Synthesis of New Quinoxaline Derivatives by Reductive Cyclization of Various 1-(2-Nitrophenyl)-2-cyanoamines

Tristan Renaud,[a] Jean-Pierre Hurvois,*[b] and Philippe Uriac[a]

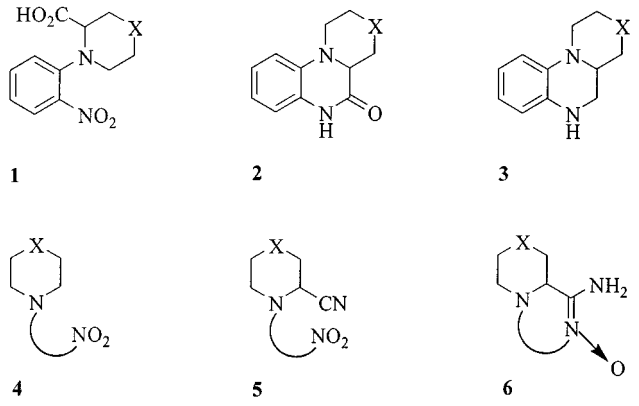
Keywords: C−C coupling / Cyclizations / Electrochemistry / Nitrogen heterocycles / Reductions

The electrochemical cyanation of various six-membered *N*-(2-nitrophenyl) heterocyclic amines, including piperidine, morpholine, thiomorpholine, and *N*-Boc-protected piperazine derivatives, was investigated. The expected cyanoamines **5** were obtained in good yields and subjected to catalytic hydrogenation to afford the corresponding cyclic amidine *N*-oxides **6**. The reductive cyclization proceeded through the formation of a hydroxylamine, which cyclized onto the cyano moiety. The stereoselectivity of the cyclization reaction was studied for the cases both of *trans*-**5f**, in which the 2-cyano substituent was axial and the 4-methyl substituent equatorial, and of *cis*-**5f**, in which both the 2-cyano and the 4-methyl substituents were equatorial. The expected tetrahydroquinoxalines **3** were conveniently prepared in a following step by the catalytic hydrogenation of cyclic amidines **6** in the presence of Pearlman's catalyst at five atmospheres of hydrogen pressure.

Introduction

The synthesis of new tetrahydroquinoxaline derivatives is of interest due to the fact that such systems are models for tetrahydrofolic acid.[1] Earlier studies of the formation of such systems were based on the reductive cyclization of suitably substituted quinoxalines, which could be prepared directly by condensation of 1,2-diaminobenzene with the desired 1,2-dicarbonyl compounds.[2a] A more recent approach, aimed at the preparation of chiral tetrahydro-2-vinylquinoxalines, showed that such derivatives could also be directly prepared by Pd^0-catalyzed condensation between substituted 1,2-diaminobenzenes and (*Z*)-1,4-bis(methoxycarbonyloxy)but-2-ene.[2b] Essentially, reductive ring-closure of nitro acids **1**, followed by the reduction of the intermediate lactam **2**, was used to synthesize the desired molecules **3**.[2c−2e] Up to now, only commercially available amino acids like proline (X = 0) or pipecolic acid (X = CH_2) have been used as starting materials for such a synthetic purpose. The difficulties found in the synthesis of modified amino acids (X = S,[3a,3b] O,[3c] NH[3d]) might be the cause of their limited synthetic use as suitable starting materials in the synthesis of modified quinoxalines **3**.

In earlier papers, we described the synthesis of various cyanoamines of type **5** which, after reduction of their nitro group under protic conditions, yielded the corresponding cyclic six-membered amidines **6** in good yield.[4] In this paper we report the extension of this methodology to nitroaryl-substituted amines **4**, which were selected as starting materials for the preparation of a set of amidines **6**. Finally, these amidines were hydrogenated in the presence of Pearlman's catalyst to afford their corresponding tetrahydroquinoxalines **3**.



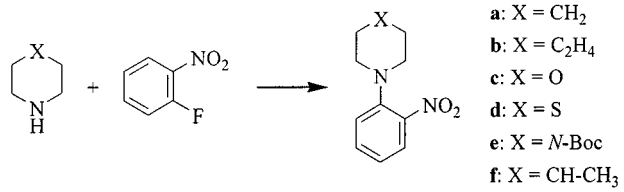
Results and Discussion

The starting nitroamines **4a−d** and **4f** were prepared without difficulty by direct treatment of 1-fluoro-2-nitrobenzene with the requisite amines, as detailed elsewhere.[2c] The synthesis of **4e** was performed in two consecutive steps, starting with the condensation of 1-fluoro-2-nitrobenzene with an equimolar amount of piperazine in a two-phase system (CH_2Cl_2/40% aq. NaOH), and followed by the introduction of a Boc protecting group at the resulting secondary amino function. This common mode of protection is

[a] Laboratoire de Chimie Pharmaceutique,
Université de Rennes I,
Avenue du Professeur Léon Bernard, 35043 Rennes Cedex, France
[b] Laboratoire d'Electrochimie et d'Organométalliques,
U.M.R. 6509, Campus de Beaulieu, 35042 Rennes Cedex, France
Fax: (internat.) +33-2/9928-1660
E-mail: Jean-Pierre.Hurvois@univ-rennes1.fr

  1434−193X/01/0305−0987 $ 17.50+.50/0

necessary to avoid overoxidation of the unprotected secondary amino group at the anode (Scheme 1).



4a-f

Scheme 1. Synthesis of nitroamines **4a−f**

Electrochemical Investigations

Prior to macroscale electrolysis, analytical investigations were performed at a glassy carbon electrode, using methanol as solvent and lithium perchlorate (20 g/L) as supporting electrolyte. Peak potentials, expressed in V. vs. SCE, are collected in Table 1.

Table 1. Voltammetric investigations: glassy carbon electrode (diameter 4.5 mm); solvent: MeOH; supporting electrolyte: $LiClO_4$ (20 g/L); product concentration 10^{-2} mol/L, scan rate: 0.1 V/s; reaction conditions: (1): in absence of NaCN, (2): in presence of 4 equiv. of NaCN per mol of substrate

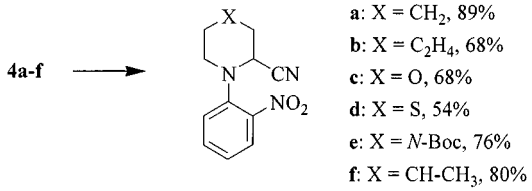
Product	$Ep_{A(1)}$	$Ep_{B(1)}$	$Ep_{A(2)}$	$Ep_{B(2)}$
4a	1.40	1.55	1.10	1.50
4b	1.20	1.60	1.10	1.50
4c	1.60[a]	–	1.25	1.65
4d	1.40[a]	–	1.25	1.65
4e	1.50[a]	–	1.15	1.55
4f	1.30	1.55	1.15	1.55

[a] In the case of compounds **4c−e** peaks $Ep_{A(1)}$ and $Ep_{B(1)}$ were superimposed.

In the absence of sodium cyanide, compounds **4a−b** and **4f** displayed two successive irreversible peaks in the range of $Ep_{A(1)}$ = +1.20−1.40 V and $Ep_{B(1)}$ = +1.55−1.60 V, while compounds **4c−e** exhibited a single irreversible peak $Ep_{A(1)}$ = +1.40−1.60 V (see footnote of Table 1), the height of which was twice that reported for $Ep_{A(1)}$. Previous studies performed in our laboratory have shown that the first oxidation peak [$Ep_{A(1)}$] was attributable to the amine → iminium transformation,[5] whilst the oxidation of the aminoether (resulting from the addition of methanol to the iminium species) occurred either at the second oxidation peak [$Ep_{B(1)}$] or at $Ep_{A(1)}$ (compounds **4c−e**; see footnote of Table 1). The addition of sodium cyanide (four equiv. per mol of substrate) caused a significant shift of the first oxidation peak towards less positive values [$Ep_{A(2)}$ = +1.10−1.25 V] and a splitting of the single oxidation peaks [$Ep_{A(1)}$; see footnote of Table 1] into two, recorded at $Ep_{A(2)}$ and $Ep_{B(2)}$ = +1.50−1.65 V. These observations are consistent with the iminium species electrogenerated at $Ep_{A(2)}$ being trapped by cyanide anions, leading to a new compound (identified as the corresponding cyanoamine), that can be oxidized at $Ep_{B(2)}$. As confirmation, a similar oxidation peak [$Ep_{B(2)}$] was recorded on voltammograms of cyanoamines **5a−f** under similar reaction conditions. Taken together, these results indicated that selective transformations might be performed at the first oxidation peak of amines **4a−f**.

Oxidation of Amines 4a−f

Firstly, we decided to focus on the electrochemical behavior of amines that differ from each other either by the size of their ring (compounds **4a−b**), or by the presence of a heteroatom (X = O, S, *N*-Boc) in the position γ to the nitrogen atom (compounds **4c−e**). The oxidation of amines **4a−e** (up to 3 g) was effected in a divided cell apparatus fitted with a planar vitreous carbon electrode (diameter 60 mm) as anode, and a carbon rod as cathode. Experiments were performed in methanol at a controlled potential (depending on the nature of the substrate, see Experimental Section), in the presence of $LiClO_4$ (20 g/L) as supporting electrolyte and four equivalents of NaCN as cyanating agent. After the consumption of 2.0−2.7 mol of electrons per mol of substrate, the completion of the reaction was attested to by the disappearance of the first oxidation peak. The addition of water resulted in the precipitation of the crude material, and cyanoamines **5a−e** were obtained in 54−89% isolated yield after crystallization or rapid passage through a silica column (Scheme 2).



