Influence of steric crowding on the electrochemical reduction of substituted tertiary pyridylcarboxamides in aqueous acidic medium

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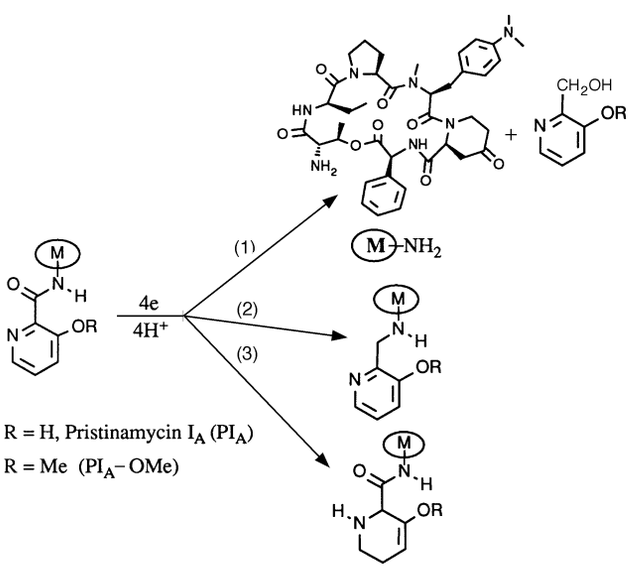
In order to assess the influence of the steric crowding on the electrochemical reduction of pyridycarboxamides, we have studied a series of tertiary aromatic or alicyclic pyridylcarboxamides. We have shown that increasing steric hindrance at the amide nitrogen led to the production of either tetrahydropyridine or aminomethylpyridine.

In a preceding paper reporting the results of a study devoted to the electrochemical reduction of the antibiotic pristinamycin I_A (PI_A) and some analogues, we demonstrated the occurrence of three competitive routes:[1] (1) splitting of the C–N bond, to yield a hydroxymethylpyridine and the free amine **M**–NH_2; (2) splitting of the C–O bond (dehydration), to give the corresponding aminomethylpyridine derivative; (3) reduction of the heterocyclic nucleus into a tetrahydropyridine derivative (Scheme 1).

When compared to previous results concerning the electrochemical reduction of pyridylcarboxamides,[2–5] this work highlighted the role of the peptidic lactone residue **M** attached to the amide nitrogen. This influence was twofold: on the one hand, it favoured the production of the aminomethylpyridine (route 2), and that of tetrahydropyridine derivatives (route 3) on the other hand.



Scheme 1

Moreover, through a series of pyridylcarboxanilides in which electronic or steric effects were generated by varying the nature of the substitution at the C-2 and C-6 positions of the phenyl ring, we established that increasing bulk at the amide nitrogen led to higher amounts of tetrahydropyridine (route 3). Thus, 2,6-diisopropylphenyl-3-methoxypicolinamide was shown to display the same cathodic behaviour as PI_A–OMe yielding 50% of free amine and 30% of tetrahydropyridine.[1] Likewise, the corresponding hydroxylated derivatives (2,6-diisopropylphenyl-3-hydroxypicolinamide and PI_A) were found identical in their electrochemical reduction process (50% of free amine, no isolated tetrahydropyridine). At that point, we hypothesized that the steric crowding generated by the peptidic macrolactone **M** at the amide nitrogen best explained the specific cathodic behaviour of PI_A.

The particular influence of **M** was further corroborated by the results obtained with the product obtained by ammonolysis of PI_A, *i.e.* a linear hexapeptide whose sequence was identical to that of macrolide **M**, but characterized by increased conformational freedom around the picolinamide nitrogen position.[6] This compound behaved as a moderately crowded secondary pyridylcarboxamide and followed the classical route (1), affording the alcohol and the free amine as the major products, without evidence of the formation of tetrahydropyridine.

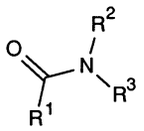
From these results, we postulated that the steric crowding around the nitrogen atom was responsible for the original electrochemical behaviour of PI_A and we suggested that the mechanism proceeded through an electron transfer to the pyridyl nucleus, which initiated the three competitive routes above reported. In order to further assess the influence of this steric crowding on the mechanism of the reduction of pyridylcarboxamides, we report in this paper the electrochemical reduction of a series of tertiary pyridylcarboxamides **1**–**7**, considered *a priori* as more sterically crowded around the nitrogen atom than the secondary amides previously studied.

Results and discussion

N-(2,6-Diisopropylphenyl)-*N*-methyl-3-methoxypicolinamide 1

From the outset, we chose to introduce a methyl group at the amide nitrogen position of *N*-(2,6-diisopropylphenyl)-3-methoxypicolinamide as a means of enhancing steric crowding. The cyclic voltammogram of compound **1**, in aqueous 0.5 mol dm^{-3} sulfuric acid solution, at a stationary mercury electrode, showed an irreversible peak Pc at −950 mV *vs.* saturated calomel electrode (SCE) at 0.2 V s^{-1}.

Reduction of **1** at −1000 mV *vs.* SCE gave $n = 4.0 \pm 0.2$ (n being the number of electrons involved in the reduction of one molecule of **1**). As the electrolysis proceeded, a decrease in the cathodic peak Pc intensity was observed. At the same time, the UV absorption band characteristic of the pyridinium nucleus at



1: R^1 = 2-(3-methoxypyridyl), R^2 = 2,6-diisopropylphenyl, R^3 = Me

2: R^1 = 2-(3-methoxypyridyl), NR^2R^3 = piperidyl

3: R^1 = 2-(3-methoxypyridyl), NR^2R^3 = 2,6-dimethylpiperidyl

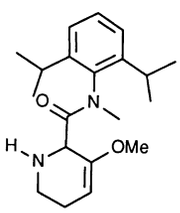
4: R^1 = 2-(3-methoxypyridyl), NR^2R^3 = 2,2,6,6-tetramethylpiperidyl

5: R^1 = 2-(3-methoxypyridyl), R^2 = cyclohexyl, R^3 = Bu^t

6: R^1 = 3-pyridyl, NR^2R^3 = piperidyl

7: R^1 = 3-pyridyl, R^2 = cyclohexyl, R^3 = Bu^t

295 nm disappeared, indicating that compound **1** was converted into reduced ring products. Finally, preparative scale electrolysis allowed the isolation, in 75% yield, of compound **8** as a tetrahydropyridine derivative, without evidence of other products.



