Monatshefte für Chemie 134, 573–583 (2003)
DOI 10.1007/s00706-002-0540-5

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Total Syntheses of the Alkaloids Ipalbidinium and Clathryimine B

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Received August 2, 2002; accepted August 9, 2002
Published online March 6, 2003

Summary. The indolizidinium alkaloid ipalbidinium and the quinolizidinium alkaloid clathryimine B were prepared starting from brominated 2-aminopyridines using two Pd-catalyzed cross-coupling reactions and a *Sandmeyer*-type diazotation/iodination protocol as the key steps.

Keywords. Alkaloids; Ipalbidinium; Clathryimine B; Palladium-catalyzed cross-coupling; Halogenation.

Introduction

In continuation of our work on pyridine [1] and quaternary pyridinium alkaloids [2] we focused our interest on the indolizidinium alkaloid ipalbidinium (**1**) and the marine quinolizidinium alkaloid clathryimine B (**2a**). Ipalbidinium (syn. ipohardine) was isolated from the seeds of *Ipomoea alba* L. [3], and its structure was confirmed by X-ray analysis [4]. Clathryimine B, together with the carboxy derivative clathryimine A (**2b**), was isolated from the marine sponge *Clathrya basilana* [5]. Up to now no data about biological activities of these alkaloids have been published.

In our previous work [2] we have developed a convenient synthesis of ficuseptine (**3**), a antimicrobial indolizidinium alkaloid with structural similarity to **1**. Here we report the extension of this work on the synthesis of ipalbidinium and clathryimine B.

These two alkaloids with a common structural element **A** should be prepared by intramolecular N-alkylation of an appropriate pyridine derivative **B** (X = leaving group). The aliphatic side chain was to be introduced by Pd-catalyzed cross-coupling of a halopyridine **C** with a C_3 or a C_4 building block, respectively.

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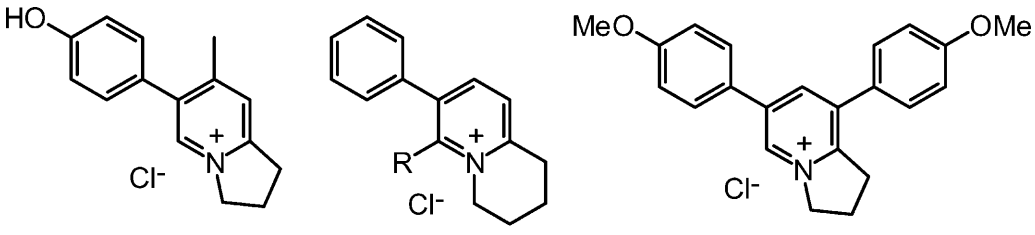
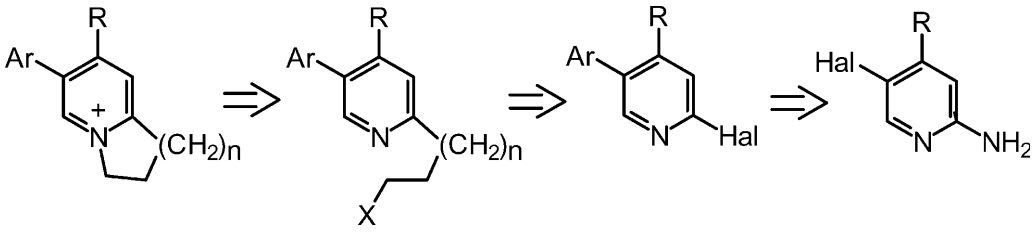


1 **2a** R = H **2b** R = COOH **3**

Scheme 1



A **B** **C** **D**

(X = leaving group)

