Pyrazolo[4',3':5,6]pyrano[2,3-*b*]quinoxalin-4(1*H*)-one: Synthesis and Characterization of a Novel Tetracyclic Ring System

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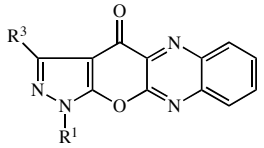
Received January 18, 2007



R^1 = Ph, R^3 = H; R^1 = Ph, R^3 = Me; R^1 = R^3 = Ph;
R^1 = *p*-methoxybenzyl, R^3 = H; R^1 = R^3 = H

Derivatives of the hitherto unknown ring system, pyrazolo[4',3':5,6]pyrano[2,3-*b*]quinoxalin-4(1*H*)-one, are synthesized in one step from the corresponding 1-substituted or 1,3-disubstituted 2-pyrazolin-5-ones and 3-chloroquinoxaline-2-carbonyl chloride using calcium hydroxide in boiling 1,4-dioxane. The parent system carrying no substituent in positions 1 and 3 is obtained upon treatment of the 1-PMB (*p*-methoxybenzyl) protected congener with trifluoroacetic acid. Detailed NMR spectroscopic investigations including unambiguous chemical shift assignments of all ^{1}H, ^{13}C, and ^{15}N resonances of the obtained tetracycles are reported.

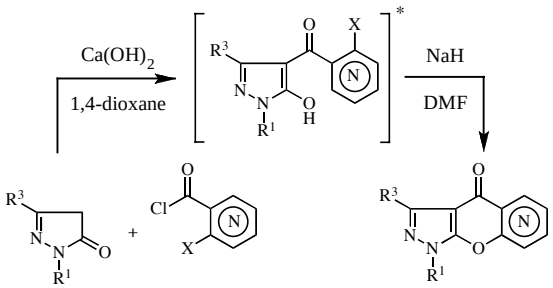
J. Heterocyclic Chem., **44**, 1139 (2007).

INTRODUCTION

Recently, we reported the preparation of novel heterocyclic ring systems containing a pyrano[2,3-*c*]-pyrazol-4(1*H*)-one moiety [1–3] as building blocks for biologically active compounds. Specifically, the reaction of 2-pyrazolin-5-ones (tautomers to 5-hydroxypyrazoles [4]) with different *o*-haloarenecarbonyl chlorides under conditions of the Jensen reaction (calcium hydroxide, refluxing 1,4-dioxane [5]) gave acylated pyrazole intermediates, which were then cyclized with sodium hydride in boiling dimethylformamide to polycyclic compounds (Scheme 1). However, we found that with N-heterocyclic acid chlorides carrying an 'activated' halogen atom in *ortho* position to the ring nitrogen (derived from 2-chloronicotinic acid, 4-chloronicotinic acid, 3-fluoro-picolinic acid, 4-chloropyridazine-3-carboxylic acid, and 3-chloroquinoxaline-2-carboxylic acid) a spontaneous intramolecular cyclization to the target polycycles was