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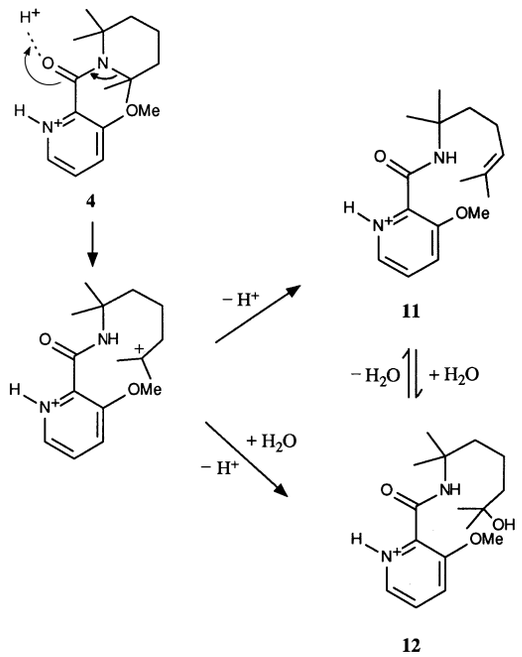
Comparison of this result with that exhibited by the corresponding secondary anilide showed that the yield of tetrahydropyridine markedly increased from 30 to 75%. So, it can be concluded that, in the case of tertiary anilide **1**, the reduction of the pyridyl nucleus became the sole route. On the basis of this finding, it became obvious that increasing steric crowding at the amide nitrogen led to enhanced reduction of the pyridyl ring. To corroborate the role of the steric crowding exerted by the substituents at the amide nitrogen position, we then turned our attention to *N*-substituted-piperidylpicolinamides, in which increasing steric crowding could be generated by varying the extent of the substitution at the C-2 and C-6 positions of the piperidyl ring.[7,8]

N-Substituted-piperidyl-3-methoxypicolinamides 2–4 and *N*-cyclohexyl-*N*-*tert*-butyl-3-methoxypicolinamide 5

The cyclic voltammogram of compound **2** (or **3**), in aqueous 0.5 mol dm^{-3} sulfuric acid solution, at a stationary mercury electrode, showed an irreversible peak Pc at *ca.* −850 mV *vs.* SCE at 0.2 V s^{-1}.

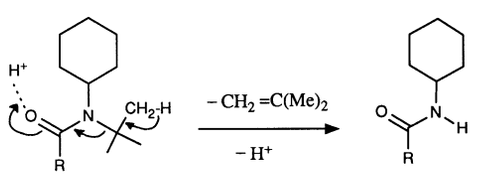
Whatever the value of *E* ranging from −850 to −1100 mV *vs.* SCE, preparative scale electrolyses afforded aldehyde **9** and alcohol **10** (Table 1). However, the yield of aldehyde **9** decreased as the cathodic potential decreased owing to its reduction into alcohol **10**. From these results, it could be deduced that compounds **2** and **3** behaved as weakly crowded pyridylcarboxamides and followed the classical route (1) which led to the formation of aldehyde **9** and alcohol **10**.

Compound **4** was remarkable in that it gave a β-elimination reaction,[9–11] unexpected under our experimental conditions. This reaction led to the opening of the piperidyl ring, probably as a consequence of the influence exerted by the four methyl groups. When working at room temperature, in 0.5 mol dm^{-3} aqueous sulfuric solutions, compound **4** was indeed largely converted into compounds **11** and **12** after 10 min (Scheme 2). Consequently, compound **4** was not a judicious choice for our study because of its instability.



Scheme 2

We next decided to investigate the electrochemical reduction of *N*-cyclohexyl-*N*-*tert*-butyl-3-methoxypicolinamide **5**, as the *tert*-butyl group has been shown to be a convenient substituent of amides to introduce increased steric effects.[12,13] As for **4**, we had to cope with the instability of compound **5** under our experimental conditions (see Experimental Section). When working at room temperature, in 0.5 mol dm^{-3} aqueous sulfuric acid solutions, compound **5** was indeed partially converted into compound **13** (Scheme 3). However, the yield of **13** could be



5: R = 2-(3-methoxypyridyl) **13**: R = 2-(3-methoxypyridyl)

7: R = 3-pyridyl **16**: R = 3-pyridyl

Scheme 3

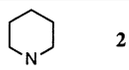
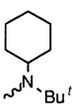
strongly decreased when working at 5 °C, where 97% of the starting material **5** was recovered after 2 h (timescale of electrolysis). Therefore, subsequent electolyses of **5** were conducted at 5 °C.

In the cyclic voltammogram of compound **5**, two irreversible peaks Pc_1 and Pc_2 were recorded at −770 and −1050 mV *vs.* SCE respectively, at 0.2 V s^{-1}.

Reduction of **5** at −850 mV *vs.* SCE gave $n = 4.0 \pm 0.2$. As the electrolysis proceeded, a decrease in the cathodic peak Pc_1 intensity was observed and the voltammogram of the exhaustively reduced solution exhibited a sole cathodic peak Pc_2 at −1050 mV *vs.* SCE. Two compounds **10** and **14** were isolated as the major products (see Table 1). Reduction of **5** at −1100 mV *vs.* SCE gave $n = 5.0 \pm 0.2$. No cathodic peak was observed in the cyclic voltammogram of the exhaustively reduced solution of **5**.

From the results of the preparative electrolyses collected in Table 1, it could be deduced that the attachment of a cyclohexyl and a *tert*-butyl to the amide nitrogen greatly favoured the formation of aminomethylpyridine **14** (50% yield), at the expense of the C–N bond splitting reaction (20% yield), in a way reminiscent of the behaviour of PI_A. Moreover, **14** could be reduced

Table 1 Products and yields of controlled potential (*E*) electrolyses[a] of tertiary amides **2**–**5** in aqueous sulfuric acid solutions

		E/ mV *vs.* SCE	**9**	**10**	**14**	**15**
	**2**	−850	50%	30%	—	—
		−1050	5%	70%	—	—
	**3**	−850	30%	46%	—	—
		−1050	5%	70%	—	—
	**5**	−850	—	20%	50%	—
		−1100	—	20%	—	30%[b]

[a] Cathode: mercury pool; anode: platinum foil; nitrogen bubbling; 25 °C. [b] Yield of 3-methoxy-2-picoline was probably higher than indicated, because significant amounts were lost upon isolation due to its volatility.

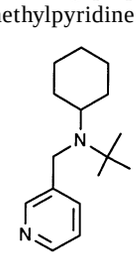
to picoline **15** at a more negative potential, as confirmed by a direct electrolysis of **14** performed at −1100 mV SCE.