rac-**5a-f**

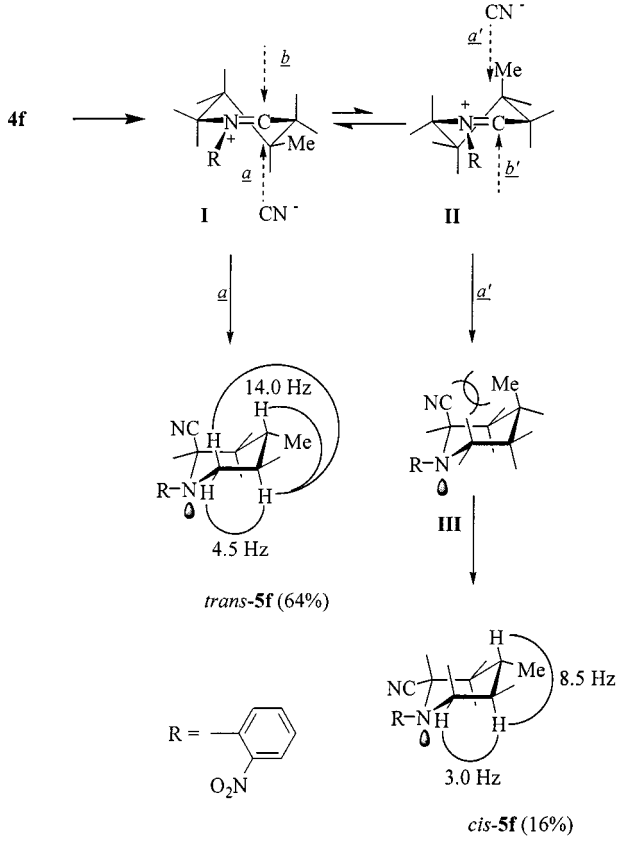
Scheme 2. Synthesis of cyanoamines **5a−f**

In all cases, the ^1H NMR spectra were consistent with a ring cyanation and included a characteristic 2-H signal at δ = 4.40−4.70, which appeared as a triplet or a broadened singlet. The ^{13}C NMR spectra exhibited a characteristic C-2 doublet resonance system found in the region δ = 52−55 and a quaternary CN signal in the region δ = 116−119. With the exception of **5e**, a weak absorption at 2220 cm^{-1} in the IR spectra indicated the presence of the cyano group. The chemistry of such compounds has received much attention since the discovery that they represent a valuable source of iminium cations, but it has also been reported that problems may arise from their instability.[6] Therefore, we were please to find that cyanoamines **5a−e** proved to be extremely stable and could be handled without difficulties and stored for a month under normal conditions without loss of quality.

A C-4 methyl-substituted piperidine derivative seemed to be a convenient substrate on which to study the stereochemical outcome of the cyanation procedure. Compound **4f** was selected as the model compound and, after being electrolyzed, afforded an 80:20 diastereomeric mixture. Both adducts, *trans*- and *cis*-**5f**, could easily be separated by careful filtration on a silica column, with a mixture of petroleum ether and diethyl ether (2:1) as eluent. The major iso-

mer *trans*-**5f** (64%) was eluted first, followed by the more polar *cis*-**5f** (16%).

The configuration of the major isomer *trans*-**5f** was determined by examination of selected ^{1}H-^{1}H coupling constants. Evidence for the equatorial disposition of 2-H was given by a broad singlet signal at δ = 4.50. On irradiation at δ = 2.98 (6-H^a), a vicinal coupling of 4.5 Hz was lost from the resonance of 5-H^a (δ = 1.37), which appeared as a large quadruplet (J = 13.0 Hz) signal, indicating that both the vicinal protons 6-H^b and 4-H were axial and, therefore, an equatorial disposition for the 4-methyl substituent. The ^{1}H NMR spectrum of *cis*-**5f** displayed a significant doublet of doublets system [^3J(2,3a) = 8.0 Hz, ^3J(2,3b) = 4.0 Hz] at δ = 4.14, placing 2-H in a pseudoaxial orientation. On irradiation at δ = 3.42 (6-H^b), a vicinal coupling constant of 3.0 Hz was lost from the resonance system of 5-H^a, which appeared as a doublet of triplets [^2J(5a,5b) = 14.0 Hz, ^3J(5a,6a) = ^3J(5a,4) = 8.5 Hz] system at δ = 1.55. The magnitudes of these coupling constants were in agreement with an equatorial disposition of the methyl group at C-4. The formation of these two diastereomers can be understood if one considers the formation of the iminium species **I**, in which the methyl group is pseudo-

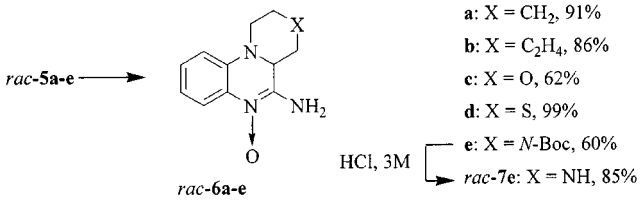


Scheme 3. Cyanide addition onto iminiums **I** and **II**

equatorial (Scheme 3). Several studies have shown that the former species can be in equilibrium with the alternate isomer **II**, in which the methyl substituent is pseudo-axial.[6] It is important to note that in both of these two cases the approach of the cyanide anions will be from the axial direction (path a and a′ for **I** and **II**, respectively) and in a stereoelectronically controlled mode so as to avoid energetically unfavorable boat-like transition states.[7a–7c] This mechanism accounts for the formation of either the major isomer *trans*-**5f** or the minor isomer *cis*-**5f** (after the ring-inversion of **III** owing to unfavorable 1–3 diaxial interactions between the methyl and the cyano substituent).

Reductive Cyclization of Cyanoamines 5a–f

Our first experiment was devoted to the reduction of the nitro group under protic conditions. Treatment of **5a** with Zn/HCl in boiling ethanol resulted in the formation of a mixture of unidentified products. At this point, it was clear that the carbon–nitrile bond had been cleaved affording the iminium species, which proved to be unstable under these reaction conditions. To overcome this drawback, catalytic hydrogenation of the aromatic nitro group seemed to us to be a promising possibility. After several attempts, the best yields and reaction rates were found to be obtained when the catalytic hydrogenation of **5a–d** was performed over $Pd(OH)_2$ [8] in ethanol at atmospheric pressure. The *N*-oxide derivatives **6a–d** (Scheme 4) were obtained, providing evidence of the partial reduction of the nitro group into the corresponding hydroxylamine.



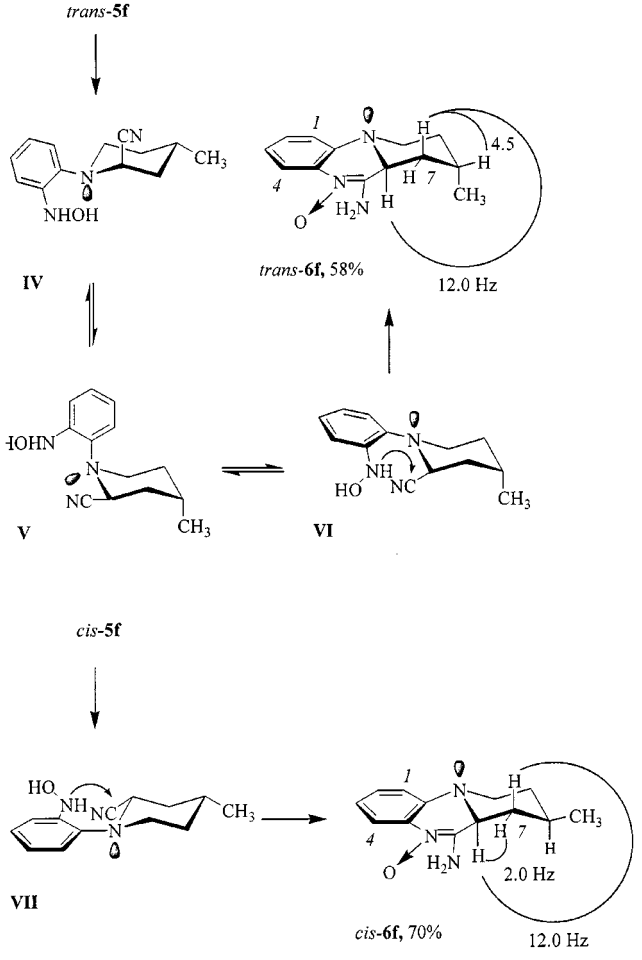
Scheme 4. Reductive cyclization of cyanoamines **5a–e**

Conversely, the syntheses of **6a–e** could readily be achieved by means of the electrochemical reduction of **5a–e** at controlled potentials in a batch cell at a mercury pool cathode. The electrolysis was performed in ethanol in the presence of acetic buffer as supporting electrolyte and consumed four mol of electron per mol of substrate; this is a direct indication of the partial reduction of the nitro group into the corresponding hydroxylamine. The products obtained in this way (50 to 70% yield) proved to be identical in all respects to those obtained from the catalytic hydrogenation of **5a–e**.

Hydrogenation of the *N*-Boc-protected cyanoamine **5e** at one atm. H_2 resulted in the formation of the corresponding amidine-*N*-oxide **6e**, together with the saturated quinoxaline **3e** in 25% yield. Attempts to reduce the formation of **3e** by using limited amounts of catalyst did not produce any alteration in the original experimental results and, in this case only, overreduction of the intermediate amidine into the corresponding saturated quinoxaline could not be totally avoided. The ^{1}H NMR spectrum of **6e** recorded in [D_4]methanol was temperature dependent and, with the exception of the resonance system of 4a-H, displayed coalescent signals at δ = 2.95–3.20 (3 H), 3.90–4.00 (2 H), and 4.17–4.25 (1 H). In keeping with these observations, the ^{13}C NMR spectrum of **6e**, recorded at 298 K, exhibited coalescent signals at δ = 41 and 44. Heating of the sample at

343 K induced decoalescence of these broad peaks and a sharpening of all signals. At that temperature, two doublets of multiplets were recorded at δ = 3.92 and 4.00 for 1-H^b and 2-H^b, respectively. Similarly, sharp signals at δ = 41.7 (C-2) and 44.2 (C-4) were recorded in the ^{13}C NMR spectrum. In a subsequent step, concomitant deprotection and formation of the hydrochloride salt of **7e** were performed by direct treatment of **6e** with a 3 M ethanolic HCl solution. The ^{1}H NMR spectrum of **7e** was recorded in D_2O and displayed a typical doublet signal (J = 11.0 Hz), attributed to the axial proton 4a-H at δ = 5.06. Likewise, the ^{1}H NMR spectra of the hydrochloride salts of **6a−d** were recorded in D_2O and displayed a similar doublet (J = 12.0 Hz) signal in the region δ = 4.25−4.55.

In order to acquire more fundamental information concerning the stereochemical outcome of the cyclization reaction, we decided to study the behavior of the two adducts *trans*- and *cis*-**5f**. As mentioned earlier, the C-2 cyano substituent could adopt either an axial or an equatorial orientation. Therefore, one might expect a noticeable difference between the cyclization rates of the two hydroxylamines **IV** and **VII** (Scheme 5).