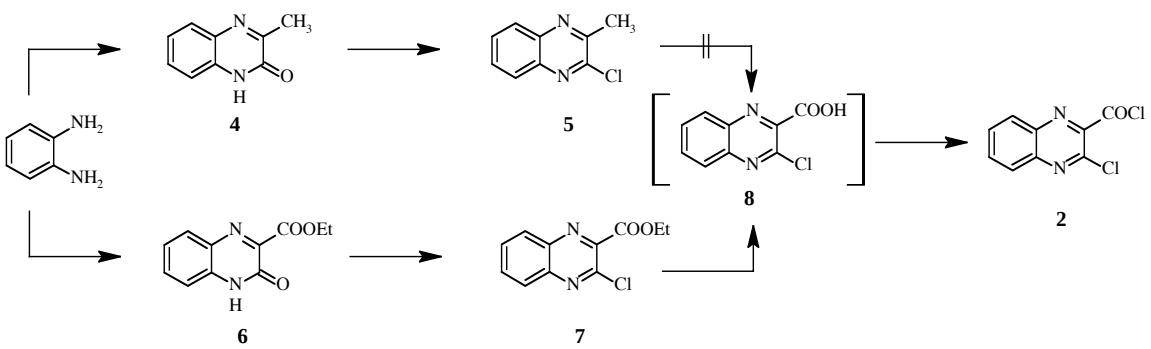
Scheme 1

Reported synthesis of pyrido-pyrano[2,3-*c*]pyrazol-4(1*H*)-ones



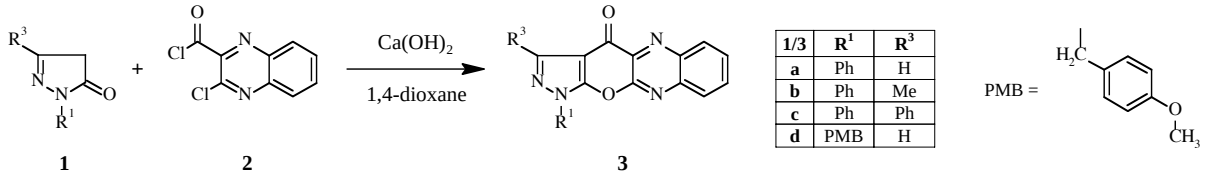
* not isolated with some *o*-halo derivatives of picolinic, nicotinic, 3-pyridazinic, and 2-quinolic acid chlorides

Scheme 2



Synthesis of the acid chloride **2**

Scheme 3



1/3	R^1	R^3
a	Ph	H
b	Ph	Me
c	Ph	Ph
d	PMB	H

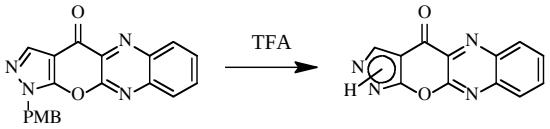
1 **2** **3**

Synthesis of the tetracyclic title compounds

observed under Jensen reaction condition (Scheme 1) [1, 3]. In contrast, no such behavior was noticed in the reactions of 3-chloroisonicotinic acid chloride and of 5-chloro-2-(methylthio)pyrimidine-4-carbonyl chloride [3].

Due to the importance of the N-heterocycle quinoxaline as a structural element in many biologically active compounds [6], even in drugs like Brimonidine (Alphagan™) [7, 8], we aimed at the enlargement of our heterocyclic portfolio to include also the new quinoxalino fused skeleton of type **3**. The synthesis of compounds **3** was envisaged as outlined in Scheme 3 and we were interested in whether the primary product in the reaction of **1** with **2** would undergo spontaneous ring closure during the acylation reaction.

Scheme 4



3d **3e**

Synthesis of the unsubstituted parent ring system

RESULTS AND DISCUSSION

Since the quinoxaline-2-carbonyl chloride **2** is not commercially available, we planned its synthesis as outlined in Scheme 2 (upper line) according to literature methods. Unfortunately, methylquinoxaline **5** was not oxidized to the corresponding acid **8**, which has been reported recently by *Mahesh et al.* [9] using Na_2CrO_7/H_2SO_4 as the oxidation reagent. Even switching to aqueous $KMnO_4$ did not yield the desired acid. Thus, we changed our plan and introduced the desired carbonyl group to the quinoxaline core in the first reaction step (Scheme 2, lower line). Subsequent transformations according to known procedures gave the acid chloride **2**.

Four different pyrazolones (**1a–d**), either commercially available or easily accessible according to known literature procedures, were reacted with 3-chloroquinoxaline-2-carbonyl chloride (**2**) using calcium hydroxide in boiling 1,4-dioxane (Scheme 3). NMR analysis of the products proved that cyclization had already occurred under the conditions of the acylation reaction – no intermediate 4-aroylpyrazol-5-ols were isolated.