A last series of tertiary amides, in which the picolinoyl nucleus was replaced by a nicotinoyl group, was finally investigated to assess the influence on the reducibility of the carboxamide group of both electronic effect exerted by the pyridinium ring (comparison **2**/**6**) and steric crowding at the amide nitrogen (comparison **6**/**7**).

N-Piperidylnicotinamide 6 and *N*-cyclohexyl-*N*-*tert*-butylnicotinamide 7

In the cyclic voltammogram of *N*-piperidylnicotinamide **6**, no cathodic peak was recorded before hydrogen evolution. In contrast, with **7**, two cathodic peaks Pc_1 and Pc_2 were recorded at −970 and −1100 mV *vs.* SCE, respectively. As for **5**, we had to cope with the instability of **7** which was converted into compound **16** under our experimental conditions (Scheme 3). As a consequence, electrolyses of **7** had to be conducted at 5 °C, where compound **7** was more stable.

Reduction of **7** at −1000 mV *vs.* SCE gave $n = 4.1 \pm 0.2$. As the electrolysis proceeded, a decrease in the cathodic peak Pc_1 intensity was observed and the voltammogram of the exhaustively reduced solution exhibited a sole cathodic peak Pc_2 at −1100 mV *vs.* SCE. Following preparative electrolysis only, could we isolate aminomethylpyridine **17** in 70% yield.



17

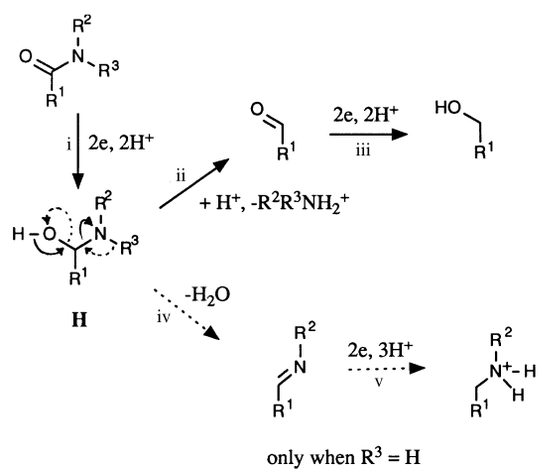
Reduction of **7** at −1150 mV *vs.* SCE gave $n = 5.5 \pm 0.2$. No stable product could be isolated after preparative scale electrolyses.

Interestingly, the electrochemical reduction of aminomethylpyridine **17** performed at −1150 mV *vs.* SCE exhibited a similar behaviour. As the electrolysis proceeded, the UV-absorption band characteristic of the pyridinium nucleus at *ca.* 260 nm disappeared, indicating that compound **17** was converted into reduced ring products which probably decomposed either under our electrolysis experimental conditions or during isolation.

Mechanistic deductions

The results above led us to distinguish several classes of tertiary pyridylcarboxamides, depending on their cathodic behaviour.

Picolinamides **2** and **3** followed the classical electrochemical reduction with formation of a transient hemiaminal species **H**. The C–N bond splitting reaction (ii, Scheme 4) then occurred, giving aldehyde **9** and alcohol **10**, without evidence of the dehydration reaction (iv, Scheme 4). In contrast, this predominated in the case of **5** and **7** leading to the aminomethylpyridine derivatives **14** and **17**, respectively, while **6** was not reducible.



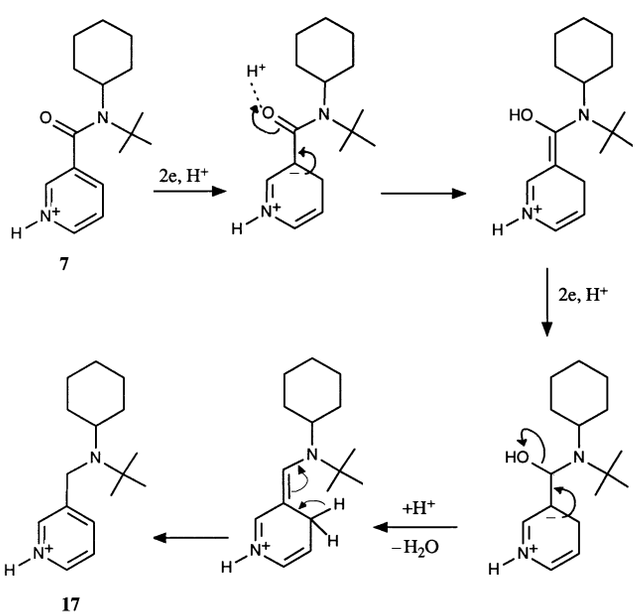
Scheme 4

Comparison of **2** (or **3**) with **5** corroborated the previous findings observed in our laboratory within the picolylanilide series.[14] Whereas *N*-phenyl-3-methoxypicolinamide was found to prefer C–O bond cleavage (iv, Scheme 4) yielding the aminomethylpyridine derivative, *N*-methyl-*N*-phenyl-3-methoxypicolinamide underwent C–N bond cleavage (ii, Scheme 4) at the expense of the C–O bond cleavage. So, it was shown that, under our experimental conditions, the hemiaminal key intermediate **H** was prone to dehydration only in the case of secondary pyridylcarboxamides ($R^3 = H$) and that it was not when $R^3 = Me$.

Consequently, tertiary picolinamide **5** appeared remarkable in that it afforded aminomethylpyridine derivative **14** as the main product, in 50% yield (Table 1). From this result, we deduced that the reduction of tertiary pyridylcarboxamide **5** was likely to proceed by another mechanism featuring an

electron transfer to the pyridyl nucleus as previously reported for PI_A and related streptogramins (see Scheme 2 in ref. 1). According to this hypothesis, the first two electrons required for the reduction would be delivered from the cathode to the pyridinium ring. From this stage, the key intermediate would be the transient carbanion species formed at the C-2 position (2 F mol^{-1}). The subsequent step would consist of an intramolecular migration of the pair of electrons from the reduced heterocyclic ring towards the side chain, followed by a second reduction (2 F mol^{-1}). This would finally result in the reductive cleavage of the C–O bond, to yield the aminomethylpyridine derivative **14**. Thus, the driving force for this electron migration would be the tendency to restore aromaticity within the heterocyclic ring.