Scheme 5. Stereochemical pathway for the reductive ring-closure of *trans*- and *cis*-**5f**

Cyclic voltammograms were performed at a hanging mercury electrode in a 1:1 mixture of ethanol and 0.5 M acetic buffer at a scan rate of 0.1 V/s. On the first cathodic scan, the reduction of the nitro group of *trans*-**5f** into the corresponding hydroxylamine **IV** occurred at Ep_c = −0.60 V. On the reversed cathodic scan, oxidation of the latter species into the corresponding nitroso derivative occurred at Ep_a = +0.05 V. On the other hand, the voltammogram of *cis*-**5f** displayed a single reduction peak at Ep_c = −0.85 V, attributed to the $NO_2 \rightarrow$ NHOH transformation, whereas the peak corresponding to the NHOH → NO oxidation was not observed during the reversed cathodic scan. This result indicated not only that, in the case of *cis*-**5f**, the intermediate hydroxylamine **VII** cyclized faster than **IV**, but also that an equatorially oriented cyano group is preferred, inducing a rapid condensation between the nitrogen nucleophile and the cyano group.

The catalytic reduction of *trans*-**5f** was performed as described above, affording *trans*-**6f** in 58% yield. The ^{1}H NMR spectrum of *trans*-**6f** displayed a typical doublet of doublets [^3J(6a,7b) = 12.0 Hz, ^3J(6a,7a) = 3.0 Hz] system at δ = 4.54, placing 6a-H in an axial orientation. A large triplet of doublets [^2J(7b,7a) = ^3J(7b,6a) = 12.0 Hz, ^3J(7b,8) = 4.5 Hz] system at δ = 1.98 was found for 7-H^b, which is a direct indication that in this molecule 8-CH_3 is axial, as shown in Scheme 5. This relative orientation suggests that a ring reversal followed by a nitrogen inversion had taken place during the *trans*-**5f** → *trans*-**6f** transformation.[9a][9b] It is also well established that conjugation of a nitrogen lone pair with a π system decreases the barrier to inversion of the nitrogen atom,[10] and this accounts for the pyramidal instability of the intermediate derivative **V**. One should also keep in mind that **IV** and **V** are in a dynamic equilibrium and that conformational mobility and nitrogen inversion allow the cyano group in the requisite conformation to react with the nitrogen nucleophile, shifting the equilibrium as the reaction proceeds.

The reduction of *cis*-**5f** was totally complete after a reaction time of five hours, demonstrating once more that the ring-forming reaction had taken place more rapidly in the case of *cis*-**5f**. The ^{1}H NMR spectrum of the hydrochloride salt of *cis*-**6f** was measured in D_2O and the coupling constants [^3J(6-a,7a) = 12.0 Hz and ^3J(6-a,7b) = 2.0 Hz] found at δ = 4.31 were indicative of the axial orientation of 6a-H, and hence an equatorial disposition for 8-CH_3. Interesting in the ^{13}C resonance systems was the significant γ-shift produced by the axially oriented methyl group at C-8.[11] For example, in the spectrum of *trans*-**6f**, the C-6a and C-10 resonance systems were found at δ = 55.9 and 44.2, respectively, whereas those observed for their counterparts in *cis*-**6f** resonated at δ = 60.5 and 48.4 (Table 2).

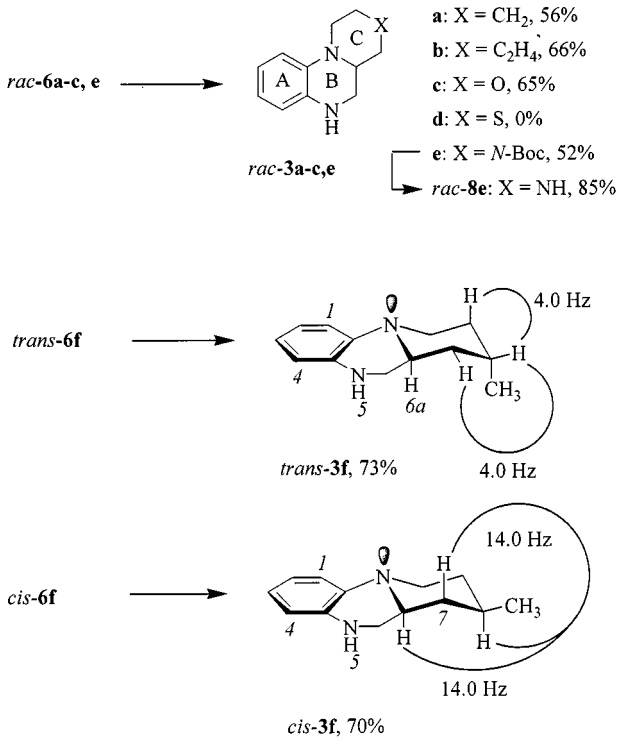
Reduction of Amidine *N*-Oxides 6a−e

Interestingly, when the cyanoamines **6a−c** were reduced at atmospheric pressure, the derivatives **3a−c** were obtained in moderate yields (up to 25%). As a further extension of this study, it was of interest to examine whether this reduction might represent a new means of access to the tetrahydroquinoxaline ring system. We first examined the direct reduction of cyanoamines **5a−c** under rather forcing condi-

Table 2. Selected ^{13}C chemical shifts for amidines *trans-, cis*-**6f**, and tetrahydroquinoxalines *trans-, cis*-**3f**

Product	C-6a	C-7	C-8	8-CH_3	C-9	C-10
trans-**6f**	55.9	33.2	27.7	19.0	28.6	44.2
cis-**6f**	60.5	35.5	30.9	23.8	33.0	48.4
trans-**3f**	48.5	35.6	25.0	17.2	31.0	42.5
cis-**3f**	53.9	38.5	30.2	22.0	33.7	47.0

tions [$Pd(OH)_2$, 5 atm. H_2] and soon observed that partial reductive decyanation occurred together with the reduction of the nitro group. Thus, it was felt that the reductive cyclization should take place first, and that reduction of the resulting amidine function should be effected in a subsequent step. Therefore, the two-step preparation of the tetrahydroquinoxaline derivatives was carried out in methanol [$Pd(OH)_2$, 1 atm. H_2] in such a way that the resulting *N*-oxides **6a−c** could easily be recovered from the methanolic solution and directly hydrogenated at five atmospheres H_2 at room temperature. The reduction proceeded sluggishly (5 days) and the expected tetrahydroquinoxalines **3a−c** were obtained in yields ranging between 52% and 66% (Scheme 6).



Scheme 6. Synthesis of the tetrahydroquinoxalines **3**

It is worth noting that reduction of the amidine function resulted in the elimination of one molecule of ammonia per molecule of substrate. Indeed, a characteristic smell of ammonia was observed on opening the reaction vessel. The ^1H NMR spectra of **3a−c** were well resolved and a complete attribution of all the protons could be performed. The axial orientation of the 6a-H proton, for example, was unambiguously determined from examination of the ^1H NMR spectrum of **3a**, in which it was found that upon irradiation at δ = 2.89 (6a-H) a large coupling constant [^3J (7a,6-a) = 12.0 Hz] was lost from the resonance system of 7-H[a]. The B/C ring junction of quinoxalines **3a−c** was presumably *trans*, despite the fact that no Bohlmann bands could be found in the 2700−2800 cm^{-1} region in the IR spectra of **3a−c**.[12] Several studies have shown that compounds in which the nitrogen lone pair is delocalized over aromatic ring orbitals do not give rise to such IR absorptions.[13] In a related field of research, NMR spectroscopic studies have demonstrated the influence of the bridgehead nitrogen lone pair on the chemical shift of α-axial protons, which absorbed at δ < 3.8, as compared to α-equatorial protons, which absorbed at δ > 3.8. In our case, in the ^1H NMR spectra of tetrahydroquinoxalines **3a−c** (see Experimental Section), absorptions attributable to the α-antiperiplanar protons were found in the region δ = 2.53−3.06, while those attributable to the corresponding α-equatorial protons resonated in the region δ = 3.49−3.82. These observations are in agreement with a *trans* B/C ring junction in which the bridgehead nitrogen lone pair is partially delocalized towards the antiperiplanar, axially oriented C−H bond. However, delocalization of the nitrogen lone pair over the benzene ring will partially or totally deactivate the α-antiperiplanar shielding effect. In our case, and in others,[12] determination, by IR or ^1H NMR spectroscopy, of whether the configuration of the B/C ring junction is *cis* or *trans* is not straightforward.

When the same reaction was conducted on the amidine **6d**, no reduction to the expected tetrahydroquinoxaline **3d** was observed. All other attempts performed at more elevated pressure conditions (up to 10 atm. H_2) were also unsuccessful, and resulted in the formation in 52% yield of the corresponding amidine derivative. Catalytic hydrogenation has been widely studied in *N*-oxide chemistry and numerous examples of removal of the *N*-oxide group to afford the parent heterocycle have been reported.[14] However, it should be noted that the presence of a sulfur atom in **6d** should diminish the reducing power of the catalyst[15] and account for the absence of the saturated quinoxaline **3d**.

The synthesis of the quinoxaline **8e**[16] was effected without difficulty by means of a two-step procedure starting from the cyanoamine **5e**. As with **3c**, the reductive cyclization was performed at 1 atm. H_2, and followed by the reduction of the amidine function at 5 atm. H_2 to afford **3e** in 52% isolated yield. The removal of the Boc protecting group was performed in ethanol with dry HCl, affording the hydrochloride salt of **8e**.

Hydrogenation of *cis*-**6f** was performed at five atmospheres H_2 and resulted in clean formation of the saturated quinoxaline *cis*-**3f** as a single diastereomer in 70% yield. The catalytic reduction of *trans*-**6f** was performed as described above and, after a reaction time of six days and rapid filtration through a silica column, afforded the expected material as an oil in 73% yield. ^1H NMR analysis revealed that this oil was a mixture (9:1) of the corresponding *trans*-**3f** (as the major compound), together with *cis*-**3f**. Further evidence of the presence of *cis*-**3f** was provided by analysis of the ^{13}C NMR spectrum, in which all the signals

arising from the minor isomer *cis*-**3f** were found. The axial orientation of the 8-CH_3 substituent in *trans*-**3f** was deduced by examination of the ^1H NMR signal of 8-H, which, after irradiation of the C-8 methyl signal at δ = 1.05, appeared as a quintet signal (J = 4.0 Hz). Also interesting was the fact that the presence of the axial CH_3 group in *trans*-**3f** caused a significant upfield shift (−5 ppm, relative to *cis*-**3f**, see Table 2) of the C-10 resonance triplet signal, providing further evidence that the CH_3 group was axial in this compound. The reduction of amidines **6a−f** has the potential to yield several intermediate species, among which we can postulate an enediamine, produced after the reduction of the *N*-oxide group. The hydrogenation at C-6a at the less-hindered side (opposite to the axial CH_3) of that enediamine might be the origin of the formation of small amounts of *cis*-**3f** during the catalytic hydrogenation of *trans*-**6f.**

Conclusion

The first part of this study was devoted to the anodic cyanation of various six-membered *N*-aryl heterocycles, which were successfully transformed into their corresponding cyanoamines. Once formed, such substrates proved to be effective for the preparation of novel tetrahydroquinoxaline derivatives by a two-step reaction sequence involving: a) reductive cyclization between the cyano substituent and the nitrogen nucleophile, and b) the reduction of the amidine moiety at a more elevated hydrogen pressure. Both the starting cyanoamines and the final tetrahydroquinoxaline derivatives are suitable precursors for further transformations, and work in this area is currently in progress.