The synthesis of the N1- and C3-unsubstituted compound **3e** was achieved by treatment of the N1-PMB (*p*-methoxybenzyl) protected congener **3d** with trifluoroacetic acid (Scheme 4).

Detailed NMR spectroscopic analyses for all prepared compounds are reported. Full and unambiguous assignment for all proton, carbon, and nitrogen resonances

Table 2

^{15}N NMR shifts of compounds **3** (solvents as in Table 1)

Comp	N-1	N-2	N-5	N-10
3a	–185.4	–85.4	–38.1	–97.5
3b	–[a]	–[a]	–[a]	–[a]
3c	–[a]	–[a]	–[a]	–[a]
3d	–188.9	–83.0	–37.9	–98.0
3e		–176.9[b]	–37.9	–98.6

[a] too badly soluble. [b] only one N-signal found.

Table 1

^{1}H NMR data of compounds **3**

Comp	Solvent	H-6	H-7	H-8	H-9	H of R^1	R^3-H or H-3
3a	DMSO-d_6	8.40[a]	8.01[a]	8.10[a]	8.18[a]	Ph: 7.55 (4), 7.71 (3,5), 7.95 (2,6)	8.52
3b	DMSO-d_6	8.41[a]	8.00[a]	8.09[a]	8.17[a]	Ph: 7.52 (4), 7.68 (3,5), 7.92 (2,6)	2.62
3c	$CDCl_3$	8.53	7.94	8.01[b]	8.17[b]	Ph: 7.49 (4), 7.64 (3,5), 8.08 (2,6)	Ph: 7.49 (4), 7.54 (3,5), 8.51 (2,6)
3d	DMSO-d_6	8.36[a]	7.98[a]	8.07[a]	8.14[a]	3.71 (OMe), 5.48 (CH_2); Ph: 6.93 (3,5), 7.36 (2,6)	8.25
3e	DMSO-d_6	8.32	7.92	8.02	8.09	13.96 (NH)	8.75

[a] ^3J(H-6,H-7) = 8.4 Hz, ^4J(H-6,H-8) = 1.4 Hz, ^5J(H-6,H-9) = 0.6 Hz, ^3J(H-7,H-8) = 6.8 Hz, ^4J(H-7,H-9) = 1.4 Hz, ^3J(H-8,H-9) = 8.4 Hz.
[b] ^3J(H-8,H-9) = 8.4 Hz.

of tetracycles **3** was achieved by combined application of standard NMR spectral techniques [10] such as NOE-difference experiments, fully ^{1}H-coupled ^{13}C NMR spectra, APT, HMQC and HMBC spectra as well as experiments with selective excitation such as 1D-TOCSY [11], 1D-HETCOR [12] and selective long-range INEPT [13, 14]. The ^{15}N NMR spectra were mainly recorded using the gradient selected, sensitivity enhanced HMBC sequence [15]. The obtained data show a high degree of consistency and are summarized in Table 1 (^{1}H NMR), in Table 2 (^{15}N NMR), and in Table 3 (^{13}C NMR).

Table 3

^{13}C NMR data of compounds **3** (solvents as in Table 1)

Comp	C-3	C-3a	C-4	C-4a	C-5a	C-6	C-7	C-8	C-9	C-9a	C-10a	C-11a	C of R^{1}	C of R^{3}
3a	137.4	108.2	171.0	136.3	140.55	130.1	130.6	133.8	127.6	140.58	152.7	152.5	Ph: 121.9 (2,6), 128.4 (4), 129.8 (3,5), 136.2 (1)	–
3b	147.7	106.4	171.7	136.7	140.6	130.1	130.6	133.8	127.6	140.6	152.9[a]	152.6[a]	Ph: 121.7 (2,6), 128.0 (4), 129.7 (3,5), 136.2 (1)	13.8 (Me)
3c	150.6	105.5	171.0	135.5	142.1	131.1	130.7	134.0	127.9	141.7	153.0[a]	151.9[a]	Ph: 122.2 (2,6), 128.4 (4), 129.7 (3,5), 136.6 (1)	Ph: 128.4 (3,5), 128.6 (2,6), 129.9 (4), 130.8 (1)
3d	136.1[b]	106.9[c]	170.8	136.5	140.42	130.0	130.4	133.6	127.5	140.43	152.7	152.7[d]	50.4[e] (CH_2), 55.1[f] (OMe); Ph: 114.1 (3,5), 127.3 (1), 129.4 (2,6), 159.1 (4)	–
3e	130.3[g]	107.3	172.8	136.1	140.0	130.1	129.8	133.5	127.5	141.0	154.0	160.3[g]	–	–