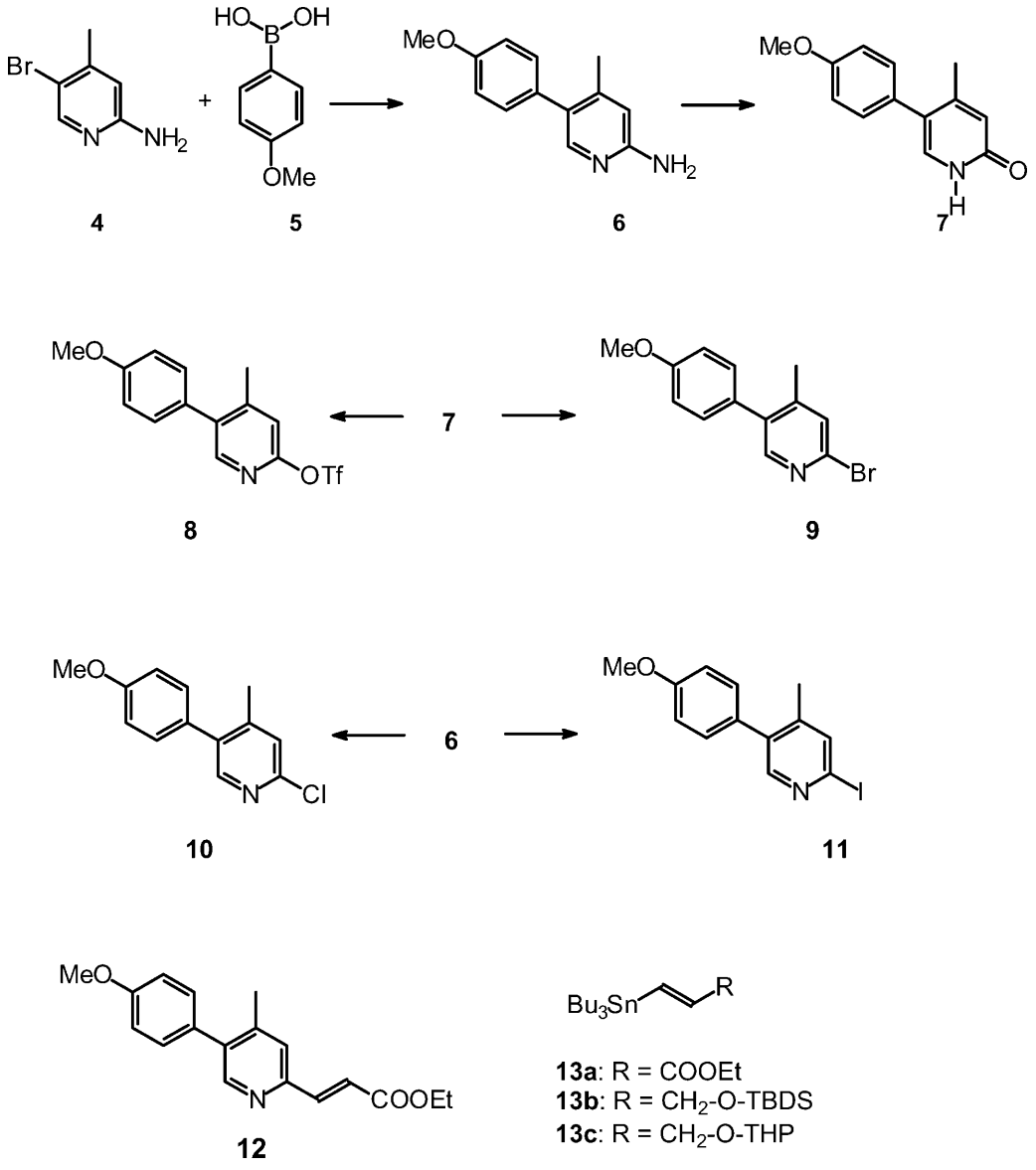
Scheme 2

The (methoxy)phenyl ring should be connected with the pyridine core in another cross-coupling reaction starting from a compound of type **D** (see retrosynthetic analysis, Scheme 2).

Results and Discussion

Total Synthesis of Ipalbidinium (**1**)

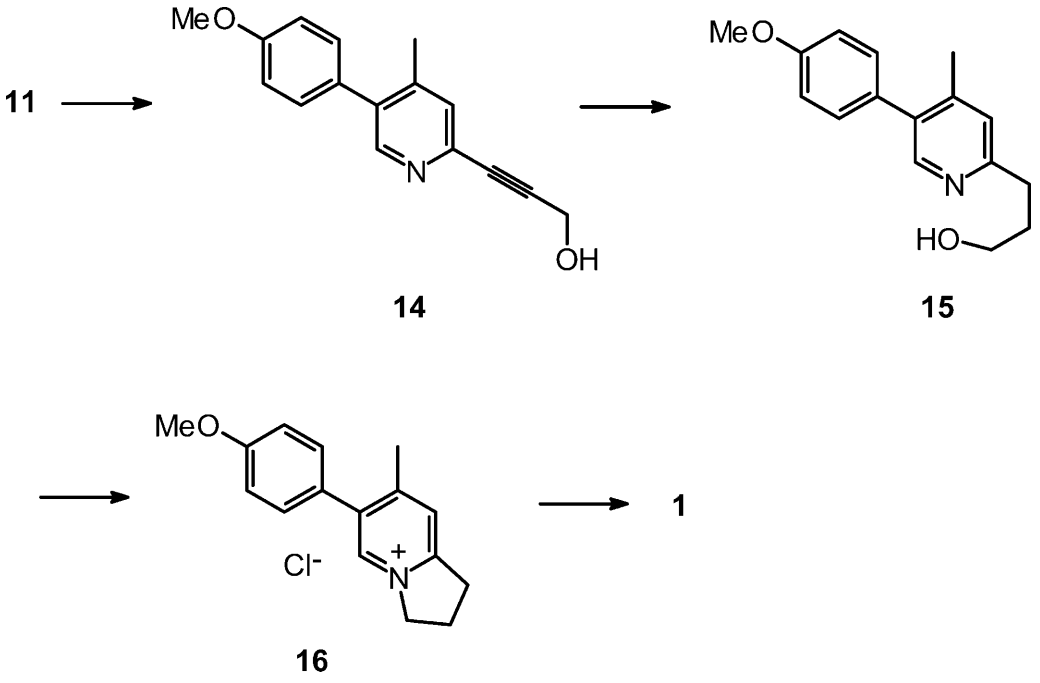
Known bromopyridine **4** [6] was converted to the arylpyridine **6** with 4-methoxyphenyl-boronic acid (**5**) under *Suzuki*-conditions [2, 7]. For the introduction of a C_3 side chain in 2-position the primary amino group had to be converted to a functional group (halogen, triflate) suitable for the next cross-coupling reaction. Diazotation of **6** in dilute sulfuric acid gave the arylpyridone **7** in 79% yield. Initial attempts to prepare **7** by cross-coupling of boronic acid **5** with 5-bromo-4-methyl-2(1*H*)pyridone [8] were without success. **7** could be converted to the pyridyl triflate **8** under standard conditions with trifluoromethanesulfonic anhydride. Bromopyridine **9** could not be obtained in pure form from the aminopyridine **6** by diazotation/bromide displacement in acidic solution (*Sandmeyer* reaction) [9], since considerable amounts of ring-brominated by-products were formed by electrophilic substitution reactions. Finally we found, that pyridone **7** can be converted to **9** in high yield by reaction with $POBr_3$ in anisole [10]. *Sandmeyer* reaction ($NaNO_2$, HCl) of **6** gave the chloro compound **10** only in minor amounts.



Scheme 3

The main product was the pyridone **7**. So we decided to apply the non-aqueous diazotation-halogenation protocol that had been developed for the preparation of halogenated pyridines for the total synthesis of ficuseptine [2]. Reaction of **6** with *tert*-butylnitrite and $CuCl_2$ in chloroform gave the chloropyridine **10** in 87% yield. Iodo compound **11** was prepared from **6** and *tert*-butylnitrite in diiodomethane solution, followed by treatment with CuI and iodine. So we had four activated pyridine derivatives in hands to examine the introduction of the side chain in 2-position.