Experimental Section

General: Purification by column chromatography was performed using 70−230 mesh silica gel (Merck). − TLC analyses were carried out on alumina sheets precoated with $60F_{254}$ silica gel; R_f values are given for guidance. − Elemental analyses were performed at the "Service Central d'Analyse, Département Analyse Elémentaire (Vernaison)". − IR spectra were recorded with a Nicolet 205 FT-IR instrument or a Perkin−Elmer FT-IR 16PC machine (KBr powder or dichloromethane). − ^1H and ^{13}C NMR spectra were recorded with a Bruker AH 300 FT (300 MHz and 75 MHz for ^1H and ^{13}C, respectively), or Bruker DMX 500 (500 MHz and 125 MHz for ^1H and ^{13}C, respectively) spectrometer at the "Centre Régional de Mesures Physiques de l'Ouest (CRMPO)". Chemical shifts are expressed in ppm downfield from TMS: s, d, dd, t, q, quint, sext, and m designate singlet, doublet, doublet of doublets, triplet, quadruplet, quintet, sextet, and multiplet; coupling constants (J) in Hz. The assignments were made on the basis of chemical shifts and coupling constants (^1J and long range coupling). ^1H NMR: AB systems are presented in the following order: Ha (δ centered) the more shielded, Hb (δ centered) the more deshielded. ^{13}C NMR: broad band and gated decoupling spectra were recorded. EI-HRMS were obtained with a Mat 311 double focusing instrument at the CRMPO, with a source temperature of 170 °C. An ion-accelerating potential of 3 kV and ionizing electrons of 70 eV were used. LSIMS−HRMS (Cs^+) were obtained with a Zab-Spec TOF Micromass instrument with a source temperature of 40 °C, using a *m*-nitrobenzyl alcohol matrix.

Caution: $LiClO_4$ may cause severe explosions when the solvent is evaporated to dryness. The addition of water (a threefold excess) to the methanolic solution resulted in precipitation of the cyanoamine during the evaporation of the solvent. After precipitation, the crude material was extracted with classical solvents such as CH_2Cl_2 or diethyl ether.

1-(2-Nitrophenyl)piperidine-2-carbonitrile (5a): A methanolic solution (100 mL) of **4a** (3 g, 14.5 mmol), containing $LiClO_4$ (20 g/L) as supporting electrolyte, was oxidized (Ep = +1.30 V, Q = 2.71 F/mol) in the presence of NaCN (4 equiv.) in a batch cell fitted with a vitreous carbon electrode. Water (200 mL) was added to the resulting solution and MeOH was evaporated under reduced pressure. The aqueous layer was extracted with 200 mL of CH_2Cl_2; the organic fraction was then dried over K_2CO_3 and evaporated. Addition of a mixture of diethyl ether and petroleum ether (8:2) led to the crystallization of **5a** (3 g, 89%) as a pale yellow powder. − M.p. 56 °C (diethyl ether/petroleum ether). − R_f = 0.5 (diethyl ether/petroleum ether, 3:7). − IR (KBr): $\tilde{\nu}$ = 2228 cm^{-1} (CN). − ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.69−1.84 (m, 4 H), 1.95−1.98 (m, 1 H), 2.11−2.16 (m, 1 H), 2.97 (dm, J = 12.0 Hz, 1 H), 3.35 (td, J = 12.0, 3.0 Hz, 1 H), 4.50 (s, br., 1 H), 7.29 (t, J = 7.0 Hz, 1 H), 7.48 (d, J = 7.0 Hz, 1 H), 7.60 (t, J = 7.0 Hz, 1 H), 7.80 (d, J = 7.0 Hz, 1 H). − ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 19.9, 25.2, 28.8, 48.6, 54.3, 117.1, 124.4, 125.2, 125.6, 133.7, 144.1, 146.3. − HRMS ($C_{12}H_{13}N_3O_2$ [M^+]): calcd. 231.10077; found 231.10111. − $C_{12}H_{13}N_3O_2$: calcd. C 62.33, H 5.67, N 18.17, O 13.84; found C 62.44, H 5.53, N 18.20, O 13.92.

1-(2-Nitrophenyl)azepane-2-carbonitrile (5b): Compound **4b** (1 g, 4.5 mmol) and NaCN (0.8 g) were dissolved in MeOH (100 Ml) containing $LiClO_4$ (20 g/l). The resulting solution was electrolyzed at Ep = +1.10 V and, after the passage of 876 C (2.0 F/mol), the cyanoamine **5b** was treated as described above to give a pale orange powder (0.760 g, 68%). − R_f = 0.28 (diethyl ether/petroleum ether, 2:8). − IR (neat): $\tilde{\nu}$ = 2226 cm^{-1} (CN). − ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.56−1.62 (m, 1 H), 1.65−1.85 (m, 5 H), 1.94−2.02 (m, 1 H), 2.25−2.31 (m, 1 H), 3.20 (dt, J = 14.0, 5.0 Hz, 1 H), 3.43 (ddd, J = 14.0, 10.0, 3.0 Hz, 1 H), 4.42 (tm, J = 6.0 Hz, 1 H), 7.29 (t, J = 7.0 Hz, 1 H), 7.54 (t, J = 7.0 Hz, 1 H), 7.59 (d, J = 7 Hz, 1 H), 7.66 (d, J = 7 Hz, 1 H). − ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 23.6, 27.5, 29.1, 33.27, 52.4, 56.2, 118.9, 124.2, 125.9, 127.2, 133.3, 144.7, 147.5. − HRMS ($C_{13}H_{15}N_3O_2$ [M^+]): calcd. 245.11643; found 245.11749. − $C_{13}H_{15}N_3O_2$: calcd. C 63.66, H 6.16, N 17.13, O 13.05; found C 63.40, H 6.04, N 16.68, O 13.92.

4-(2-Nitrophenyl)morpholine-3-carbonitrile (5c): As described above, **4c** (1.50 g, 7.2 mmol) was electrolyzed at Ep = +1.10 V. After the disappearance of the first anodic wave and the consumption of 1390 C (Q = 2.0 F/mol), electrolysis was stopped. Water (100 mL) was added to the resulting solution, and the usual workup afforded **5c** (0.760 g, 68%) as an orange powder. − M.p. 125 °C (diethyl ether/petroleum ether). − R_f = 0.13 (diethyl ether/petroleum ether, 2:8). − IR (KBr): $\tilde{\nu}$ = 2230 cm^{-1} (CN). − ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.82 (d, J = 12.0 Hz, 1 H), 3.66 (td, J = 11.0, 3.0 Hz, 1 H), 3.75 (td, J = 11.0, 3.0 Hz, 1 H), 3.99 (dd, J = 12.0, 3.0 Hz, 1 H), 4.02 (dm, J = 12.0 Hz, 1 H), 4.08 (dm, J = 12.0, Hz, 1 H), 4.40 (s, br., 1 H), 7.36 (t, J = 8.0 Hz, 1 H), 7.52 (d, J = 8.0 Hz, 1 H), 7.66 (t, J = 8.0 Hz, 1 H), 7.84 (d, J = 8.0 Hz, 1 H). − ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 47.7, 53.9, 67.0, 68.0, 116.0, 124.4, 125.4, 126.5, 134.0, 142.5, 146.7. − HRMS

($C_{11}H_{11}N_3O_3$ [M^+]): calcd. 233.08003; found 233.08066. − $C_{11}H_{11}N_3O_3$: calcd. C 56.65, H 4.75, N 18.02, O 20.58; found C 55.44, H 4.57, N 17.31, O 18.95.

4-(2-Nitrophenyl)thiomorpholine-3-carbonitrile (5d): Compound **4d** (0.404 g, 1.8 mmol) was electrolyzed (*E*p = +1.20 V, Q = 2.0 F/mol) at a carbon electrode to afford the cyano adduct **5d** (0.241 g, 54%) as a pale orange powder. − M.p. 91 °C (diethyl ether/petroleum ether). − R_f = 0.69 (CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 2228 cm^{-1} (CN). − ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.58 (dm, *J* = 14.0 Hz, 1 H), 2.77 (dt, *J* = 14.0, 3.0 Hz, 1 H), 2.98 (ddd, *J* = 13.0, 12.0, 3.0 Hz, 1 H), 3.20 (dt, *J* = 13.0, 3.0 Hz, 1 H), 3.36 (dd, *J* = 13.0, 3.5 Hz, 1 H), 3.68 (td, *J* = 12.0, 3.0 Hz, 1 H), 4.70 (t, *J* = 4.0 Hz, 1 H), 7.37 (td, *J* = 8.5, 1.0 Hz, 1 H), 7.54 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.64 (td, *J* = 8.0, 1.0 Hz, 1 H), 7.80 (dd, *J* = 8.0, 1.0 Hz, 1 H). − ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 27.6, 30.4, 49.7, 54.7, 115.9, 125.1, 125.2, 126.7, 133.8, 143.7, 146.9. − HRMS ($C_{11}H_{11}N_3O_2S$ [M^+]): calcd. 249.05719; found 249.05780. − $C_{11}H_{11}N_3O_2S$: calcd. C 53.00, H 4.45, N 16.86, O 12.84, S 12.86; found C 52.78, H 4.41, N 16.38, O 12.67, S 13.18.