Comparison of **2** with **6** provided evidence for the crucial role of the 2-pyridinium moiety on the reducibility of the carboxamide group. As nicotinamide **6** was not reducible under our experimental conditions, similarly, we thought that nicotinamide **7** would not be reducible. Contrary to this hypothesis, **7** was found to give aminomethylpyridine **17** as the exclusive product. This result substantiated the influence of the steric crowding at the amide nitrogen. Furthermore, it indicated that the reduction of **7** very likely did not follow the classical electrochemical route, but it was consistent with the reduction of the 3-pyridyl nucleus and the formation of transient carbanion species formed at the C-3 position, after consumption of two and four electrons per mole of **7**, as indicated in Scheme 5.



Scheme 5

These findings corroborated the influence of the steric crowding exerted by the substituents attached to the amide nitrogen. First, bulky substituent would hinder protonation of the amide nitrogen, so that the amino group would be a poor leaving group, and the C–N bond splitting reaction would be no longer observed. Secondly, the steric hindrance induced a severe decrease of the amidic resonance,[15] and this increased the electron-withdrawing ability of the amide group, so that the 2- or 3-pyridyl ring could be more easily reduced.

The reducibility of the pyridine nucleus, in aqueous alcoholic acidic solution, is further substantiated by the following observations.

In the case of **14**, formation upon electrolysis of 2-picoline **15** was likely to proceed through the evolution of the C-2 carbanion, according to a route similar to that previously reported in ref. 1.

In contrast, the formation of 3-picoline was not observed in the case of **17**. To explain these findings, we assumed that, in the case of **17**, the position of the electrogenerated carbanionic charge was inadequate to promote the C–N bond cleavage reaction. Thus, as reported above, no defined product could be isolated. Compound **17** was probably converted into reduced ring products which further decomposed *via* hydration.[16,17]

Finally, through a series of tertiary pyridylcarboxamides, we have demonstrated that sterically crowded aromatic substituents could render exclusively the production of the tetrahydropyridine derivative and that sterically crowded alicyclic substituents enhanced the formation of aminomethylpyridine. However, none of the substituents studied in this work were found to mimic completely the peptidic lactone residue **M** of PI_A. Neither **1** nor **5** was indeed able to afford, upon electrochemical reduction, both the tetrahydropyridine and the aminomethylpyridine derivatives. These conclusions stress the particular steric and electronic properties of the macrolactonic moiety of pristinamycin I_A.

Experimental

Materials

UV–VIS spectra were recorded on a Varian Cary 13E spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 300 spectrometer operating at 300 MHz for ^{1}H observations. Chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane. *J* values are given in Hz. The measurements were carried out using the standard pulse sequences. The carbon type (methyl, methylene, methine or quaternary) was determined by DEPT experiments. Mass spectra were recorded on a Nermag R 10-10 C spectrometer, equipped with desorption chemical ionization (DCI) mode. Samples were introduced by means of a direct insertion probe. Ammonia was used as the reagent gas. Melting points were determined on a Köfler block and were uncorrected.

Electrochemical measurements were made with a Radiometer-Tacussel PRG 5 multipurpose polarograph that was used only as a rapid-response potentiostat. For cyclic voltammetry, triangular waveforms were supplied by a Tacussel GSTP 4 function generator. Current–potential curves were recorded on a Sefram SI 8312 instrument. The cell was a Tacussel CPRA water-jacketed cell working at a temperature of 20 °C. The reference electrode was an aqueous saturated calomel electrode (SCE) (Tacussel C-10), to which all potentials quoted are referred. The counter electrode was a platinum electrode Tacussel Pt 11. The working electrode was a Tacussel CMT 10/24 capillary. The aqueous or alcoholic (50 : 50) sulfuric acid solutions (20 cm^3) of compounds **1**–**7** (0.04 mmol) were deaerated prior to use by bubbling nitrogen through the solution for 15 min. Scanning started from −0.3 V *vs.* SCE towards −1.2 V and returned to −0.3 V at a rate of 0.2 V s^{-1}. Controlled potential electrolyses were carried out using a three-compartment water jacketed cell protected from light. A Tacussel PJT 120-1 potentiostat and a Tacussel IG6-N electronic integrator were included in the circuit. The reference electrode has been mentioned above. The counter electrode was a platinum foil. The working electrode was a mercury pool (60 cm^2 area).

Analytical TLC were performed on Merck Silica Gel 60 F 254 (lot 5714). Column chromatography was conducted on open glass columns packed with Merck Silica Gel 60 (lot 9385).

The solvents used for extractions and chromatography were obtained from S.D.S. Methanol, sulfuric acid and sodium carbonate were obtained from Prolabo (analysis purity grade). Piperidine, 2,6-dimethypiperidine, 2,2,6,6-tetramethylpiperidine, *N*-cyclohexyl-*N*-*tert*-butylamine and nicotinoyl chloride were obtained from Aldrich.

Compounds **1**–**7** were synthesized as follows.

***N*-(2,6-Diisopropylphenyl)-*N*-methyl-3-methoxypicolinamide 1.** A solution of *N*-methyl-2,6-diisopropylaniline (0.75 g, 3.9 mmol, synthesized using the method previously reported in the literature)[18] and triethylamine (0.79 g, 7.8 mmol), in dry

toluene (10 cm^3), was stirred and heated to 80 °C. A solution of 3-methoxypicolinoyl chloride (0.67 g, 3.9 mmol, synthesized following the procedure previously reported for picolinoyl chloride),[19] in dry toluene (10 cm^3), was added dropwise. After addition, stirring was continued for 4 h at 80 °C. Then the solvent was evaporated under reduced pressure at 50 °C. The residue was poured onto dichloromethane (50 cm^3) and washed with water (20 cm^3) to remove the triethylammonium salt. The organic phase was dried over anhydrous magnesium sulfate and treated with activated charcoal. After filtration, the solvent was removed under reduced pressure, at 35 °C. Chromatography on silica gel, with toluene–acetone (95:5) as the eluent, afforded compound **1** (0.84 g, 67%), mp 103–105 °C, as an amorphous white solid.

1 (Found: C, 73.55; H, 7.99; N, 8.60. $C_{20}H_{26}N_2O_2$ requires C, 73.61; H, 7.97; N, 8.59%); δ_H(300 MHz; $CDCl_3$) 1.20 (12 H, m, Me, isopropyl), 3.30 (2 H, septuplet, *J* 6, CH, isopropyl), 3.40 (3 H, s, NMe), 3.85 (3 H, s, OMe), 7.00 to 7.20 [5 H, m, 4-H, 5-H and CH (diisopropylphenyl)]; δ_C(75 MHz; $CDCl_3$) 22.9 and 25.8 (Me, isopropyl), 28.2 (CH, isopropyl), 37.7 (NMe), 55.4 (OMe), 117.6 (C-4, diisopropylphenyl), 123.5 (C-3 and C-5, diisopropylphenyl), 124.1 (C-5), 128.2 (C-4), 138.2 (C-2), 139.2 (C-6), 143.8 (C-1, diisopropylphenyl), 146.9 (C-2 and C-6, diisopropylphenyl), 152.6 (C-3), 167.6 (CO, amide); *m/z* 327 (MH^+).