In a first attempt, triflate **8** was reacted with ethyl acrylate under Pd^{2+}-catalysis [11], but the desired pyridylacrylate **12** was obtained, even after extensive optimisation of the reaction conditions, in yields not higher than 18%. Analogous *Heck*

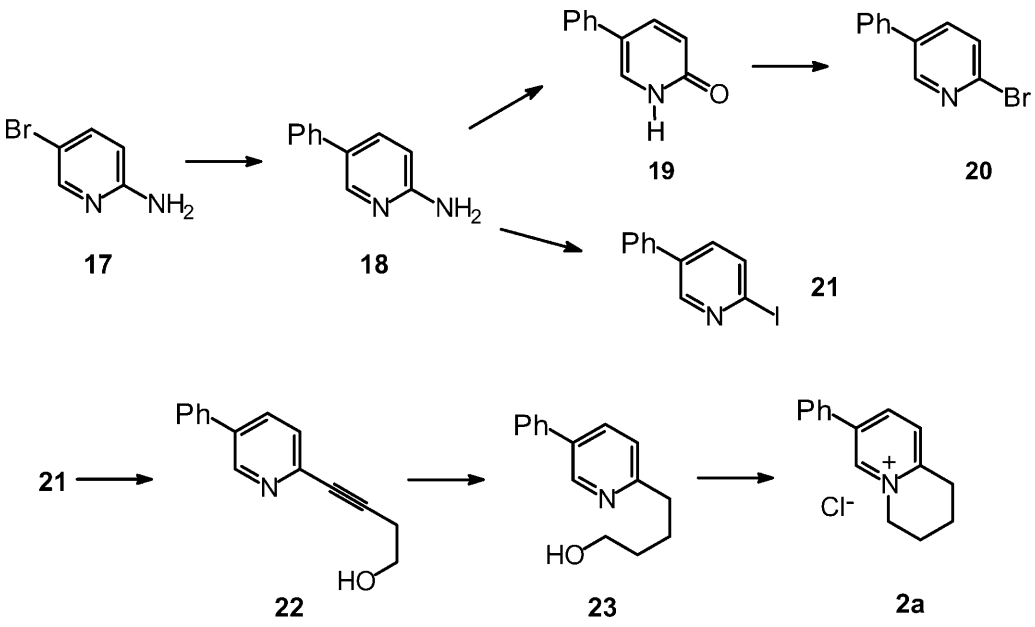


Scheme 4

reactions of bromo compound **9** gave mainly debrominated product, whereas iodopyridine **11** gave mainly a symmetric bipyridyl as the product of undesired homo-coupling. We also examined Pd-catalysed cross-couplings of triflate **9** with other functionalized C_3-building blocks. But none of the vinylstannanes **13a–c**, prepared by hydrostannylation of the corresponding terminal alkynes with Bu_3SnH [12], gave the desired coupling product in appreciable yield. Finally we found, that *Sonogashira* coupling [2, 13] of the iodopyridine **11** with propynol was the most effective method (86% yield) for the introduction of the side chain. Catalytic hydrogenation of the coupling product **14** gave the pyridylpropanol **15**, which resembles the desired intermediate **B** of the retrosynthetic considerations. Treatment with mesyl chloride/Et_3N gave the indolizidinium compound **16**. In the final step the methoxy group was cleaved with BBr_3 to give the alkaloid ipalbidinium (**1**). Purification of the ionic product was difficult (Al_2O_3 and ion exchange chromatography, followed by crystallisation) and so the product was obtained in only 19% yield.

Total Synthesis of Clathryimine B (**2a**)

The related quinolizidinium alkaloid clathryimine B (**2a**) was prepared in a similar manner. Thus, 2-amino-5-bromopyridine (**17**) [8, 14] was coupled with phenylboronic acid under *Suzuki*-conditions to give the phenylpyridine **18** [15] in 92% yield. In contrast to the synthesis of arylpyridine **6**, a Pd(0)-catalyst was superior to the Pd^{2+}-catalyst here. In analogy to the methods described above, **18** could be converted to the pyridone **19** [16] and further to the bromo derivative **20** [17]. Diazotation/iodination under anhydrous conditions gave the iodopyridine **21**. Again the iodo compound was found to be most suitable for the introduction of



Scheme 5

the side chain. *Sonogashira* coupling of **21** with 3-butyn-1-ol gave the alkynylated product **22** in excellent yield. Catalytic hydrogenation of the triple bond, followed by cyclisation with mesyl chloride/Et_3N gave the alkaloid **2a**.

Antimicrobial Activity of **1** *and* **2a**

Both alkaloids were screened for antimicrobial activities in an agar diffusion assay on *Aspergillus niger*, *Candida albicans*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. Both compounds exhibit only very weak antibacterial activity against *E. coli*. In contrast to ficuseptine (**3**) [2, 18] they do not show any activity against *C. albicans* and *S. aureus*.

Conclusion

We have developed the first total syntheses of the alkaloids ipalbidinium and clathryimine B. Once again *Sandmeyer*-type iodination of aminopyridines under anhydrous conditions, followed by *Sonogashira* coupling with alkynols were found to be a very convenient strategy for the synthesis of alkaloids containing a 2-alkylpyridine partial structure.

Experimental

General

Elemental analyses were performed on a Carlo Erba CHNO Elemental Analyzer 1106. The obtained values agreed favourably with the calculated ones. Melting points were determined on a Büchi SMP 20 apparatus. FTIR spectra were recorded on a Pye-Unicam PU-9800 spectrometer. NMR spectra were

recorded with *TMS* as internal standard on a Bruker AM 400 NMR spectrometer (400.1 MHz for ^{1}H, 100.5 MHz for ^{13}C). Mass spectra were recorded on a Finnigan MAT-8430 spectrometer. For FAB-MS 3-nitrobenzylalcohol was used as a matrix. Flash column chromatography (FCC) was carried out on Merck Kieselgel 60 (230–400 mesh). The organic solvents were dried using standard technologies.