[a] not unambiguously assigned. [b] ^{1}J = 194.5 Hz. [c] ^{2}J(C-3a,H-3) = 10.5 Hz. [d] ^{3}J(C-11a,CH_2) = 2.6 Hz. [e] ^{1}J = 142.5 Hz. [f] ^{1}J = 144.4 Hz. [g] broad signal.

EXPERIMENTAL

Materials and Methods: Melting points were determined on a Reichert–Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV) and on a Finnigan MAT 8230 instrument (EI, 70 eV, HRMS). IR spectra were recorded on a Perkin-Elmer FTIR spectrum 1000 spectrophotometer. Elemental analyses were performed at the Microanalytical Laboratory, University of Vienna, using a Perkin-Elmer 2400 CHN Elemental Analyzer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian UnityPlus 300 spectrometer at 28 °C (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) or on a Bruker Avance 500 spectrometer at 293 K (500.13 MHz for ^{1}H, 125.77 MHz for ^{13}C). The centre of the solvent signal was used as an internal standard which was related to TMS with δ = 7.26 ppm (^{1}H in $CDCl_3$), δ = 2.49 ppm (^{1}H in DMSO-d_6), δ = 77.0 ppm (^{13}C in $CDCl_3$), and δ = 39.5 ppm (^{13}C in DMSO-d_6). ^{15}N-NMR spectra were obtained on a Bruker Avance 500 instrument with a 'directly' detecting broadband observe probe and were referenced against external nitromethane (coaxial capillary). Systematic names according to IUPAC recommendations were generated with ACD/Name [16] and subsequently proved manually to ensure correct nomenclature within this publication [17]. Starting materials **1** were commercially available or prepared according to literature procedures: **1a** [18], **1c** [19], **1d** [20]. Product yields were not optimized.

General Procedure for the Synthesis of Tetracycles 3. Under anhydrous conditions, to a suspension of pyrazolone **1a–d** (3 mmol) and $Ca(OH)_2$ (6 mmol) in anhydrous 1,4-dioxane (5 mL) was added a suspension of acid chloride **2** (3 mmol) in anhydrous 1,4-dioxane (5 mL). The reaction mixture was refluxed for 3 h under stirring. After cooling to room temperature, the mixture was treated with 2 *M* HCl (15–20 mL), stirred for 15 min, and poured into H_2O (20 mL). After 30 min, the solid product was collected by filtration, washed with H_2O, and recrystallized. NMR data are presented in Tables 1–3.

1-Phenylpyrazolo[4',3':5,6]pyrano[2,3-*b*]quinoxalin-4(1*H*)-one (**3a**). This compound was obtained in 47% yield as beige crystals (1-propanol), mp 298–299 °C; IR: CO 1698 cm^{-1}; MS: *m/z* 315 (M^+ + 1, 19), 314 (M^+, 100), 186 (28), 91 (35), 77 (30). *Anal.* Calcd. for $C_{18}H_{10}N_4O_2$: C, 68.79; H, 3.21; N, 17.83. Found: C, 68.49; H, 3.22; N, 17.62.