3-Cyano-4-(2-nitrophenyl)piperazine-1-carboxylic Acid *tert*-Butyl Ester (5e): Compound **4e** (1 g, 3.3 mmol) was dissolved in methanol (100 mL) in the presence of $LiClO_4$ and electrolyzed at *E*p = +1.25 V. After the passage of 628 C (2.15 F/mol), electrolysis was stopped. Usual workup led to an oil, which crystallized upon addition of a mixture of diethyl ether and petroleum ether to afford **5e** as an orange powder (0.815 g, 76%). − M.p. 103 °C (diethyl ether/petroleum ether). − R_f = 0.44 (CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 2226 cm^{-1} (CN, weak). − ^1H NMR (C_6D_6, 70 °C, 500 MHz): δ = 1.21 (s, 9 H), 1.90 (d, *J* = 11.5 Hz, 1 H), 2.30 (t, *J* = 11.5 Hz, 1 H), 2.66 (d, *J* = 12.0 Hz, 1 H), 2.79 (t, *J* = 11.0 Hz, 1 H), 3.56 (s, 1 H), 3.75 (s, coal., 2 H), 6.37 (t, *J* = 8.0 Hz, 1 H), 6.65 (t, *J* = 8.0 Hz, 1 H), 6.73 (d, *J* = 8.0 Hz, 1 H), 7.09 (d, *J* = 8.0 Hz, 1 H). − ^{13}C NMR (C_6D_6, 70 °C, 125 MHz): δ = 28.4, 43.1, 46.7, 47.4, 53.6, 80.5, 115.8, 124.9, 125.3, 126.2, 133.5, 143.0, 147.1, 154.1. − HRMS ($C_{16}H_{20}N_4O_4$ [M^+]): calcd. for 332.14844; found 332.14789. − $C_{16}H_{20}N_4O_4$: calcd. C 57.82, H 6.07, N 16.86, O 19.26; found C 57.80, H 6.08, N 16.64, O 19.27.

Electrolysis of 4f: The electrolysis of **4f** was performed as described above (1.35 g, 6.13 mmol, *E*p = +1.20 V, Q = 2.12 F/mol) to afford a mixture (80:20) of diastereomers. The crude material (1.3 g, 85%) was chromatographed through a silica column (eluent: diethyl ether/petroleum ether, 1:2) to give *trans*-**5f** (1.02 g, 64%), followed by the more polar *cis*-**5f** (0.250 g, 16%).

(2*R,4*R**)-4-Methyl-1-(2-nitrophenyl)piperidine-2-carbonitrile (*trans*-5f):** Yellow powder, m.p. 74 °C (diethyl ether/petroleum ether). − R_f = 0.71 (diethyl ether/petroleum ether, 1:2) − IR (KBr): $\tilde{\nu}$ = 2225 cm^{-1}(CN). − ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.02 (d, *J* = 6.0 Hz, 3 H, 4-CH_3), 1.37 [qd, ^2J(5a,5b) = ^3J(5a,6b) = ^3J(5a,4) = 13.0 Hz, ^3J(5a,6a) = 4.5 Hz, 1 H, 5-H^a], 1.70−2.00 (m, 4 H, 3-H, 4-H, 5-H^b), 2.98 [dm, ^2J(6a,6b) = 12.0 Hz, 1 H, 6-H^a], 3.37 [td, ^2J(6b,6a) = ^3J(6b,5a) = 12.0 Hz, ^3J(6b,5b) = 2.5 Hz, 1 H, 6-H^b], 4.50−4.53 (m, 1 H, 2-H), 7.29 (td, *J* = 9.0, 2.0 Hz, 1 H), 7.48 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.60 (td, *J* = 9.0, 2.0 Hz, 1 H), 7.90 (dd, *J* = 8.0, 2.0 Hz, 1 H). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.3 (4-CH_3), 26.8 (C-4), 33.7 (C-3), 36.6 (C-5), 48.4 (C-6), 54.2 (C-2), 117.2 (CN), 124.4, 125.2, 125.6 (C-4′ or C-5′ or C-6′), 133.7 (C-3′), 143.9 (C-1′), 146.3 (C-2′). − HRMS ($C_{13}H_{15}N_3O_2$ [M^+]): calcd. 245.11642; found 245.11553. − $C_{13}H_{15}N_3O_2$: calcd. C 63.66, H 6.16, N 17.13, O 13.05; found C 63.60, H 6.06, N 17.06, O 13.17.

(2*R,4*S**)-4-Methyl-1-(2-nitrophenyl)piperidine-2-carbonitrile (*cis*-5f):** Orange powder, m.p. 92 °C (diethyl ether/petroleum ether) − R_f = 0.38 (diethyl ether/petroleum ether, 1:2) − IR (KBr): $\tilde{\nu}$ = 2242 cm^{-1}(CN). − ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.14 (d, *J* = 6.5 Hz, 3 H, 4-CH_3), 1.46−1.57 (m, 1 H, 5-H^a), 1.70−1.85 (m, 3 H, 3-H^a, 4-H, 5-H^b), 2.21 [dt, ^2J(3b,3a) = 11.50 Hz, ^3J(3b,2) = (3b,4) = 4.0 Hz, 1 H, 3-H^b], 2.69 [ddd, ^2J(6a,6b) = 12.0 Hz, ^3J(6a,5b) = 8.5 Hz, ^3J(6a,5a) = 3.0 Hz, 1 H, 6-H^a], 3.42 (m, 1 H, 6-H^b), 4.14 [dd, ^3J(2,3a) = 8.0 Hz, ^3J(2,3b) = 4.0 Hz, 1 H, 2-H], 7.32 (t, *J* = 8.0 Hz, 1 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 7.60 (t, *J* = 8.0 Hz, 1 H), 7.77 (d, *J* = 8.0 Hz, 1 H). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.2 (4-CH_3), 27.9 (C-4), 32.5 (C-5), 36.8 (C-3), 51.2 (C-2), 51.4 (C-6), 118.5 (CN), 124.9, 124.9 (C-6′ or C-4′) 126.3 (C-3′), 133.2 (C-5′), 143.6 (C-1′), 147.7 (C-2′).

7,8,9,10-Tetrahydro-6a*H*-5-oxypyrido[1,2-*a*]quinoxalin-6-ylamine Hydrochloride (6a): Pearlman′s catalyst (0.15 g), **5a** (0.670 g, 2.9 mmol), and dioxane (4 mL) were placed in a low-pressure hydrogenator. Air was removed from the reactor by alternately filling it with hydrogen and venting it three times. The desired hydrogen pressure (7.35 × 10^2 Torr) was applied, and the reaction mixture was stirred for 48 h at room temperature. The catalyst was filtered off and washed with methanol (20 mL). The combined solutions were evaporated under reduced pressure to afford the amidine **6a** (0.602 g, 91%) as a white powder. Addition of diethyl ether saturated with gaseous HCl resulted in the formation of the hydrochloride salt of **6a**. − M.p. 155−160 °C (dec.). − IR (KBr): $\tilde{\nu}$ = 740, 1658, 3082 (br.) cm^{-1}. − ^1H NMR (D_2O, 500 MHz): δ = 1.40−1.65 (m, 5 H), 1.73−1.80 (br. d, 1 H), 2.81 (quint, *J* = 8.0 Hz, 1 H), 3.67 (d, *J* = 14.0 Hz, 1 H), 4.23 (d, *J* = 12.0 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 6.86 (t, *J* = 8.0 Hz, 1 H), 7.11 (t, *J* = 8.0 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 1 H). − ^{13}C NMR (D_2O): δ = 20.3, 23.6, 25.6, 46.2, 58.2, 114.0, 114.9, 119.8, 125.6, 128.1, 134.8, 156.4. − HRMS (FAB +): calcd. for $C_{12}H_{16}N_3O$ [M + H^+] 218.1293; found 218.1292.

6a,7,8,9,10,11-Hexahydro-5-oxyazepino[1,2-*a*]quinoxalin-6-ylamine·HCl (6b): Compound **5b** (0.26 g, 1.06 mmol) was dissolved in ethanol (4 mL) and placed in a low-pressure catalytic hydrogenator in the presence of Pearlman's catalyst (0.1 g). The desired hydrogen pressure (7.35 × 10^2 Torr, 1 bar) was applied and after stirring (24 h) at room temperature, the catalyst was removed, and washed with methanol. The resulting solutions were evaporated to dryness and the crude material was taken up with diethyl ether to afford **6b** as a white powder (0.210 g, 86%). The hydrochloride salt of **6b** was obtained as described above. − M.p. 170−175 °C (dec.). − IR (KBr): $\tilde{\nu}$ = 1506, 1668 cm^{-1}. − ^1H NMR (D_2O, 500 MHz): δ = 1.38−1.45 (m, 1 H), 1.60−1.85 (m, 5 H), 1.87−1.95 (m, 1 H), 2.15−2.22 (m, 1 H), 3.19−3.26 (m, 1 H), 3.87 (ddd, *J* = 13.0, 4.0, 1.0 Hz, 1 H), 4.55 (dd, *J* = 11.5, 4.0 Hz, 1 H), 6.90−7.00 (m, 2 H), 7.25 (t, *J* = 8.0 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 1 H). − ^{13}C NMR (D_2O, 125 MHz): δ = 25.2, 25.9, 27.8, 32.1, 49.1, 59.9, 112.6, 114.9, 118.2, 124.3, 128.1, 134.9, 155.1. − HRMS (FAB +): calcd. for $C_{13}H_{18}N_3O$ [M + H^+] 232.1450; found 232.1452.

1,3,4,10a-Tetrahydro-9-oxy-2-oxa-4a,9-diazaphenanthren-10-ylamine·HCl (6c): Compound **5c** (0.5 g, 2.14 mmol) was dissolved in ethanol (5 mL) and reduced in the presence of Pearlman's catalyst (0.130 g). The desired hydrogen pressure (7.35 10^2 Torr, 1 bar) was applied and, after 6 hours stirring at room temperature, the catalyst was filtered off by suction and the crude material was washed with diethyl ether to afford the amidine **6c** as a white powder. Addition of diethyl ether saturated with gaseous HCl resulted in the formation of the hydrochloride salt of **6c** (0.3 g, 62%). − M.p. 170−175 °C (dec.). − IR (KBr): $\tilde{\nu}$ = 1278, 1492, 1672, 3048 (br.) cm^{-1}. − ^1H NMR (D_2O, 500 MHz): δ = 3.02 (td, *J* = 13.0, 3.0 Hz, 1 H), 3.59 (d, *J* = 13.0 Hz, 1 H), 3.63−3.70 (m, 2 H), 3.94

(dd, J = 13.0, 3.0 Hz, 1 H), 4.11 (dd, J = 12.0, 2.0 Hz, 1 H), 4.30 (dd, J = 10.5, 3.5 Hz, 1 H), 6.90 (d, J = 8.0 Hz, 1 H), 7.02 (t, J = 7.0 Hz, 1 H), 7.24 (t, J = 7.0 Hz, 1 H), 7.39 (d, J = 8.0 Hz, 1 H). − ^{13}C NMR (D_2O, 125 MHz): δ = 45.4, 55.3, 64.7 (2 carbons), 113.8, 115.1, 121.1, 126.0, 128.3, 135.1, 153.9. − HRMS (FAB +): calcd. for $C_{11}H_{14}N_3O_2$ [M + H$^+$] 220.1086; found 220.1086.