2-Amino-5-(4-methoxyphenyl)-4-methylpyridine (**6**, $C_{13}H_{14}N_2O$)

0.76 g (5.0 mmol) 4-Methoxyphenylboronic acid (**5**) were dissolved in 5 cm^3 *Me*OH and a solution of 0.93 g (5.0 mmol) of bromopyridine **4** in 25 cm^3 toluene, and 20 cm^3 of a 50% Na_2CO_3 suspension were added and the mixture was degassed by ultrasound irradiation (5 min) under N_2. 0.04 g (0.05 mmol) $Pd(Ph_3P)_2Cl_2$ were added and the mixture was refluxed under N_2 with magnetic stirring for 25 h. Then 100 cm^3 water were added, and the mixture was extracted with ethyl acetate. The crude organic product was purified by FCC (hexanes:ethyl acetate 1:1, then ethyl acetate, then ethyl acetate:methanol 20:1) and the product was crystallised from cyclohexane to give 0.77 g (72%) of **6** as white crystals. Mp 103–104.5°C; MS (70 eV): m/z (%) = 214 (100, M^+), 199 (68), 184 (5), 171 (8); IR (KBr): $\bar{\nu}$ = 3440, 3170, 1645, 1606, 1490, 1442, 1247, 1179, 1039, 830 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.90 (s, 1H, Pyr-CH), 7.19 (dt, J = 5.0, 8.7 Hz, 2H, aromat. CH), 6.94 (dt, J = 5.0, 8.7 Hz, 2H, aromat. CH), 6.39 (s, 1H, Pyr-CH), 4.30–4.65 (br. s, 2H, NH_2), 3.83 (s, 3H, OCH_3), 2.16 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$): δ = 158.6 (quart. C), 157.5 (quart. C), 148.1 (Pyr-CH), 146.6 (quart. C), 130.8 (quart. C), 130.6 (2C, aromat. CH), 128.6 (quart. C), 113.7 (2C, aromat. CH), 109.3 (Pyr-CH), 55.3 (OCH_3), 20.2 (CH_3) ppm.

5-(4-Methoxyphenyl)-4-methyl-2(1H)-pyridone (**7**, $C_{13}H_{13}NO_2$)

An ice-cooled solution of 3.22 g (15.0 mmol) aminopyridine **6** in 90 cm^3 3.5 M H_2SO_4 was treated dropwise with 40 cm^3 1 M $NaNO_2$ solution and stirred until the reaction was complete (tlc-control). Then 20 cm^3 water were added and the mixture was refluxed for 1 h. The mixture was neutralised with Na_2CO_3, 5 g NaOH were added, and the mixture was refluxed for another 30 min. The organic compounds were extracted with ethyl acetate and purified by FCC (ethyl acetate, then ethyl acetate: methanol 10:1) The product was crystallised from chloroform/hexanes to give 2.55 g (79%) **7** as white crystals. Mp 202–203°C; MS (70 eV): m/z (%) = 215 (100, M^+), 200 (24), 172 (20); IR (KBr): $\bar{\nu}$ = 1655, 1618, 1514, 1444, 1242, 799 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 13.3–13.6 (br. s, 1H, NH), 7.23 (s, 1H, Pyr-CH), 7.15 (dt, J = 5.1, 8.7 Hz, 2H, aromat. CH), 6.93 (dt, J = 5.1, 8.7 Hz, 2H, aromat. CH), 6.48 (s, 1H, Pyr-CH), 3.84 (s, 3H, OCH_3), 2.14 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$): 164.8 (quart. C), 159.1 (quart. C), 152.7 (quart. C), 133.1 (Pyr-CH), 130.5 (2C, aromat. CH), 128.9 (quart. C), 123.1 (quart. C), 119.1 (Pyr-CH), 113.9 (2C, aromat. CH), 55.3 (OCH_3), 21.1 (CH_3) ppm.

5-(4-Methoxyphenyl)-4-methyl-2-pyridyl Trifluoromethanesulfonate (**8**, $C_{14}H_{12}F_3NO_4S$)

0.32 g (1.5 mmol) Pyridone **7** were dissolved in 30 cm^3 anhydrous CH_2Cl_2 and treated with 0.18 g (1.8 mmol) Et_3N, 0.51 g (1.8 mmol) trifluoromethanesulfonic anhydride, and 0.05 g 4-*N*,*N*-dimethyl-aminopyridine. The mixture was stirred under N_2 for 1 h and then refluxed for 1 h. After evaporation the residue was purified by FCC (hexanes:ethyl acetate 1:1) to give 0.46 g (89%) **8** as a yellow oil. MS (70 eV): m/z (%) = 347 (16, M^+), 241 (36), 214 (100), 198 (4), 186 (97), 183 (22); IR (KBr): $\bar{\nu}$ = 1611, 1599, 1517, 1474, 1422, 1248, 1216, 1139, 1122, 952, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 8.18 (s, 1H, Pyr-CH), 7.22 (dt, J = 4.9, 8.7 Hz, 2H, aromat. CH), 7.07 (s, 1H, Pyr-CH), 7.00 (dt, J = 4.9, 8.7 Hz, 2H, aromat. CH), 3.86 (s, 3H, OCH_3), 2.35 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$): δ = 159.7 (quart. C), 154.9 (quart. C), 150.8 (quart. C), 148.4 (Pyr-CH), 138.6 (quart. C), 130.4 (2C, aromat. CH), 128.2 (quart. C), 117.1 (CF_3), 115.9 (Pyr-CH), 114.2 (2C, aromat. CH), 55.4 (OCH_3), 20.4 (CH_3) ppm.

