)-H (N-4), 5-H (N-4), 8-H (N-1); MS (EI) *m*/*z* 279 (M^+); HPLC (Waters 991, eluent: n-hexane–ethanol–propan-2-ol, 800 : 150 : 50; analysis time: 50 min, detection: 234 nm) [t_R(major) 38.08, t_R(minor) 34.23 min]. Ratio of integration major : minor 80 : 20.

Quinoxalin-2(1*H*)-one oximes 12 and 13. General procedure

A 1,2-diaminobenzene derivative **1a** or **1b** (5 mmol) was dissolved or suspended in 96% EtOH (4 ml) at room temperature, (*Z*)-2-[(*E*)-hydroxyimino]acetohydroximoyl chloride **11** (0.67 g, 5.5 mmol) was added, and then a solution of $NaHCO_3$ (0.46 g, 5.5 mmol) in water (16 ml) was added dropwise. After storage at room temperature for 1 day the precipitate was filtered off, and washed with water.

5,7-Dichloroquinoxalin-2(1*H*)-one oxime 12a and 6,8-dichloroquinoxalin-2(1*H*)-one oxime 13a. (0.97 g, 84%) as yellow crystals (Found: C, 41.6; H, 2.0; N, 18.3. Calc. for $C_8H_5Cl_2N_3O$: C, 41.8; H, 2.2; N, 18.3%); the two isomers were separated by flash-vacuum chromatography twice on silica gel; eluents were $CHCl_3$–MeOH 95 : 5 and Et_2O, respectively.

5,7-Dichloroquinoxalin-2(1*H*)-one oxime 12a. Yellow crystals, mp 213–215 °C; δ_H (400 MHz) 7.15 (d, 1H, $J_{6,8}$ 2.0, 6-H), 7.22 (d, 1H, 8-H), 7.94 (s, 1H, 3-H), 10.51 (br s, 1H, NH), 10.83 (s, 1H, OH); δ_C (100 MHz) 113.1 (ddd, $J_{C8,8H}$ 170.0, $J_{C8,6H}$ 6.0, $J_{C8,NH}$ 3, C-8), 121.0 (dd, $J_{C6,6H}$ 173.7, $J_{C6,8H}$ 6.0, C-6), 128.4 (m, $J_{C4a,3H}$ 11, $J_{C4a,NH} = J_{C4a,6H} = J_{C4a,8H} = 5.5$, C-4a), 132.9 (d $J_{C5,6H}$ 4.5, C-5), 133.7 (t, $J_{C7,6H} = J_{C7,8H} = 5.0$, C-7), 135.9 (s, C-8a), 141.6 (dd, $J_{C2,3H}$ 10.7, $J_{C2,OH}$ 7.0, C-2), 151.7 (dd, $J_{C3,3H}$ 190.2, $J_{C3,NH}$ 4.5, C-3); MS (EI) *m*/*z* 229 (M^+).

6,8-Dichloroquinoxalin-2(1*H*)-one oxime 13a. Yellow crystals, mp 190 °C (decomp.); δ_H (400 MHz) 7.49 (d, 1H, $J_{5,7}$ 2.0, 5-H), 7.64 (d, 1H, 7-H), 8.03 (s, 1H, 3-H), 8.13 (br s, 1H, NH), 11.28 (s, 1H, OH); δ_C (100 MHz) 118.0 (dd, $J_{C8,NH}$ 5.4, $J_{C8,7H}$ 4.5, C-8), 125.1 (dd, $J_{C6,7H}$ 4.7, $J_{C6,5H}$ 3.8, C-6), 126.9 (dd, $J_{C5,5H}$ 168.7, $J_{C5,7H}$ 5.4, C-5), 128.3 (t, $J_{C8a,7H} = J_{C8a,5H} = 6.5$, C-8a), 128.7 (dd, $J_{C7,7H}$ 172.9, $J_{C7,5H}$ 5.4, C-7), 134.5 (ddd, $J_{C4a,3H}$ 14.6, $J_{C4a,NH}$ 6.7, $J_{C4a,5H}$ 2.7, C-4a), 141.3 (dd, $J_{C2,3H}$ 11.7, $J_{C2,OH}$ 6.7, C-2), 152.6 (dd, $J_{C3,3H}$ 190.8, $J_{C3,NH}$ 5.2, C-3); MS (EI) *m*/*z* 229 (M^+).

6-Chloro-7-(trifluoromethyl)quinoxalin-2(1*H*)-one oxime 13b and 7-chloro-6-(trifluoromethyl)quinoxalin-2(1*H*)-one oxime 12b. (1.03 g, 78%) as orange crystals, mp 197 °C (decomp.); they were purified by flash-vacuum chromatography on silica gel, eluent was diethyl ether, to give yellow crystals (Found: C, 41.2; H, 2.15; N, 16.2. Calc. for $C_9H_5ClF_3N_3O$: C, 41.0; H, 1.9; N, 15.9%); δ_H (400 MHz) **13b**: 7.54 and 7.64 (each s, each 0.77H, 5-, 8-H), 7.95 (d, 0.77H, $J_{3,NH}$ 1.9, 3-H), 10.51 (d, 0.77H, NH), 10.86 (s, 0.77H, OH); **12b**: 7.38 and 7.61 (each s, each 0.23H, 5-, 8-H), 7.90 (d, 0.23H, $J_{3,NH}$ 1.4, 3-H), 10.68 (d, 0.23H, NH), 10.93 (s, 0.23H, OH); δ_C (100 MHz) **13b**: 113.4 (q, $J_{C8,F}$ 5.7, C-8), 121.0 (s, C-6), 122.4 (q, $J_{C,F}$ 273.0, CF_3), 126.3 (q, $J_{C7,F}$ 30.8, C-7), 129.9 (s, C-5), 132.4 (s, C-8a), 135.5 (s, C-4a), 141.6 (s, C-2), 154.4 (s, C-3); **12b**: 116.3 (s, C-8), 118.3 (q, $J_{C6,F}$ 31.8, C-6), 122.8 (q, $J_{C,F}$ 271.8, CF_3), 126.8 (q, $J_{C5,F}$ 5.1, C-5), 130.8 (s, C-8a), 137.1 (s, C-4a), 141.1 (s, C-2), 152.2 (s, C-3); MS (EI) *m*/*z* 263 (M^+).

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