***N*-Piperidyl-3-methoxypicolinamide 2.** The same method applied to 3-methoxypicolinoyl chloride (0.69 g, 4 mmol), piperidine (0.34 g, 4 mmol) and triethylamine (0.82 g, 8 mmol), afforded, after chromatography on silica gel, with toluene–acetone (50:50) as the eluent, compound **2** (0.66 g, 74%), mp 92–94 °C, as an amorphous white solid.

2 (Found: C, 65.13; H, 7.25; N, 12.78. $C_{12}H_{16}N_2O_2$ requires C, 65.45; H, 7.27; N, 12.73%); δ_H(300 MHz; $CDCl_3$) 1.50 (2 H, m, 4-CH_2, piperidyl), 1.65 (4 H, m, 3-CH_2 and 5-CH_2, piperidyl), 3.10 (2 H, t, *J* 6, 2-H_{ax} and 6-H_{ax}, piperidyl), 3.75 (2 H, m, 2-H_{eq} and 6-H_{eq}, piperidyl), 3.85 (s, 3 H, OMe), 7.25 (2 H, m, 4-H and 5-H), 8.20 (1 H, dd, *J* 5 and 2, 6-H); δ_C(75 MHz; $CDCl_3$) 24.5, 25.3 and 26.1 (C-3, C-4 and C-5, piperidyl), 42.3 and 47.5 (C-2 and C-6, piperidyl), 55.5 (OMe), 118.3 and 124.2 (C-4 and C-5), 141.0 (C-6), 145.2 (C-2), 152.2 (C-3), 165.7 (CO, amide); *m/z* 221 (MH^+).

***N*-(2,6-Dimethylpiperidyl)-3-methoxypicolinamide 3.** The same method applied to 3-methoxypicolinoyl chloride (0.8 g, 4.6 mmol), 2,6-dimethylpiperidine (0.52 g, 4.6 mmol) and triethylamine (0.95 g, 9.2 mmol), afforded, after chromatography on silica gel, with toluene–acetone (70:30) as the eluent, compound **3** (0.92 g, 70%), mp 168–170 °C, as an amorphous white solid.

3 (Found: C, 67.74; H, 8.15; N, 11.27. $C_{14}H_{20}N_2O_2$ requires C, 67.74; H, 8.06; N, 11.29%); δ_H(300 MHz; $CDCl_3$) 1.15 and 1.35 (3 H, d, *J* 7, Me, dimethylpiperidyl), 1.45 (2 H, m, 4-CH_2, dimethylpiperidyl), 1.70 (4 H, m, 3-CH_2 and 5-CH_2, dimethylpiperidyl), 3.65 (1 H, m, 2-H or 6-H, dimethylpiperidyl), 3.85 (3 H, s, OMe), 4.95 (1 H, m, 2-H or 6-H, dimethylpiperidyl), 7.20 (2 H, m, 4-H and 5-H), 8.15 (1 H, dd, *J* 5 and 2, 6-H); δ_C(75 MHz; $CDCl_3$) 14.0 (C-4, dimethylpiperidyl), 20.6 and 21.2 (C-3 and C-5, dimethylpiperidyl), 43.5 and 49.1 (C-2 and C-6, dimethylpiperidyl), 55.4 (OMe), 118.2 and 123.8 (C-4 and C-5), 140.9 (C-6), 146.2 (C-2), 151.8 (C-3), 166.9 (CO, amide); *m/z* 249 (MH^+).

***N*-(2,2,6,6-Tetramethylpiperidyl)-3-methoxypicolinamide 4.** When applied to 3-methoxypicolinoyl chloride (1.00 g, 5.8 mmol), 2,2,6,6-tetramethylpiperidine (0.82 g, 5.8 mmol) and triethylamine (1.20 g, 11.6 mmol), the method above yielded, after 12 h, a dark-red residue. Chromatography on silica gel, with toluene–acetone (90:10) as the eluent, afforded **4** (0.5 g, 31%), mp 80–82 °C, as an amorphous white solid.

4 (Found: C, 69.44; H, 8.54; N, 10.07. $C_{16}H_{24}N_2O_2$ requires C, 69.56; H, 8.69; N, 10.15%); δ_H(300 MHz; $CDCl_3$) 1.40 (12 H, s, Me, tetramethylpiperidyl), 1.80 (6 H, s, CH_2, tetramethylpiperidyl), 3.85 (3 H, s, OMe), 7.20 (2 H, m, 4-H and 5-H), 8.10 (1 H, dd, *J* 5 and 2, 6-H); δ_C(75 MHz; $CDCl_3$) 15.0 (C-4, tetramethylpiperidyl), 29.6 (Me, tetramethylpiperidyl), 37.7 (C-3 and C-5, tetramethylpiperidyl), 55.5 (OMe), 56.9 (C-2 and C-6, tetramethylpiperidyl), 118.2 and 123.8 (C-4 and C-5), 139.3 (C-6), 149.9 (C-2), 152.5 (C-3), 170.4 (CO, amide); *m/z* 277 (MH^+).

***N*-Cyclohexyl-*N*-*tert*-butyl-3-methoxypicolinamide 5.** When applied to 3-methoxypicolinoyl chloride (1.0 g, 5.8 mmol), *N*-cyclohexyl-*N*-*tert*-butylamine (0.9 g, 5.8 mmol) and triethylamine (1.20 g, 11.6 mmol), the method above yielded, after 4 h, a dark-red residue. Chromatography on silica gel, with toluene–acetone (80:20) as the eluent, afforded **5** (1.2 g, 71%), mp 139–141 °C, as an amorphous solid.