2-Bromo-5-(4-methoxyphenyl)-4-methylpyridine (**9**, $C_{13}H_{12}BrNO$)

0.13 g (0.60 mmol) Pyridone **7**, 2.87 g (10.0 mmol) $POBr_3$, and 5 cm^3 anisole were heated under N_2 in a closed pyrex vessel for 3 h at 160°C. After cooling to room temperature the mixture was poured onto 25 cm^3 ice-cooled 20% HCl and extracted with diethyl ether (3×5 cm^3) to remove the anisole. The aqueous layer was neutralised with Na_2CO_3 and then extracted with ethyl acetate. After evaporation the residue was purified by FCC (hexanes:ethyl acetate 5:1) to give 0.10 g (60%) of **9** as white crystals. Mp 86–88°C; MS (70 eV): m/z (%) = 279 (100, M^+), 277 (98, M^+), 264 (19), 262 (18), 198 (23), 183 (33); IR (KBr): $\bar{\nu}$ = 1609, 1579, 1459, 1438, 1338, 1249, 1178, 1098, 1036, 838 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 8.17 (s, 1H, Pyr-CH), 7.38 (s, 1H, Pyr-CH), 7.21 (dt, J = 4.9, 8.7 Hz, 2H, aromat. CH), 6.98 (dt, J = 4.9, 8.7 Hz, 2H, aromat. CH), 3.86 (s, 3H, OCH_3), 2.26 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$): δ = 159.5 (quart. C), 150.0 (Pyr-CH), 147.9 (quart. C), 140.4 (quart. C), 136.9 (quart. C), 130.3 (2C, aromat. CH), 128.9 (Pyr-CH), 128.8 (quart. C), 114.1 (2C, aromat. CH), 55.4 (OCH_3), 19.8 (CH_3) ppm.

2-Chloro-5-(4-methoxyphenyl)-4-methylpyridine (**10**, $C_{13}H_{12}ClNO$)

A solution of 0.22 g (1.0 mmol) aminopyridine **6** in 5 cm^3 $CHCl_3$ was treated with 0.17 g (1.65 mmol) *tert-Bu*ONO and 0.21 g (1.56 mmol) $CuCl_2$, and stirred for 24 h with exclusion of light. Then satd. Na_2CO_3 solution was added, and the mixture was extracted with ethyl acetate. The organic product was purified by FCC (CH_2Cl_2) and crystallised from cyclohexane to give 0.21 g (87%) **10** as pale yellow crystals. Mp 76°C; MS (70 eV): m/z (%) = 235 (32, M^+), 233 (100, M^+), 220 (9), 218 (26), 202 (9), 190 (12); IR (KBr): $\bar{\nu}$ = 1609, 1584, 1510, 1461, 1439, 1341, 1251, 1179, 1107, 1037, 838 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 8.17 (s, 1H, Pyr-CH), 7.20 (s, 1H, Pyr-CH), 7.20 (dt, J = 4.9, 8.7 Hz, 2H, aromat. CH), 6.97 (dt, J = 4.9, 8.7 Hz, 2H, aromat. CH), 3.84 (s, 3H, OCH_3), 2.26 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$): δ = 159.4 (quart. C), 149.6 (quart. C), 149.5 (Pyr-CH), 148.0 (quart. C), 136.4 (quart. C), 130.3 (2C, aromat. CH), 128.7 (quart. C), 125.0 (Pyr-CH), 114.0 (2C, aromat. CH), 55.2 (OCH_3), 19.9 (CH_3) ppm.

2-Iodo-5-(4-methoxyphenyl)-4-methylpyridine (**11**, $C_{13}H_{12}INO$)

A solution of 2.20 g (10.3 mmol) aminopyridine **6** in 50 cm^3 CH_2I_2 was treated with 1.63 g (15.8 mmol) *tert-Bu*ONO. After 5 min 0.96 g (5.0 mmol) CuI were added with stirring, followed by 2.65 g (10.4 mmol) I_2. The mixture was stirred under exclusion of light for 15 h, then treated with 50 cm^3 water, made alkaline with solid NaOH and finally treated with 4.74 g (30.0 mmol) $Na_2S_2O_3$. The solvents were removed by azeotropic distillation (further aliquots of water have to be added until all of the CH_2I_2 has been removed). The residue was extracted with ethyl acetate and the organic product was purified by FCC (CH_2Cl_2, then diethyl ether). Crystallisation from cyclohexane gave 2.73 g (82%) of **11** as pale yellow crystals. Mp 93°C; MS (70 eV): m/z (%) = 325 (100, M^+), 198 (59), 183 (21); IR (KBr): $\bar{\nu}$ = 1454, 1437, 1333, 1247, 1177, 1091, 1034, 992, 837 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 8.15 (s, 1H, Pyr-CH), 7.62 (s, 1H, Pyr-CH), 7.20 (dt, J = 4.9, 8.7 Hz, 2H, aromat. CH), 6.98 (dt, J = 4.9, 8.7 Hz, 2H, aromat. CH), 3.85 (s, 3H, OCH_3), 2.22 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$): δ = 159.4 (quart. C), 150.6 (Pyr-CH), 146.9 (quart. C), 137.2 (quart. C), 135.7 (Pyr-CH), 130.3 (2C, aromat. CH), 128.9 (quart. C), 116.2 (quart. C), 114.1 (2C, aromat. CH), 55.3 (OCH_3), 19.5 (CH_3) ppm.

3-[5-(4-Methoxyphenyl)-4-methyl-2-pyridyl]-propyn-1-ol (**14**, $C_{16}H_{15}NO_2$)

0.030 g (0.16 mmol) CuI were suspended in 3 cm^3 Et_3N and treated with 3 drops of propynol. Then a solution of 0.33 g (1.0 mmol) iodopyridine **11** in 12 cm^3 Et_3N, 0.030 g (0.043 mmol) $Pd(Ph_3P)_2Cl_2$, and 0.29 g (5.2 mmol) propynol were added with stirring, and the mixture was refluxed for 3 h. After addition of water and extraction with ethyl acetate the product was purified by FCC (ethyl acetate).