1,3,4,10a-Tetrahydro-9-oxy-2-thia-4a,9-diazaphenanthren-10-ylamine·HCl (6d): Compound **5d** (0.570 g, 2.3 mmol) was dissolved in ethanol (6 mL) and placed in a low-pressure hydrogenator in the presence of Pearlman's catalyst (0.3 g). The desired hydrogen pressure (7.35 10^2 Torr, 1 bar) was applied and, after 24 h stirring at room temperature, the usual workup led to the precipitation of the hydrochloride salt of **6d** (0.538 g, 99%), m.p. 160−165 °C (dec.). − IR (KBr): ṽ = 1298, 1502, 1674, 3036 (br) cm^{-1}. − ^{1}H NMR (D_2O, 500 MHz): δ = 2.28 (d, J = 13.5 Hz, 1 H), 2.35 (d, J = 13.0 Hz, 1 H), 3.08 (dd, J = 15.5, 11.5 Hz, 1 H), 3.18 (td, J = 13.0, 2.0 Hz, 1 H), 3.56 (ddd, J = 14.0, 12.5, 3.0 Hz, 1 H), 4.28 (d, J = 15.0 Hz, 1 H), 5.00 (dd, J = 11.5, 2.0 Hz, 1 H), 7.00−7.08 (m, 2 H), 7.31 (t, J = 7.0 Hz, 1 H), 7.47 (d, J = 7.0 Hz, 1 H). − ^{13}C NMR (D_2O, 125 MHz): δ = 19.8, 23.6, 47.1, 59.6, 114.4, 115.2, 119.9, 125.6, 128.5, 133.2, 153.1. − HRMS (FAB +): calcd. for $C_{11}H_{14}N_3OS$ [M + H$^+$] 236.0858; found 236.0860.

Synthesis of 7e: Compound **5e** (0.228 g, 0.7 mmol) was dissolved in a 1:1 mixture of ethanol and dioxane (3.0 mL) and placed in a low-pressure hydrogenator in the presence of Pearlman's catalyst (0.067 g). The desired hydrogen pressure (7.35 × 10^2 Torr, 1 bar) was applied and, after 20 h stirring at room temperature, the addition of diethyl ether resulted in the precipitation of **6e** (0.127 g, 60%), which was further purified by rapid filtration through a silica column, with a mixture (80:20) of dichloromethane and methanol as eluent. Addition of HCl in ethanol (3 M, 8 mL) to the resulting powder resulted in the precipitation of the hydrochloride salt of **7e**.

5-Amino-1,2,4,4a-tetrahydropyrazino[1,2-*a*]quinoxaline-3-carboxylic Acid *tert*-Butyl Ester (6e): M.p. 170−175 °C (dec.). − R_f = 0.8 (CH_2Cl_2/MeOH, 80:20). − IR (KBr): ṽ = 744, 1654 (C=N), 1688 (C=O) cm^{-1}. − ^{1}H NMR (CD_3OD, 300 MHz, 55 °C): δ = 1.49 (s, 9 H, (C*H*$_3$)$_3$−C), 2.95−3.16 (m, 3 H, 1-H^a, 2-H^a, 4-H^a), 3.92 [dm, ^2J(1b,1a) = 13.0 Hz, 1 H, 1-H^b], 4.00 [dm, ^2J(2b,2a) = 13.0 Hz, 1 H, 2-H^b], 4.24 [dm, ^2J(4b,4a) = 13.0 Hz, 1 H, 4-H^b], 4.33 [dd, ^3J(4-a,4a) = 11.0 Hz, ^2J(4-a,4b) = 4.0 Hz, 1 H, 4a-H], 6.87−6.95 (m, 2 H), 7.15 (t, 1 H), 7.74 (d, 1 H). − ^{13}C NMR (CD_3OD, 75 MHz, 55 °C): δ = 28.5 [(*C*H$_3$)$_3$−C], 41.7 (coalescent, C-2), 44.2 (coalescent, C-4), 46.0 (C-1), 57.1 (C-4a), 82.1 [(CH$_3$)$_3$−C], 113.4, 117.7, 120.6, 128.2, (C-7, C-8, C-9, C-10), 129.7, (C-6a), 136.3 (C-10a), 147.3 (C-5), 156.2 (C=O). − HRMS (FAB +): calcd. for $C_{16}H_{23}N_4O_3$ [M + H$^+$] 319.1770; found 319.1769.

2,3,4,4a-Tetrahydro-1*H*-6-oxypyrazino[1,2-*a*]quinoxalin-5-ylamine (7e): M.p. 200−205 °C (dec.). − IR (KBr): ṽ = 1508, 1602, 1672, 2486, 3006 cm^{-1}. − ^{1}H NMR (D_2O, 300 MHz): δ = 3.30−3.60 (m, 5 H), 4.22 (d, J = 15.0 Hz, 1 H), 5.06 (dd, J = 11.0, 3.0 Hz, 1 H), 7.07 (d, 1 H), 7.13 (t, 1 H), 7.36 (t, 1 H), 7.53 (d, 1 H). − ^{13}C NMR (D_2O, 75 MHz): δ = 42.0, 43.1, 44.7, 56.6, 116.5, 118.2, 123.9, 128.3, 131.2, 135.1, 154.4. − HRMS (FAB +): calcd. for $C_{11}H_{15}N_4O$ [M + H$^+$] 219.1246; found 219.1246.

(6a*R,8*R**)-7,8,9,10-Tetrahydro-6a*H*-8-methyl-5-oxopyrido[1,2-*a*]quinoxalin-6-ylamine·HCl (*trans*-6f):** Compound *trans*-**5f** (0.736 g, 3.0 mmol) was dissolved in a 1:1 mixture of ethanol and dioxane (3.0 mL) and placed in a low-pressure hydrogenator in the presence of Pearlman's catalyst (0.375 g). The desired hydrogen pressure (7.35·10^2 Torr) was applied and, after 48 h stirring at room temperature, the usual workup resulted in the precipitation of the hydrochloride salt of *trans*-**6f** (0.401 g, 58%). − M.p. 170−175 °C (dec.). − IR (KBr): ṽ = 1286, 1493, 1644, 2955 (br) cm^{-1}. − ^{1}H NMR (D_2O, 300 MHz): δ = 1.10 (d, ^3J = 7.0 Hz, 3 H, 8-CH$_3$), 1.32 [dm, ^2J(9a,9b) = 12.0 Hz, 1 H, 9-H^a], 1.49 [dm, ^2J(7a,7b) = 12.0 Hz, 1 H, 7-H^a], 1.88 [tm, ^2J(9b,9a) = ^3J(9b,10a) = 12.0 Hz, 1 H, 9-H^b], 1.98 [td, ^2J(7b,7a) = ^3J(7b,6a) = 12.0 Hz, ^3J(7b,8) = 3.5 Hz, 1 H, 7-H^b], 2.03−2.15 (m, 1 H, 8-H), 3.17 [td, ^2J(10a,10b) = ^3J(10a,9b) = 12.0 Hz, ^3J(10a,9a) = 3.0 Hz, 1 H, 10-H^a], 3.53 [dt, ^2J(10b,10a) = 12.0 Hz, ^3J(10b,9b) = ^3J(10b,9a) = 3.5 Hz, 1 H, 10-H^b], 4.54 [dd, ^3J(6a,7b) = 12.0 Hz, ^3J(6a,7a) = 3.0 Hz, 1 H, 6a-H], 6.97−7.03 (m, 2 H), 7.23 (t, 1 H), 7.40 (d, 1 H). − ^{13}C NMR (D_2O, 75 MHz): δ = 19.0, 27.7, 28.6, 33.2, 44.2, 55.9, 117.4, 117.7, 123.2, 129.0, 130.5, 137.4, 159.5. − HRMS (FAB +): calcd. for $C_{13}H_{18}N_3O$ [M + H$^+$] 232.1450; found 232.1452.

(6a*R,8*S**)-7,8,9,10-Tetrahydro-6a*H*-8-methyl-5-oxopyrido[1,2-*a*]-quinoxalin-6-ylamine·HCl (*cis*-6f):** Compound *cis*-**5f** (0.368 g, 1.5 mmol) was dissolved in ethanol (5 mL) and placed in a low-pressure hydrogenator in the presence of Pearlman's catalyst (0.368 g). After 5 h stirring at room temperature, the usual workup resulted in the precipitation of the hydrochloride salt of *cis*-**6f** (0.242 g, 70%). − M.p. 175−180 °C (dec.). − IR (KBr): ṽ = 1496, 1648, 3100 (br) cm^{-1}. − ^{1}H NMR (D_2O, 300 MHz) δ = 0.82 (d, ^3J = 7.0 Hz, 3 H, 8-CH$_3$), 1.11−1.29 (m, 2 H, 7-H^a, 9-H^a), 1.54 [dm, ^2J(9b,9a) = 14.0 Hz, 1 H, 9-H^b], 1.67 [dm, ^2J(7b,7a) = 14.0 Hz, 1 H, 7-H^b], 1.70−1.80 (m, 1 H, 8-H), 2.90 [t, ^2J(10a,10b) = ^3J(10a,9a) = 13.0 Hz, 1 H, 10-H^a], 3.82 [dm, ^2J(10b,10a) = 13.0 Hz, 1 H, 10-H^b], 4.31 [dd, ^3J(6a,7a) = 12.0 Hz, ^3J(6a,7b) = 2.0 Hz, 1 H, 6a-H], 6.89−6.96 (m, 2 H), 7.19 (t, 1 H), 7.35 (d, 1 H), − ^{13}C NMR (D_2O, 75 MHz): δ = 23.8, 30.9, 33.0, 35.5, 48.4, 60.5, 116.9, 117.4, 122.6, 128.5, 130.5, 137.2, 159.1.