5 (Found: C, 70.34; H, 8.97; N, 9.55. $C_{17}H_{26}N_2O_2$ requires C, 70.34; H, 8.96; N, 9.65%); δ_H(300 MHz; $CDCl_3$) 1.00 to 1.90 [19 H, broad m, CH_2 (cyclohexyl) and Me (*tert*-butyl)], 3.25 (1 H, m, 1-H, cyclohexyl), 3.80 (3 H, s, OMe), 7.15 (2 H, m, 4-H and 5-H), 8.10 (1 H, d, *J* 5, 6-H); δ_C(75 MHz; $CDCl_3$) 25.4, 27.1 and 33.0 (CH_2, cyclohexyl), 29.7 (Me, *tert*-butyl), 55.4 [OMe and C_Q (*tert*-butyl)], 59.5 (C-1, cyclohexyl), 118.1 and 123.4 (C-4 and C-5), 140.0 (C-6 and C-2), 151.8 (C-3), 163.0 (CO, amide); *m/z* 291 (MH^+).

***N*-Piperidyl nicotinamide 6.** A reaction mixture of nicotinic acid (1.6 g, 13.2 mmol), 1-hydroxybenzotriazole (0.4 g, 3 mmol) and piperidine (1.1 g, 13.2 mmol), in dichloromethane (50 cm^3), was stirred and cooled to 5 °C in an ice–water bath. A solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.8 g, 14.6 mmol) in dichloromethane (50 cm^3), was added dropwise. After addition, stirring was continued for 2 h at 5 °C, and for an additional 12 h at 20 °C. The reaction mixture was then washed with water (50 cm^3). The organic phase was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure at 35 °C. Chromatography of the residue on silica gel, with toluene–acetone (90:10) as the eluent, afforded **6** (2.4 g, 95%) as a colourless oil.

6 (Found: C, 69.47; H, 7.41; N, 14.69. $C_{11}H_{14}N_2O$ requires C, 69.47; H, 7.41; N, 14.73%). δ_H(300 MHz; $CDCl_3$) 1.55 (2 H, m, 4-CH_2, piperidyl), 1.70 (4 H, m, 3-CH_2 and 5-CH_2, piperidyl), 3.35 (2 H, m, 2-H_{ax} and 6-H_{ax}, piperidyl), 3.75 (2 H, m, 2-H_{eq} and 6-H_{eq}, piperidyl), 7.35 (1 H, dd, *J* 5 and 2.5, 5-H), 7.75 (1 H, dt, *J* 8 and 1.5, 4-H), 8.15 (2 H, m, 2-H and 6-H); δ_C(75 MHz; $CDCl_3$) 24.3, 25.5 and 26.4 (C-3, C-4 and C-5, piperidyl), 43.1 and 48.9 (C-2 and C-6, piperidyl), 123.3 and 134.7 (C-4 and C-5), 147.6 (C-6), 132.2 (C-3), 167.5 (CO, amide); *m/z* 191 (MH^+).

***N*-Cyclohexyl-*N*-*tert*-butylnicotinamide 7.** When applied to nicotinoyl chloride (0.53 g, 3 mmol), *N*-cyclohexyl-*N*-*tert*-butylamine (0.46 g, 3 mmol) and triethylamine (0.61 g, 6 mmol), the method above described for **1**, yielded, after 24 h, a dark-red residue. Chromatograhy on silica gel, with toluene–acetone (80:20) as the eluent, afforded **7** (0.26 g, 33%), mp 90–92 °C, as an amorphous white solid.

7 (Found: C, 73.97; H, 9.22; N, 11.07. $C_{16}H_{24}N_2O$ requires C, 73.85; H, 9.23; N, 10.77%); δ_H(300 MHz; $CDCl_3$) 0.90 to 1.90 (10 H, m, CH_2, cyclohexyl), 1.40 (9 H, s, Me, *tert*-butyl), 3.30 (1 H, m, 1-H, cyclohexyl), 7.30 (1 H, dd, *J* 8 and 5, 5-H), 7.70 (1 H, d, *J* 8, 4-H), 8.60 (2 H, m, 2-H and 6-H); δ_C(75 MHz; $CDCl_3$) 25.2, 27.1 and 34.1 (CH_2, cyclohexyl), 29.4 (Me, *tert*-butyl), 58.5 (C_Q, *tert*-butyl), 59.1 (C-1, cyclohexyl), 122.9 (C-5), 134.8 (C-4), 137.2 (C-3), 148.1 and 150.2 (C-6 and C-2), 172.7 (CO, amide); *m/z* 261 (MH^+).

Isolation and spectroscopic data of products 8–17

***N*-(2,6-Diisopropylphenyl)-*N*-methyl-3-methoxy-1,2,5,6-tetrahydropicolinamide 8.** 200 cm^3 of a water–alcoholic (50:50) sulfuric acid solution (0.5 mol dm^{-3}) of compound **1** (131 mg, 0.4 mmol) was reduced under nitrogen, at 25 °C, at a mercury pool electrode ($E = -1000$ mV *vs.* SCE). After exhaustive electrolysis (4.2 ± 0.2 F mol^{-1}), *i.e.* when a steady state minimum value of the current was recorded, the alcoholic solution was concentrated to 100 cm^3 under reduced pressure at 40 °C. The resulting

solution was neutralized by an aqueous solution of sodium carbonate (5 mol dm^{-3}) and extracted with dichloromethane (100 cm^3). The organic phase was dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure at 30 °C. Chromatography on silica gel, with toluene–acetone (95:5) as the eluent, afforded compound **8** (93 mg, 71%) as a colourless oil.

8 (Found: C, 72.38; H, 9.16; N, 8.42. $C_{20}H_{30}N_2O_2$ requires C, 72.73; H, 9.09; N, 8.48%); δ_H(300 MHz; $CDCl_3$) 1.20 (12 H, m, Me, isopropyl), 1.70, 1.95, 2.20 and 2.55 (4 H, m, 5-CH_2 and 6-CH_2), 3.15 (2 H, m, CH, isopropyl), 3.25 (NMe), 3.50 (OMe), 3.80 (1 H, s, 2-H), 4.80 (1 H, m, 4-H), 7.25 (3 H, m, CH, diisopropylphenyl); δ_C(75 MHz; $CDCl_3$) 23.1 and 25.8 (Me, isopropyl), 24.5 (C-5), 27.8 and 28.0 (CH, isopropyl), 37.5 (NMe), 41.0 (C-6), 53.7 (C-2), 55.2 (OMe), 94.1 (C-4), 124.3 and 128.7 (C-3, C-4 and C-5, diisopropylphenyl), 138.1 (C-1, diisopropylphenyl), 146.6 and 147.1 (C-2 and C-6, diisopropylphenyl), 153.7 (C-3), 172.4 (CO, amide); *m/z* 331 (MH^+).