Recrystallisation from ethanol/water gave 0.22 g (86%) **14** as a pale yellow powder. Mp 141–142°C (dec.); MS (70 eV): m/z (%) = 253 (100, M^+), 236 (4), 224 (94), 209 (22); IR (KBr): $\bar{\nu}$ = 3414, 3403, 3347, 3337, 3274, 1609, 1593, 1511, 1476, 1435, 1362, 1293, 1246, 1178, 1044, 1017, 998, 840 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 8.36 (s, 1H, Pyr-CH), 7.34 (s, 1H, Pyr-CH), 7.22 (dt, J = 2.8, 8.7 Hz, 2H, aromat. CH), 6.97 (dt, J = 2.8, 8.7 Hz, 2H, aromat. CH), 4.56 (s, 2H, CH_2O), 3.85 (s, 3H, OCH_3), 3.80 (br. s, 1H, OH), 2.27 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$): δ = 159.4 (quart. C), 150.0 (Pyr-CH), 145.1 (quart. C), 140.8 (quart. C), 137.0 (quart. C), 130.4 (2C, aromat. CH), 129.4 (quart. C), 128.7 (Pyr-CH), 114.0 (2C, aromat. CH), 88.2 (quart. C), 84.3 (quart. C), 55.4 (OCH_3), 51.2 (CH_2O), 19.9 (CH_3) ppm.

3-[5-(4-Methoxyphenyl)-4-methyl-2-pyridyl]-propan-1-ol (**15**, $C_{16}H_{19}NO_2$)

0.67 g (2.6 mmol) Alkynol **14** were dissolved in 50 cm^3 *Et*OH (60%), 0.20 g Pd/C (5%) were added, and the mixture was shaken under H_2. After filtration and evaporation the residue was purified by FCC ($CHCl_3$, then ethyl acetate, then ethyl acetate/*Me*OH 20:1) to give 0.58 g (85%) **15** as a yellow oil. MS (70 eV): m/z (%) = 257 (2, M^+), 240 (4), 226 (10), 213 (100), 198 (16), 182 (3); IR (KBr): $\bar{\nu}$ = 1606, 1516, 1486, 1455, 1443, 1291, 1248, 1179, 1056, 1038, 1019, 834 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 8.29 (s, 1H, Pyr-CH), 7.22 (dt, J = 5.0, 8.7 Hz, 2H, aromat. CH), 7.08 (s, 1H, Pyr-CH), 6.69 (dt, J = 5.0, 8.7 Hz, 2H, aromat. CH), 4.32 (br. s, 1H, OH), 3.84 (s, 3H, OCH_3), 3.74 (t, J = 5.9 Hz, 2H, CH_2O), 2.94 (t, J = 7.0 Hz, 2H, Pyr-CH_2), 2.25 (s, 3H, CH_3), 2.01 (m, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$): δ = 159.6 (quart. C), 159.1 (quart. C), 148.8 (Pyr-CH), 145.5 (quart. C), 135.0 (quart. C), 130.4 (2C, aromat. CH), 130.0 (quart. C), 124.6 (Pyr-CH), 113.9 (2C, aromat. CH), 62.1 (CH_2OH), 55.3 (OCH_3), 34.7 (CH_2), 32.0 (CH_2), 19.9 (CH_3) ppm.

6-(4-Methoxyphenyl)-7-methyl-1,2,3-trihydroindolizidinium Chloride (**16**, $C_{16}H_{18}ClNO$)

0.90 g (3.5 mmol) of the pyridinepropanol **15** were dissolved in 100 cm^3 anhydrous CH_2Cl_2 and treated with 1.09 g (10.8 mmol) Et_3N and 0.81 g (7.1 mmol) mesyl chloride and stirred at room temperature. After completion of the reaction (tlc control) 100 cm^3 brine was added to the mixture, followed by NaOH solution to reach *pH* 12. The volatile organic solvents were removed by distillation. The remaining aqueous layer was washed with ethyl acetate, saturated with NaCl and extracted with $CHCl_3/CH_2Cl_2$ (1:1). The organic extract was dried over $CaCl_2$ and evaporated. The residue was crystallised from *i-Pr*OH to give 0.31 g (32%) **16** as white crystals. Mp 208–212°C (dec.); MS (FAB, NBA, pos.): m/z (%) = 240 (100, M^+); IR (KBr): $\bar{\nu}$ = 3422, 3000, 1637, 1609, 1500, 1444, 1254, 1175, 1027, 853 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 9.14 (s, 1H, Pyr-CH), 7.85 (s, 1H, Pyr-CH), 7.41 (dt, J = 4.8, 8.7 Hz, 2H, aromat. CH), 7.01 (dt, J = 4.8, 8.7 Hz, 2H, aromat. CH), 5.26 (t, J = 7.5 Hz, 2H, N-CH_2), 3.86 (s, 3H, OCH_3), 3.61 (t, J = 7.7 Hz, 2H, Pyr-CH_2), 2.59 (m, 2H, CH_2), 2.53 (s, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$): δ = 160.5 (quart. C), 156.3 (quart. Pyr-C), 155.1 (quart. Pyr-C), 140.6 (Pyr-CH), 139.8 (quart. C), 130.7 (2C, aromat. CH), 125.5 (quart. C), 125.4 (Pyr-CH), 114.6 (2C, aromat. CH), 59.1 (N-CH_2), 55.5 (OCH_3), 32.1 (Pyr-CH_2), 22.0 (CH_2), 21.5 (CH_3) ppm.