3-Methyl-1-phenylpyrazolo[4',3':5,6]pyrano[2,3-*b*]quinoxalin-4(1*H*)-one (**3b**). This compound was obtained in75% yield as a beige powder, mp 295–297 °C; IR: CO 1678 cm^{-1}; MS: *m/z* 329 (M^+ + 1, 17), 328 (M^+, 100), 91 (83), 77 (47). *Anal.* Calcd. for $C_{19}H_{12}N_4O_2$: C, 69.51; H, 3.68; N, 17.06. Found: C, 69.25; H, 3.63; N, 16.81.

1,3-Diphenylpyrazolo[4',3':5,6]pyrano[2,3-*b*]quinoxalin-4(1*H*)-one (**3c**). This compound was obtained in 45% yield as a yellowish powder (toluene–hexanes), mp 301–303 °C; IR: CO 1676 cm^{-1}; MS: *m/z* 391 (M^+ + 1, 20), 390 (M^+, 100), 361 (31), 91 (35), 77 (48), 51 (20). *Anal.* Calcd. for $C_{24}H_{14}N_4O_2 \cdot 0.3\ H_2O$: C, 72.83; H, 3.72; N, 14.16. Found: C, 72.81; H, 3.90; N, 14.11.

1-(4-Methoxybenzyl)pyrazolo[4',3':5,6]pyrano[2,3-*b*]-quinoxalin-4(1*H*)-one (**3d**). This compound was obtained in 25% yield as brownish crystals (toluene), mp 225–227 °C; IR: CO 1687 cm^{-1}; MS: *m/z* 358 (M^+, 16), 121 (100). *Anal.* Calcd. for $C_{20}H_{14}N_4O_3$: C, 67.03; H, 3.94; N, 15.63. Found: C, 67.13; H, 4.03; N, 15.38.

Pyrazolo[4',3':5,6]pyrano[2,3-*b*]quinoxalin-4(1*H*)-one (**3e**). Under anhydrous conditions, a solution of **3d** and excess TFA (5 mL) was stirred overnight at 70 °C. After removal of TFA under reduced pressure, the residue was dried over solid KOH for 1 h. Then ice-cold Et_2O–acetone (2:1, 5 mL) was added and the resulting suspension was filtered and the solid was washed with cold Et_2O to give the unsubstituted parent compound **3e** in 81% yield as a brownish powder, mp > 320 °C; IR: CO 1674 cm^{-1}; MS: *m/z* 238 (M^+, 100), 110 (80), 53 (28). HRMS Calcd. for $C_{12}H_6N_4O_2$: 238.0491. Found: 238.0487. NMR data are presented in Tables 1–3.

3-Methylquinoxalin-2(1*H*)-one (**4**). *o*-Phenylenediamine (21.63 g, 200 mmol), pyruvic acid (17.61 g, 200 mmol), and ethanol (96%,

700 mL) were refluxed for 90 min. The reaction mixture was allowed to gain room temperature. Upon staying in the refrigerator overnight, the product separated as orange crystals, which were filtered off and washed with cold ethanol to yield 19.90 g (62%) of **4**, mp 237–239 °C (lit. [21] 241–243 °C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.37 (3H, s, Me), 7.22 (1H, m, H-6), 7.24 (1H, m, H-8), 7.42 (1H, m, H-7), 7.65 (1H, m, H-5), 12.25 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4 (Me, ^1J = 128.4 Hz), 115.2 (C-8, ^1J = 163.3 Hz, ^3J(C-8,H-6) = 7.9 Hz), 122.9 (C-6, ^1J = 163.1 Hz, ^3J(C-6,H-8) = 8.5 Hz), 127.8 (C-5, ^1J = 161.6 Hz, ^3J(C-5,H-7) = 7.7 Hz), 129.2 (C-7, ^1J = 163.3 Hz, ^3J(C-7,H-5) = 8.5 Hz), 131.6 (C-4a), 131.9 (C-8a), 154.9 (C-2, ^3J(C-2,Me) = 2.7 Hz), 159.1 (C-3, ^2J(C-3,Me) = 7.1 Hz); ^{15}N NMR (50 MHz, DMSO-d_6): δ –233.0 (N-1), –53.5 (N-4); MS: *m/z* 160 (M^+, 82), 132 (97), 131 (100).