3-Methoxypicolyl aldehyde 9 and 3-methoxypicolyl alcohol 10. *N*-Piperidyl-3-methoxypicolinamide **2** (110 mg, 0.5 mmol) was dissolved in 200 cm^3 of an aqueous sulfuric acid solution (0.5 mol dm^{-3}). The electrochemical procedure described for **1**, with $E = -850$ mV *vs.* SCE (2.6 F mol^{-1}), yielded, after chromatography on silica gel with toluene–acetone–methanol (7.5:2.0:0.5) as the eluent, compounds **9** (49 mg, 45%), mp 54–56 °C, and **10** (17 mg, 15%), mp 71–73 °C, as amorphous white solids.

9 δ_H(300 MHz; $CDCl_3$) 4.00 (3 H, s, OMe), 7.40 (1 H, dd, *J* 9 and 1, 4-H), 7.50 (1 H, dd, *J* 9 and 5, 5-H), 8.40 (1 H, dd, *J* 5 and 1, 6-H), 10.35 (1 H, s, CHO); δ_C(75 MHz; $CDCl_3$) 55.8 (OMe), 120.1 and 128.8 (C-4 and C-5), 141.0 (C-2), 142.0 (C-6), 157.9 (C-3), 190.5 (CHO); *m/z* 138 (MH^+).

10 (Found: C, 60.39; H, 6.51; N, 10.11. $C_7H_9NO_2$ requires C, 60.43; H, 6.47; N, 10.07%); δ_H(300 MHz; $CDCl_3$) 3.80 (3 H, s, OMe), 4.30 (1 H, t, *J* 4, D_2O exchanged), 4.65 (2 H, d, *J* 4, CH_2), 7.05 (1 H, dd, *J* 9 and 1, 4-H), 7.15 (1 H, dd, *J* 9 and 5, 5-H), 8.10 (1 H, dd, *J* 5 and 1, 6-H); δ_C(75 MHz; $CDCl_3$) 54.8 (OMe), 59.7 (CH_2), 116.1 and 122.3 (C-4 and C-5), 139.0 (C-6), 148.1 (C-2), 152.0 (C-3); *m/z* 140 (MH^+).

The same procedure applied to *N*-(2,6-dimethylpiperidyl)-3-methoxypicolinamide **3** (149 mg, 0.6 mmol) afforded after chromatography, **9** (25 mg, 30%) and **10** (38 mg, 46%).

Using the same method, but working at −1100 mV *vs.* SCE (4.0 ± 0.2 F mol^{-1}), preparative scale electrolysis of **2** (or **3**) afforded, after chromatography, **9** (4 mg, 5%) and **10** (48 mg, 70%).

***N*-(2,6-Dimethylhept-5-en-2-yl)-3-methoxypiolinamide 11 and *N*-(2,6-dimethyl-6-hydroxyheptan-2-yl)-3-methoxypicolinamide 12.** *N*-(2,2,6,6-Tetramethylpiperidyl)-3-methoxypicolinamide **4** (138 mg, 0.5 mmol) was dissolved in 250 cm^3 of an aqueous sulfuric acid soludion (0.5 mol dm^{-3}). The resulting solution was stirred at 25 °C for 10 min, then adjusted to pH 6 by addition of an aqueous solution of sodium carbonate (5 mol dm^{-3}), and extracted with dichloromethane (50 cm^3). The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure at 35 °C. Chromatography on silica gel, with toluene–acetone (50:50), as the eluent afforded compounds **11** (56 mg, 41%) and **12** (44 mg, 32%) as colourless oils.

11 δ_H(300 MHz; $CDCl_3$) 1.50 (6 H, s, 1-Me, hexenyl), 1.60 and 1.70 (3 H, s, 5-Me, hexenyl), 1.85 (2 H, m, 2-CH_2, hexenyl), 2.05 (2 H, m, 3-CH_2, hexenyl), 3.95 (3 H, s, OMe), 5.15 (1 H, m, 4-H, hexenyl), 7.35 (2 H, m, 4-H and 5-H), 7.70 (1 H, broad s, NH, D_2O exchanged), 8.15 (1 H, dd, *J* 5 and 2, 6-H); δ_C(75 MHz; $CDCl_3$) 17.5 and 25.6 (5-Me, hexenyl), 22.8 (3-CH_2, hexenyl), 26.7 (1-Me, hexenyl), 40.3 (2-CH_2, hexenyl), 53.4 (C-1, hexenyl), 55.8 (OMe), 120.4 and 126.6 (C-4 and C-5), 124.3 (C-4, hexenyl), 131.3 (C-5, hexenyl), 139.4 (C-6), 155.9 (C-3), 163.4 (CO, amide); *m/z* 277 (MH^+).

12 δ_H(300 MHz; $CDCl_3$) 1.20 (6 H, s, 1-Me, hexanol), 1.30 to 1.50 (10 H, m, 5-Me, 2-CH_2 and 3-CH_2, hexanol), 1.85 (2 H, m, 4-CH_2, hexanol), 2.00 (1 H, broad s, OH, alcohol, D_2O exchanged), 3.95 (3 H, s, OMe), 7.35 (2 H, m, 4-H and 5-H), 7.65 (1 H, broad s, NH, D_2O exchanged), 8.15 (1 H, dd, *J* 5 and 2, 6-H); δ_C(75 MHz; $CDCl_3$) 18.7 (3-CH_2, hexanol), 26.9 (1-Me, hexanol), 29.2 (5-Me, hexanol), 40.5 (2-CH_2, hexanol), 44.0 (5-CH_2, hexanol), 53.5 (C-1, hexanol), 55.8 (OMe), 120.4 and 126.6 (C-4 and C-5), 139.5 (C-6), 155.8 (C-3), 163.5 (CO, amide); *m/z* 295 (MH^+).

***N*-Cyclohexyl-3-methoxypicolinamide 13.** *N*-Cyclohexyl-*N*-*tert*-butyl-3-methoxypicolinamide **3** (115 mg, 0.4 mmol) was dissolved in 200 cm^3 of an aqueous sulfuric acid solution (0.5 mol dm^{-3}). The resulting solution was stirred at room temperature for 15 h, and then treated following the method described for **4**. Chromatography on silica gel, with toluene–acetone (80:20) as the eluent, afforded **13** (43 mg, 46%), mp 88–90 °C, as an amorphous white solid along with 25% of starting material (30 mg).