6-(4-Hydroxyphenyl)-7-methyl-1,2,3-trihydroindolizidinium Chloride
(*Ipalbidinium*, **1**, $C_{15}H_{16}ClNO_5$)

0.28 g (1.0 mmol) 6-(4-Methoxyphenyl)-7-methyl-1,2,3-trihydroindolizidinium chloride **16** were dissolved in 10 cm^3 anhydrous CH_2Cl_2 and treated with 10 cm^3 (10.0 mmol) 1 M BBr_3 solution in CH_2Cl_2. The mixture was stirred at room temperature for 16 h then poured onto ice. The organic components, obtained by extraction with CH_2Cl_2 were purified by FCC (ethyl acetate, then ethyl acetate:*Me*OH 5:1) over Al_2O_3 followed by washing over an anion exchange resin (chloride), and finally recrystallisation from *i-Pr*OH to give 50 mg (19%) of the alkaloid **1** as a white solid. Mp > 295°C (dec.) (Ref. [3]: no

mp given); MS (FAB, NBA, pos.): m/z (%) = 226 (100, M^+); MS (70 eV): m/z (%) = 226 (6, M^+), 225 (39), 224 (100), 223 (13), 222 (6); IR (KBr): $\bar{\nu}$ = 3456, 1609, 1507, 1499, 1272, 1175, 850 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 8.68 (s, 1H, Pyr-CH), 7.91 (s, 1H, Pyr-CH), 7.30 (dt, J = 5.0, 8.7 Hz, 2H, aromat. CH), 6.94 (dt, J = 5.0, 8.7 Hz, 2H, aromat. CH), 4.83 (t, J = 7.7 Hz, 2H, N-CH_2), 3.53 (t, J = 7.7 Hz, 2H, Pyr-CH_2), 2.54 (s, 3H, CH_3), 2.53 (m, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$): δ = 159.9 (quart. C), 158.1 (quart. C), 157.2 (quart. C), 141.3 (quart. C), 140.8 (Pyr-CH), 131.8 (2C, aromat. CH), 126.5 (Pyr-CH), 126.1 (quart. C), 116.9 (2C, aromat. CH), 59.7 (N-CH_2), 32.8 (Pyr-CH_2), 22.7 (CH_2), 21.4 (CH_3) ppm.

2-Amino-5-phenylpyridine (**18**, $C_{11}H_{10}N_2$)

5.90 g (34.1 mmol) Bromopyridine **17** [14] and 6.00 g (49.2 mmol) phenylboronic acid were dissolved in 100 cm^3 toluene and 20 cm^3 *Me*OH and treated with 120 cm^3 50% Na_2CO_3 suspension. Then 0.20 g (0.17 mmol) Pd(*Ph*$_3$P)$_4$ were added and the mixture was refluxed for 12 h under N_2. After addition of water and extraction with ethyl acetate the crude organic product was purified by FCC (ethyl acetate:hexanes 1:1 to 9:1) to give 5.30 g (92%) of **18** as a white solid. Mp 132°C (Ref. [15]: 133°C); MS (70 eV): m/z (%) = 170 (100, M^+), 143 (34); IR (KBr): $\bar{\nu}$ = 3353, 3156, 1656, 1609, 1515, 1482, 1387, 699 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 8.32 (d, J = 2.4 Hz, 1H, Pyr-CH), 7.65 (dd, J = 2.4, 8.4 Hz, 1H, Pyr-CH), 7.49 (m, 2H, aromat. CH), 7.40 (m, 2H, aromat. CH), 7.30 (m, 1H, aromat. CH), 6.55 (d, J = 8.4 Hz, 1H, Pyr-CH), 4.65 (br. s, 2H, NH_2) ppm; ^{13}C NMR ($CDCl_3$): δ = 157.8 (quart. C), 146.4 (Pyr-CH), 138.3 (quart. C), 136.5 (Pyr-CH), 128.9 (2H, aromat. CH), 127.3 (quart. C), 126.9 (aromat. CH), 126.2 (2H, aromat. CH), 108.5 (Pyr-CH) ppm.

5-Phenyl-2(1H)-pyridone (**19**, $C_{11}H_9NO$)

3.00 g (17.6 mmol) Aminopyridine **18** were dissolved in 50 cm^3 3.5 M H_2SO_4 and cooled to 0°C. 100 cm^3 2 M $NaNO_2$ solution were added with vigorous stirring. After completion of the reaction (tlc control) the mixture was brought to *pH* 12 with NaOH solution (8.5%) and extracted with ethyl acetate. The organic layer was purified by FCC (ethyl acetate, then ethyl acetate:*Me*OH 10:1) to give 2.40 g (80%) of **19** as a white solid. Mp 128°C (Ref. [16a]: 116–117°C, Ref. [16b]: 173–174°C); MS (70 eV): m/z (%) = 171 (100, M^+), 143 (46), 115 (38); IR (KBr): $\bar{\nu}$ = 3422, 1646, 1557, 1428, 1358, 1318, 1291, 1264, 763, 698 cm^{-1}; ^1H NMR (*DMSO-d*$_6$): δ = 9.36 (br. s, 1H, NH), 8.15 (dd, J = 2.5, 9.4 Hz, 1H, Pyr-CH), 8.05 (d, J = 2.5 Hz, 1H, Pyr-CH), 7.64 (m, 2H, aromat. CH), 7.46 (m, 2H, aromat. CH), 7.36 (m, 1H, aromat. CH), 6.79 (d, J = 9.4 Hz, 1H, Pyr-CH) ppm; ^{13}C NMR (*DMSO-d*$_6$): δ = 161.2 (C = O), 142.3 (Pyr-CH), 135.3 (quart. C), 133.6 (Pyr-CH), 129.1 (2H, aromat. CH), 127.5 (aromat. CH), 125.8 (2H, aromat. CH), 122.1 (quart. C), 117.5 (Pyr-CH) ppm.