6,6a,7,8,9,10-Hexahydro-5*H*-pyrido[1,2-*a*]quinoxaline (3a): The amidine *N*-oxide **6a** (0.680 g, 3.1 mmol) was dissolved in methanol (50 mL) and placed in a high-pressure hydrogenation apparatus in the presence of Pearlman's catalyst (0.345 g). The desired pressure (3.75·10^3 Torr) was applied and the resulting solution was shaken for 7 days at room temperature. The catalyst was removed by filtration and washed with methanol. The combined solutions were evaporated to dryness. The crude material was further chromatographed on silica (eluent: CH_2Cl_2) to afford **3a** as a colorless oil, which solidified upon cooling (0.33 g, 56%). − Pale yellow powder, m.p. 97 °C (diethyl ether/petroleum ether). − R_f = 0.33 (CH_2Cl_2). − IR (KBr): ṽ = 740, 1500,3330 cm^{-1} (NH). − ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.24−1.44 (m, 2 H, 8-H^a and 7-H^a), 1.56−1.68 (m, 2 H, 7-H^b and 9-H^a), 1.74−1.84 (m, 2 H, 8-H^b and 9-H^b), 2.53 [td, ^2J(10a,10b) = ^3J(10a,9a) = 12.0 Hz, ^3J(10a,9b) = 3.0 Hz, 1 H, 10-H^a], 2.88−2.95 (m, 1 H, 6a-H), 3.19−3.26 (m, 2 H, 6-H), 3.40−3.50 (s, br., 1 H, NH), 3.80 [dm, ^2J(10b,10a) = 12.0 Hz, 1 H, 10-H^b], 6.43 (dd, J = 7.5, 1.5 Hz, 1 H), 6.57−6.65 (m, 2 H), 6.73 (d, J = 8.0 Hz, 1 H). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.6 (C-8), 24.2 (C-9), 29.0 (C-7), 46.2 (C-10), 46.8 (C-6), 53.2 (C-6a), 111.7 and 113.1 (C-1 or C-4), 117.5 and 117.9 (C-2 or C-3), 134.1 and 134.7 (C-4a or C-10b). − HRMS ($C_{12}H_{16}N_2$ [M$^+$]): calcd. 188.1313; found 188.1313. − $C_{12}H_{16}N_2$: calcd. C 76.55, H 8.57, N 14.88; found C 76.31, H 8.43, N 14.43.

5,6,6a,7,8,9,10,11-Octahydroazepino[1,2-*a*]quinoxaline (3b): Compound **6b** (0.5 g, 2.16 mmol) was dissolved in methanol (35 mL), and placed in a high-pressure apparatus in the presence of

Pearlman's catalyst (0.511 g). The hydrogen pressure was applied at 3.75×10^3 Torr, and the reaction mixture was shaken for 7 days at room temperature. Workup as described above gave **3b** as a colorless oil (0.29 g, 66%). − R_f = 0.33 (CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 1281, 1509, 1597, 3379 cm^{-1} (NH). − ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.40−1.63 (m, 5 H, 8-H, 9-H, 10-H^a), 1.70−1.80 (m, 2 H, 7-H), 1.90−2.23 (m, 1 H, 10-H^b), 3.01 [dd, ^2J(6a, 6b) = 10.5 Hz, ^3J(6a,6-a) = 3.5 Hz, 1 H, 6-H^a], 3.06 [ddd, ^2J(11a,11b) = 15.0 Hz, ^3J(11a,10b) = 10.5 Hz, ^3J(11a, 10a) = 3.5 Hz, 1 H, 11-H^a], 3.25 [dd, ^2J(6b, 6a) = 10.5 Hz, ^3J(6b, 6-a) = 3.5 Hz, 1 H, 6-H^b], 3.40−3.55 (m, 2 H, 6a-H and NH), 3.75 [dt, ^2J (11b,11a) = 15.0 Hz, ^3J (11b,10) = 4.5 Hz, 1 H, 11-H^b], 6.45−6.51 (m, 3 H), 6.60−6.65 (m, 1 H). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 25.4, 26.9, 27.2, 34.7, 45.2, 48.9, 56.8, 109.5, 113.7, 115.5, 119.3, 132.5, 134.7. − HRMS ($C_{13}H_{18}N_2$ [M^+]): calcd. 202.1470; found 202.1477. − $C_{13}H_{18}N_2$: calcd. C 77.18, H 8.97, N 13.85; found C 77.23, H 8.74, N 13.83.

1,3,4,9,10,10a-Hexahydro-2-oxa-4a,9-diazaphenanthrene (3c): The cyanoamine **5c** (1.03 g, 4.44 mmol) was dissolved in methanol (25 mL), and placed in a high-pressure apparatus in the presence of Pearlman's catalyst (0.5 g). The hydrogen pressure was applied at 7.35×10^2 Torr and the reaction mixture was shaken for 1 day at room temperature. The hydrogen pressure was raised to 3.75×10^3 Torr, and the solution was shaken for 7 additional days. The crude reaction mixture was chromatographed over a silica column (eluent: CH_2Cl_2) to afford **3c** as a white solid (0.515 g, 65%). − M.p. 116 °C. − R_f = 0.56 (CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 744, 1501, 2859, 3334 cm^{-1} (NH). − ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.83 [td, ^2J(4a,4b) = ^3J(4a,3a) = 12.0 Hz, ^3J(4a,3b) = 4.0 Hz, 1 H, 4-H^a], 3.09−3.22 (m, 3 H, 10-H, 10a-H), 3.26 [t, ^2J(1a,1b) = ^3J(1a,10-a) = 10.0 Hz, 1 H, 1-H^a], 3.49 [dm, ^2J(4b,4a) = 12.0 Hz, 1 H, 4-H^b], 3.71 [td, ^2J(3a,3b) = ^3J(3a,4a) = 12.0 Hz, ^3J(3a,4b) = 3.0 Hz, 1 H, 3-H^a], 3.87 [dm, ^2J(1b,1a) = 10.0 Hz, 1 H, 1-H^b], 4.03 [dm, ^2J(3b,3a) = 12.0 Hz, 1 H, 3-H^b], 6.45−6.50 (m, 1 H), 6.64−6.68 (m, 3 H). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 43.0 (C-10), 46.1 (C-4), 52.2 (C-10a), 66.9 (C-3), 69.3 (C-1), 112.1, 114.0 (C-5 or C-8), 118.3, 119.9 (C-6 or C-7), 134.5, 134.7 (C-4b or C-8a). − HRMS ($C_{11}H_{14}N_2O$ [M^+]): calcd. 190.11060; found 190.1105. − $C_{11}H_{14}N_2O$: calcd. C 69.45, H 7.42, N 14.73, O 8.41; found C 69.35, H 7.70, N 14.68, O 8.15.

Synthesis of 8e: The cyanoamine **5e** (0.8g, 2.41 mmol) was dissolved in methanol (25 mL), and placed in a high-pressure apparatus in the presence of Pearlman's catalyst (0.4 g). Hydrogen pressure was applied at 7.35×10^2 Torr for 1 day at room temperature; the rate of the reductive cyclization was monitored by TLC. After completion, the hydrogen pressure was raised to 3.75×10^3 Torr and the solution was shaken for 5 additional days. Workup as described above produced **3e** (m.p. 124 °C) as a pale yellow solid (0.364 g, 52%). The addition of 3 N ethanolic HCl solution (8 mL) resulted in the precipitation of **8e** as a gray hygroscopic solid.

***tert*Butyl 1,2,4a,5-Tetrahydro-4*H*,6*H*-pyrazino[1,2-*a*]quinoxaline-3-carboxylate (3e):** − R_f = 0.19 (CH_2Cl_2). − IR (CH_2Cl_2): $\tilde{\nu}$ = 735, 1255, 1680 (CO), 3373 cm^{-1} (NH). − ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.47 [s, 9 H, C(CH_3)], 2.60−2.65 (coalescent, 1 H), 2.71 (td, *J* = 12.0, 3.0 Hz, 1 H), 3.00−3.10 (m, 2 H), 3.24 (dd, *J* = 11.0, 8.0 Hz, 1 H), 3.36 (dd, *J* = 11.0, 3.0 Hz, 1 H), 3.68 (d, *J* = 8.5 Hz, 1 H), 4.00−4.20 (coalescent, 2 H), 6.48−6.52 (m, 1 H), 6.65−6.68 (m, 2 H), 6.72−6.73 (m, 1 H). − ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 28.4, 42.0 (coalescent), 44.5, 46.4, 47.0 (coalescent), 52.7, 80.0, 112.9, 114.4, 118.7, 119.9, 134.5, 134.8, 154.6. − HRMS ($C_{16}H_{23}N_3O_2$ [M^+]): calcd. 289.1790; found 289.1797. − $C_{16}H_{23}N_3O_2$:calcd. C 66.41, H 8.01, N 14.52; found C 66.43, H 8.09, N 14.43.

2,3,4,4a,5,6-Hexahydro-1*H*-pyrazino[1,2-*a*]quinoxaline·2HCl (8e): M.p. 170−180 °C (dec.). − IR (KBr): $\tilde{\nu}$ = 756, 1610, 2392 cm^{-1}. − ^1H NMR (D_2O, 300 MHz): δ = 3.03−3.16 (m, 2 H, 4-H^a and 1-H^a), 3.29 [td, ^2J(2a,2b) = ^3J(2a,1a) = 13.0 Hz, ^3J(2a,1b) = 4.0 Hz, 1 H, 2-H^a], 3.39 [dd, ^2J(5a,5b) = 12.0 Hz, ^3J(5a,4a) = 10.0 Hz, 1 H, 5-H^a], 3.58−3.61 (m, 2 H, 4-H^b and 2-H^b), 3.67−3.80 (m, 2 H, 4a-H and 5-H^b), 4.10 [dm, ^2J(1b,1a) = 12.0 Hz, 1 H, 1-H^b], 6.93 (t, ^3J = 7.0 Hz, 1 H), 7.09 (d, ^3J = 8.0 Hz, 1 H), 7.21 (d, ^3J = 7.0 Hz, 1 H), 7.35 (t, ^3J = 8.0 Hz, 1 H). − ^{13}C NMR (D_2O, 75 MHz): δ = 45.3 (C-1), 45.4 (C-5), 45.6 (C-2), 47.0 (C-4), 51.2 (C-4a), 118.0, 120.7, 123.1, 126.1, 133.3, 141.7. − HRMS ($C_{11}H_{15}N_3$ [M^+]): calcd. 189.1266; found 189.1269.