13 (Found: C, 66.40; H, 7.73; N, 11.89. $C_{13}H_{18}N_2O_2$ requires C, 66.6; H, 7.69; N, 11.96%); δ_H(300 MHz; $CDCl_3$) 1.20 to 2.10 (10 H, m, CH_2, cyclohexyl), 3.90 (3 H, s, OMe), 3.95 (1 H, m, CH, cyclohexyl), 7.35 (2 H, m, 4-H and 5-H), 7.55 (1 H, broad s, NH, D_2O exchanged), 8.15 (1 H, dd, *J* 5 and 2, 6-H); δ_C(75 MHz; $CDCl_3$) 24.7, 25.6 and 32.9 (CH_2, cyclohexyl), 47.8 (CH, cyclohexyl), 55.9 (OMe), 120.5 and 126.5 (C-4 and C-5), 139.5 (C-2), 139.8 (C-6), 155.7 (C-3), 163.2 (CO, amide); *m/z* 235 (MH^+).

***N*-Cyclohexyl-*N*-*tert*-butyl-2-aminomethyl-3-methoxypyridine 14.** 200 cm^3 of an aqueous sulfuric acid (0.5 mol dm^{-3}) solution of **5** (174 mg, 0.6 mmol) was cooled to 5 °C in an ice–water bath. Then, the resulting solution was reduced, under nitrogen, at 5 °C, at a mercury pool working electrode ($E = -850$ mV SCE, 4.0 ± 0.2 F mol^{-1}), following the method above described for compound **1**. Chromatography on silica gel, with toluene–acetone–methanol (70:20:10) as the eluent, afforded compound **14** (83 mg, 50%) as a pale-yellow oil, along with **9** (20 mg, 20%).

14 (Found: C, 73.88; H, 10.22; N, 10.10. $C_{17}H_{28}N_2O$ requires C, 73.91; N, 10.14; N, 10.14%); δ_H(300 MHz; $CDCl_3$) 0.90 to 1.80 [19 H, m, CH_2(cyclohexyl) and Me(*tert*-butyl)], 3.00 (1 H, m, CH, cyclohexyl), 3.85 (3 H, s, OMe), 4.00 (2 H, s, CH_2-N), 7.05 (2 H, m, 4-H and 5-H), 8.20 (1 H, dd, *J* 5 and 1, 6-H); δ_C(75 MHz; $CDCl_3$) 26.1, 26.7 and 32.7 (CH_2, cyclohexyl), 29.0 (Me, *tert*-buty), 43.8 (CH_2-N), 55.0 (OMe), 55.6 (C_Q, *tert*-butyl), 57.0 (CH, cyclohexyl), 116.3 and 121.3 (C-4 and C-5), 140.3 (C-6), 153.2 and 153.9 (C-2 and C-3); *m/z* 277 (MH^+).

3-Methoxy-2-picoline 15. Using the same method, but working at −1050 mV *vs.* SCE (5.0 ± 0.2 F mol^{-1}), preparative scale electrolysis of **5** afforded, after chromatography, **10** (20 mg, 20%) and **15** (22 mg, 30%) as a colourless volatile oil. δ_H(300 MHz; $CDCl_3$) 2.50 (3 H, s, Me), 3.80 (3 H, s, OMe), 7.10 (2 H, m, 4-H and 5-H), 8.05 (1 H, dd, *J* 5 and 2, 6-H).

***N*-Cyclohexylnicotinamide 16.** *N*-cyclohexyl-*N*-*tert*-butylnicotinamide **7** (157 mg, 0.6 mmol) was dissolved in 200 cm^3 of an aqueous sulfuric acid solution (0.5 mol dm^{-3}). The resulting solution was stirred at 25 °C for 8 h, and then treated following the method described for **4**. Chromatography on silica gel, with toluene–acetone (80:20) as the eluent, afforded **16** (73 mg, 60%), mp 140–142 °C as an amorphous white solid, along with 35% of starting material **7**.

16 (Found: C, 70.72; H, 8.02; N, 13.77. $C_{12}H_{16}N_2O$ requires C, 70.59; H, 7.84; N, 13.72%); δ_H(300 MHz; $CDCl_3$) 1.20 to 2.10 (10 H, m, CH_2, cyclohexyl), 3.95 (1 H, m, CH, cyclohexyl), 6.45 (1 H, d, *J* 6, NH, D_2O exchanged), 7.35 (1 H, *J* 9 and 5, 5-H), 8.10 (1 H, d, *J* 9, 4-H), 8.75 (1 H, d, *J* 5, 6-H), 8.95 (1 H, s, 2-H); δ_C(75 MHz; $CDCl_3$) 24.8, 25.4 and 33.0 (CH_2, cyclohexyl), 48.9 (CH, cyclohexyl), 123.3 (C-5), 130.7 (C-3), 135.1 (C-4), 147.7 (C-6), 151.7 (C-2) and 164.6 (CO, amide); *m/z* 205 (MH^+).

***N*-Cyclohexyl-*N*-*tert*-butyl-3-aminomethylpyridine 17.** 200 cm^3

of an aqueous sulfuric acid (0.5 mol dm^{-3}) solution of **7** (156 mg, 0.6 mmol) was cooled to 5 °C in an ice–water bath. Then, the solution was reduced, under nitrogen, at 5 °C, at a mercury pool working electrode ($E = -1000$ mV *vs.* SCE, 3.9 ± 0.2 F mol^{-1}), following the method above described for compound **1**. Chromatography on silica gel, with toluene–acetone (90 : 10) as the eluent, afforded compound **17** (103 mg, 70%) as a colourless oil.

17 δ_H(300 MHz; $CDCl_3$) 0.90 to 1.75 (10 H, m, CH_2, cyclohexyl), 1.1 (9 H, s, Me, *tert*-butyl), 2.95 (1 H, m, CH, cyclohexyl), 3.85 (2 H, s, CH_2-N), 7.15 (1 H, dd, *J* 8 and 5, 5-H), 7.75 (1 H, dd, *J* 8 and 2, 4-H), 8.35 (1 H, dd, *J* 5 and 1, 6-H), 8.60 (1 H, d, *J* 2, 2-H); δ_C(75 MHz; $CDCl_3$) 25.9, 26.6 and 33.3 (CH_2, cyclohexyl), 29.0 (Me, *tert*-butyl), 44.5 (CH_2-N), 55.0 (OMe), 55.6 (C_Q, *tert*-butyl), 56.5 (CH, cyclohexyl), 122.7 (C-5), 134.7 (C-4), 141.4 (C-3), 147.0 (C-6), 148.8 (C-2); *m/z* 247 (MH^+).

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