2-Chloro-3-methylquinoxaline (**5**). Quinoxalinone **4** (11.69 g, 73 mmol) and excess $POCl_3$ (150 mL) were refluxed for 90 min. Under reduced pressure, $POCl_3$ was distilled off and the residue was poured onto ice-water (~ 300 mL). Upon treatment of the solution with concd. NH_3 (pH was brought to 3–4) and standing for 3 h, the red–brownish product **5** separated (6.17 g, 47%), mp 91–93 °C (lit. [22] 90–92 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.81 (3H, s, Me), 7.68* (1H, m, H-7), 7.71* (1H, m, H-6), 7.94* (1H, m, H-8), 7.98* (1H, m, H-5); * the differenttiation between H-5/8 and H-6/7 was not unambiguously possible; ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2 (Me, ^1J = 129.2 Hz), 128.1* (C-8), 128.4* (C-5), 129.9* (C-7), 130.0* (C-6), 140.8* (C-8a), 140.9* (C-4a), 147.7 (C-2, ^3J(C-2,Me) = 3.8 Hz), 152.7 (C-3, ^2J(C-3,Me) = 7.0 Hz); * the differentiation between C-4a/8a, C-5/8, and C-6/7 was not unambiguously possible; ^{15}N NMR (50 MHz, $CDCl_3$): δ –67.3 (N-1), –50.6 (N-4); MS: *m/z* 180 (M^+, 12), 178 (M^+, 39), 143 (100), 102 (29).

Ethyl 3-Oxo-3,4-dihydroquinoxaline-2-carboxylate (**6**). To a suspension of diethyl oxomalonate (26.56 g, 150 mmol) in ethanol (96%, 250 mL) was added *o*-phenylenediamine (16.44 g, 150 mmol). The mixture was refluxed for 2 h and the hot solution was filtered. After addition of water (400 mL) the mixture was refluxed again until the solution became clear. This solution was filtered again, and upon standing at room temperature overnight, product **6** crystallized as yellowish needles (24.51 g, 75%), mp 176–178 °C (lit. [23] 175.5–176.5 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (3H, t, ^3J(CH_3,CH_2) = 7.1 Hz, CH_3), 4.54 (2H, q, ^3J(CH_2,CH_3) = 7.1 Hz, CH_2), 7.39 (1H, m, H-7), 7.47 (1H, m, H-5), 7.61 (1H, m, H-6), 7.93 (1H, m, H-8), 12.95 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (CH_3, ^1J = 127.4 Hz, ^2J(CH_3,CH_2) = 2.6 Hz), 62.5 (CH_2, ^1J = 148.7 Hz, ^2J(CH_2,CH_3) = 4.5 Hz), 116.4 (C-5), 124.9 (C-7), 130.1 (C-8), 132.0 (C-8a), 132.2 (C-4a), 132.7 (C-6), 148.5 (C-2), 154.6 (C-3), 163.4 (CO); ^{15}N NMR (50 MHz, $CDCl_3$): δ –225.0 (N-4), –40.3 (N-1); MS: *m/z* 218 (M^+, 56), 174 (31), 146 (100), 145 (34), 144 (35), 118 (68), 90 (58).