(6a*R,8*R**)-6,6a,7,8,9,10-Hexahydro-5*H*-8-methylpyrido[1,2-*a*]-quinoxaline (*trans*-3f):** The amidine *trans*-**6f** (0.245 g, 1.06 mmol) was dissolved in methanol (40 mL) and placed in a high-pressure apparatus in the presence of Pearlman's catalyst (0.51 g). Hydrogen pressure was applied at 3.75×10^3 Torr and the solution was shaken for 6 days at room temperature. The catalyst was removed by suction and the resulting solution was evaporated under reduced pressure. The crude reaction mixture was chromatographed through a silica column (eluent CH_2Cl_2) to afford *trans*-**3f** as pale yellow oil (0.157 g, 73%). − R_f = 0.39 (CH_2Cl_2). − IR (neat): $\tilde{\nu}$ = 735, 1503, 1598, 3389 (NH) cm^{-1}. − ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.05 (d, ^3J = 7.0 Hz, 3 H, 8-CH_3), 1.50−1.62 (m, 3 H, 7-H and 9-H^a), 1.90 [tt, ^2J(9b,9a) = ^3J(9b,10a) = 12.0 Hz, ^3J(9b,10b) = ^3J(9b,8) = 5.0 Hz, 1 H, 9-H^b], 2.04 (m, 1 H, 8-H), 2.85 [td, ^2J(10a,10b) = ^3J(10a,9b) = 12.0 Hz, 1 H, 10-H^a], 3.17−3.22 (m, 3 H, 6-H and 6a-H), 3.50 [dt, ^2J(10b,10a) = 12.0 Hz, ^3J(10b,9) = 5.0 Hz, 1 H, 10-H^b], 6.44−6.48 (m, 1 H), 6.60−6.67 (m, 2H), 6.75−6.80 (m, 1 H). − ^{13}C NMR ($CDCl_3$, 75 MHz): 17.2 (8-CH_3), 25.0 (C-8), 31.0 (C-9), 35.6 (C-7), 42.5 (C-10), 47.4 (C-6), 48.5 (C-6a), 113.6, 114.1 (C-1 or C-4), 118.3, 119.4 (C-2 or C-3), 135.3, 135.9 (C-4a or C-10a). − HRMS ($C_{13}H_{18}N_2$ [M^+]): calcd. for 202.1470; found 202.1466.

(6a*R,8*S**)-6,6a,7,8,9,10-Hexahydro-5*H*-8-methylpyrido[1,2-*a*]-quinoxaline (*cis*-3f):** The amidine *cis*-**6f** (0.250 g, 1.08 mmol) was dissolved in methanol (25 mL) and placed in a high-pressure apparatus in the presence of Pearlman's catalyst (0.45 g). Hydrogen pressure was applied at 3.75×10^3 Torr and the solution was shaken for 5 days at room temperature. The catalyst was removed by suction and the resulting solution was evaporated under reduced pressure. The crude reaction mixture was chromatographed through a silica column (eluent CH_2Cl_2) to afford *cis*-**3f** as pale yellow solid, (0.148 g, 70%). − M.p. 55 °C (CH_2Cl_2) − R_f = 0.23 (CH_2Cl_2). − IR (CH_2Cl_2): $\tilde{\nu}$ = 735, 1598, 3380 (NH) cm^{-1}. − ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.96 (d, *J* = 6.5 Hz, 3 H, 8-CH_3), 0.98 [q, ^2J(7a,7b) = ^3J(7a,6a) = ^3J(7a,8) = 12.0 Hz, 1 H, 7-H^a], 1.28 [qd, ^2J(9a,9b) = ^3J(9a,10a) = ^3J(9a,8) = 12.5 Hz, ^3J(9a,10b) = 4.5 Hz, 1 H, 9-H^a], 1.50−1.63 (m, 1 H, 8-H), 1.66 [dq, ^2J(7b,7a) = 12.5 Hz, ^3J(7b,6-a) = ^3J(7b,8) = ^4J(7b,9b) = 3.0 Hz, 1 H, 7-H^b], 1.76 [dquint, ^2J(9b,9a) = 13.0 Hz, ^3J(9b,10a) = ^3J(9b,10b) = ^3J(9b,8) = ^4J(9b,7b) = 3.0 Hz, 1 H, 9-H^b], 2.57 [td, ^2J(10a,10b) = ^3J(10a,9a) = 12.5 Hz, ^3J(10a,9b) = 3.0 Hz, 1 H, 10-H^a], 2.91−3.00 (m, 1 H, 6a-H), 3.20−3.32 (m, 3 H, NH and 6-H), 3.82 [dm, ^2J(10b,10a) = 12.0 Hz, 1 H, 10-H^b], 6.46 (dd, *J* = 7.0, 2.0 Hz, 1 H), 6.60 (td, *J* = 7.0, 2.0 Hz, 1 H), 6.64 (td, *J* = 7.0, 2.0 Hz, 1 H), 6.75 (dd, *J* = 7.0, 2.0 Hz, 1 H). − ^{13}C NMR ($CDCl_3$, 75 MHz): 22.0 (8-CH_3), 30.2 (C-8), 33.7 (C-9), 38.5 (C-7), 47.0 (C-10), 47.8 (C-6), 53.9 (C-6a), 112.8, 114.1 (C-1 or C-4), 118.6, 119.0 (C-2 or

C-3), 135.0, 135.6 (C-4a or C-10b). – HRMS ($C_{13}H_{18}N_2$ [M^+]): calcd. for 202.1470; found 202.1466.

[1] [1a] G. H. Fisher, H. P. Schultz, *J. Org. Chem.* **1974**, *39*, 635–640. – [1b] S. J. Benkovic, T. H. Barrows, P. R. Farina, *J. Am. Chem. Soc.* **1973**, *95*, 8414–8420. – [1c] T. H. Barrows, P. R. Farina, R. L. Chrzanowski, P. A. Benkovic, S. J. Benkovic, *J. Am. Chem. Soc.* **1976**, *98*, 3678–3689. – [1d] S. J. Benkovic, P. A. Benkovic, D. R. Comfort, *J. Am. Chem. Soc.* **1969**, *91*, 1860–1861.

[2] [2a] E. C. Taylor, A. McKillop, *J. Am. Chem. Soc.* **1965**, *87*, 1984–1990. – [2b] M. Massacret, P. Lhoste, D. Sinou, *Eur. J. Org. Chem.* **1999**, 129–134. – [2c] M. Abou-Gharbia, M. E. Freed, R. J. McCaully, P. J. Silver, R. L. Wendt, *J. Med. Chem.* **1984**, *27*, 1743–1746. – [2d] E. A. Adegoke, B. Alo, *J. Heterocyclic Chem.* **1983**, *20*, 1509–1512. – [2e] B. I. Alo, A. G. Avent, J. R. Hanson, A. E. Ode, *J. Chem. Soc., Perkin Trans. 1* **1988**, 1997–1999.

[3] [3a] U. Larsson, R. Carlson, *Acta Chemica Scandinavica* **1994**, *48*, 517–525. – [3b] K. Sakai, N. Yoneda, *Chem. Pharm. Bull.* **1981**, *29*, 1554–1560. – [3c] C. F. Bigge, S. J. Hays, P. M. Novak, J. T. Drummond, G. Johnson, T. P. Bobovski, *Tetrahedron Lett.* **1989**, *30*, 5193–5196. – [3d] Y. Kogami, K. Okawa, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2963–2966.

[4] [4a] E. Le Gall, T. Renaud, J. P. Hurvois, A. Tallec, C. Moinet, *Synlett* **1998**, 513–515. – [4b] J. Y. David, J. P. Hurvois, A. Tallec, L. Toupet, *Tetrahedron* **1995**, *51*, 3181–3196.

[5] S. Michel, E. Le Gall, J. P. Hurvois, C. Moinet, A. Tallec, P. Uriac, L. Toupet, *Liebigs Ann.* **1997**, 2089–2101.

[6] [6a] D. S. Grierson, M. Harris, H. P. Husson, *J. Am. Chem. Soc.* **1980**, *102*, 1064–1082. – [6b] M. Bonin, J. R. Romero, D. S. Grierson, H. P. Husson, *J. Org. Chem.* **1984**, *49*, 2392–2400. – [6c] C. Yue, I. Gaultier, J. Royer, H. P. Husson, *J. Org. Chem.* **1996**, *61*, 4949–4954.

[7] [7a] P. Deslongchamps, in *Stereoelectronic Effects in Organic Chemistry* (Ed.:J. Baldwin), Pergamon Press, Oxford, **1983**. – [7b] R. V. Stevens, *Acc. Chem. Res.* **1984**, *17*, 289–296. – [7c] R. V. Stevens, A. W. M. Lee, *J. Am. Chem. Soc.* **1979**, *101*, 7032–7035.

[8] O. King, I. Shinkai, in *Encyclopedia of Reagents for Organic Synthesis* (Ed.:L. A. Paquette), John Wiley & Sons, Chichester, **1995**, vol.6, p. 3888–3889.

[9] [9a] J. J. Delpuech, in *Cyclic Organonitrogen Stereodynamics* (Eds.:J. B. Lambert, Y. Takeuchi); VCH Publishers, New York, **1992**. – [9b] J. B. Lambert, in *Topics in Stereochemistry*, (Eds.:N. L. Allinger, E. L. Eliel), Wiley Interscience, New York, **1971**, p. 19–107.

[10] J. D. Andose, J. M. Lehn, K. Mislow, J. Wagner, *J. Am. Chem. Soc.* **1970**, *92*, 4050–4056.

[11] N. K. Wilson, J. B. Stothers, in *Topics in Stereochemistry* (Eds.:E. L. Eliel, N. L. Allinger), Wiley Interscience, New York, **1974**, p. 1–158.

[12] T. A. Crabb, R. F. Newton, D. Jackson, *Chem. Rev.* **1971**, *71*, 109–126.

[13] D. Tourwe, W. Van den Brandt, G. Van Binst, *Bull. Soc. Chim. Belg.* **1978**, *87*, 427–435.

[14] R. Katritzky, J. M. Lagowski, in *Chemistry of the Heterocyclic N-Oxides* (Ed. A. T. Blomquist), Academic Press, New York, **1971**.

[15] D. L. Trimm, in *Handbook of Heterogeneous Catalysis* (Eds.:G. Ertl, H. Knözinger, J. Weitkamp), VCH, Weinheim, **1997**, vol.3, p. 1264.

[16] For an alternate synthesis of **8e** see also: N. Kumar, P. C. Jain, N. Anand, *Indian J. Chem.* **1979**, *17b*, 244–245.

Received May 30, 2000
[O00288]