Ethyl 3-Chloroquinoxaline-2-carboxylate (**7**). A mixture of quinoxalinone **6** (18.95 g, 85 mmol) and excess $POCl_3$ (100 mL) was refluxed for 30 min. Under reduced pressure, $POCl_3$ was distilled off and the residue was poured onto ice-water (~ 300 mL). Upon neutralization with concentrated NH_3, product **7** separated and was then collected by filtration. To increase the yield, the filtrate was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were washed once with water (10 mL), dried over anhydrous Na_2SO_4, and concentrated to dryness under reduced pressure. Compound **7** was obtained as a beige solid in a total yield of 95% (19.11 g), mp 40 °C (lit. [24] 40 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (3H, t, ^3J(CH_3,CH_2) = 7.2 Hz, CH_3), 4.55 (2H, q, ^3J(CH_2,CH_3) = 7.2 Hz, CH_2), 7.80* (1H, m, H-7), 7.85* (1H, m, H-6), 8.03* (1H, m, H-5), 8.15* (1H, m, H-8); * the differentiation between H-5/8 and H-6/7 was not unambiguously possible; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3, ^1J = 127.5 Hz, ^2J(CH_3,CH_2) = 2.7 Hz), 62.9 (CH_2, ^1J = 148.9 Hz, ^2J(CH_2,CH_3) = 4.5 Hz), 128.3* (C-5), 129.6* (C-8), 130.9* (C-7), 132.5* (C-6), 139.6* (C-8a), 142.1* (C-4a), 143.8* (C-2), 144.7* (C-3), 163.8 (CO); * the differentiation between C-2/3, C-4a/8a, C-5/8, and C-6/7 was not unambiguously possible; ^{15}N NMR (50 MHz, $CDCl_3$): δ –61.2 (N-4), –47.7 (N-1); MS: 238 (M^+, 3), 236 (M^+, 8), 192 (23), 166 (33), 165 (21), 164 (100), 163 (40), 129 (42), 102 (50), 75 (21).

3-Chloroquinoxaline-2-carboxylic Acid (**8**). To ester **7** (9.94 g, 42 mmol), dissolved in aqueous methanol (80%, 200 mL), was added Na_2CO_3 (2.50 g, 24 mmol) and the reaction mixture was refluxed for 4 h. Then the solution was acidified with 2 *M* HCl and the solvent was removed under reduced pressure to yield the crude acid **8**, which was used 'as is' in the next reaction, mp 142–145 °C (lit. [23] 146–147 °C); MS: *m/z* 210 (M^+, 13), 208 (M^+, 39), 166 (34), 164 (100), 129 (80), 102 (95), 76 (32), 75 (40), 50 (27).

3-Chloroquinoxaline-2-carbonyl Chloride (**2**). A suspension of the crude acid **8** in toluene (30 mL) was treated with DMF (1 drop) and with excess $SOCl_2$ (30 mL) and the mixture was refluxed for 3 h. The solution was filtered, and the $SOCl_2$ was removed under reduced pressure. Upon further concentration under reduced pressure, the acid chloride **2** separated as yellow crystals (3.46 g, 36%), mp 106–110 °C (lit. [25] 117–119 °C, lit. [26] 127 °C); IR: CO 1778 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92* (1H, m, H-7), 7.98* (1H, m, H-6), 8.10* (1H, m, H-5), 8.24* (1H, m, H-8); * the differentiation between H-5/8 and H-6/7 was not unambiguously possible; ^{13}C NMR (125 MHz, $CDCl_3$): δ 128.3* (C-5), 130.1* (C-8), 131.7* (C-7), 134.3* (C-6), 139.4* (C-8a), 142.8* (C-4a), 142.9* (C-2), 143.0* (C-3), 166.0 (CO); * the differentiation between C-2/3, C-4a/8a, C-5/8, and C-6/7 was not unambiguously possible; ^{15}N NMR (50 MHz, $CDCl_3$): δ –57.8 (N-4), –40.6 (N-1); MS: *m/z* 230 (M^+, 2), 228 (M^+, 10), 226 (M^+, 15), 193 (17), 191 (47), 165 (31), 163 (100), 102 (49), 75 (19). *Anal.* Calcd. for $C_9H_4Cl_2N_2O$: C, 47.61; H, 1.78; N, 12.34. Found: C, 47.79; H, 2.01; N, 12.39.

Acknowledgement. We are grateful to Dr. L. Jirovetz for recording the mass spectra.

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