2-Bromo-5-phenyl-pyridine (**20**, $C_{11}H_8NBr$)

2.00 g (11.68 mmol) Pyridone **19** were dissolved in 10 cm^3 anisole and treated with 10.0 g (34.9 mmol) $POBr_3$. The mixture was refluxed for 3 h, and then poured onto ice. The organic products were extracted with ethyl acetate and purified by FCC (hexanes:ethyl acetate 9:1 to 4:1) to give 0.89 g (33%) of **20** as a pale yellow powder. Mp 75°C; MS (70 eV): m/z (%) = 235 (93, M^+), 233 (90, M^+), 154 (100), 128 (22), 77 (13); IR (KBr): $\bar{\nu}$ = 1578, 1550, 1446, 1091, 759, 695 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 8.57 (d, J = 2.8 Hz, 1H, Pyr-CH), 7.71 (dd, J = 2.8, 8.2 Hz, 1H, Pyr-CH), 7.53 (m, 2H, aromat. CH), 7.52 (d, J = 8.2 Hz, 1H, Pyr-CH), 7.47 (m, 2H, aromat. CH), 7.42 (m, 1H, aromat. CH) ppm; ^{13}C NMR ($CDCl_3$): δ = 148.4 (Pyr-CH), 140.9 (quart. C), 136.9 (Pyr-CH), 136.4 (quart. C), 136.0 (quart. C), 129.2 (2C, aromat. CH), 128.5 (Pyr-CH), 128.0 (aromat. CH), 127.0 (2C, aromat. CH) ppm.

2-Iodo-5-phenyl-pyridine (**21**, $C_{11}H_8IN$)

6.14 g (36.1 mmol) Aminopyridine **18** were dissolved in 50 cm^3 CH_2I_2 and treated with 5.53 g (53.6 mmol) *tert-Bu*ONO. After 5 min 3.43 g (18.0 mmol) CuI were added with stirring, followed by 9.39 g (37.0 mmol) I_2, and the mixture was stirred under exclusion of light for 17 h. Then 50 cm^3 water were added, followed by neutralisation with satd. Na_2CO_3 solution and addition of solid $Na_2S_2O_3$. The organic solvents were removed by azeotropic distillation and the residue was extracted with ethyl acetate. Purification by FCC (diethyl ether), followed by crystallisation from acetone gave 4.53 g (45%) of **21** as pale yellow crystals. Mp 104°C; MS (70 eV): m/z (%) = 281 (92, M^+), 154 (100), 127 (50), 77 (16); IR (KBr): $\bar{\nu}$ = 1445, 1361, 1077, 836, 759, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 8.58 (d, J = 2.5 Hz, 1H, Pyr-CH), 7.77 (d, J = 7.6 Hz, 1H, Pyr-CH), 7.54 (m, 1H, Pyr-CH), 7.52 (m, 2H, aromat. CH), 7.47 (m, 2H, aromat. CH), 7.42 (m, 1H, aromat. CH) ppm; ^{13}C NMR ($CDCl_3$): δ = 149.1 (Pyr-CH), 136.6 (quart. C), 136.3 (quart. C), 136.1 (Pyr-CH), 134.7 (Pyr-CH), 129.2 (2C, aromat. CH), 128.5 (aromat. CH), 126.9 (2C, aromat. CH), 116.3 (quart. C) ppm.

4-(5-Phenyl-2-pyridinyl)-3-butyn-1-ol (**22**, $C_{15}H_{13}NO$)

0.14 g (0.74 mmol) CuI were suspended in 10 cm^3 Et_3N and treated with 3 drops of 3-butyn-1-ol. Then a solution of 0.89 g (3.17 mmol) iodopyridine **21** in 15 cm^3 Et_3N, 0.10 g (0.14 mmol) $Pd(Ph_3P)_2Cl_2$ and 1.15 g (16.4 mmol) 3-butyn-1-ol were added with stirring and the mixture was refluxed for 6 h. After addition of water and extraction with ethyl acetate the organic product was purified by FCC (CH_2Cl_2, then EtOAc) to give 0.69 g (97%) **22** as a viscous yellow oil. MS (70 eV): m/z (%) = 223 (2, M^+), 192 (2), 77 (100); IR (KBr): $\bar{\nu}$ = 3322, 1472, 1369, 1054, 769 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 8.73 (d, J = 2.0 Hz, 1H, Pyr-CH), 7.80 (dd, J = 2.0, 8.1 Hz, 1H, Pyr-CH), 7.53 (m, 2H, aromat. CH), 7.42 (m, 4H, 3 aromat. CH and 1 Pyr-H), 4.72 (br. s, 1H, OH), 3.90 (t, J = 6.4 Hz, 2H, CH_2O), 2.75 (t, J = 6.4 Hz, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$): δ = 147.7 (Pyr-CH), 141.7 (quart. C), 136.8 (quart. C), 135.5 (quart. C), 134.7 (Pyr-CH), 129.1 (2C, aromat. CH), 128.4 (aromat. CH), 127.0 (2C, aromat. CH), 126.8 (Pyr-CH), 89.6 (quart. C), 81.1 (quart. C), 60.6 (CH_2O), 24.0 (CH_2) ppm.

4-(5-Phenyl-2-pyridyl)-butan-1-ol (**23**, $C_{15}H_{17}NO$)

1.13 g (5.06 mmol) Alkynol **22** were dissolved in 50 cm^3 *Et*OH (60%), 0.20 g Pd/C (5%) were added and the mixture was shaken under H_2. After filtration and evaporation the oily residue was purified by FCC (ethyl acetate). The product was crystallised from methanol/water to give 0.99 g (86%) of **23** as a pale yellow solid. Mp 214–216°C (dec.); MS (70 eV): m/z (%) = 227 (4, M^+), 210 (4), 196 (22), 182 (32), 169 (100), 168 (10); IR (KBr): $\bar{\nu}$ = 3424, 2933, 2859, 1485, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 8.71 (d, J = 2.2 Hz, 1H, Pyr-CH), 7.78 (dd, J = 2.2, 8.1 Hz, 1H, Pyr-CH), 7.54 (m, 2H, aromat. CH), 7.44 (m, 2H, aromat. CH), 7.37 (m, 1H, aromat. CH), 7.21 (d, J = 8.1 Hz, 1H, Pyr-CH), 3.71 (t, J = 6.4 Hz, 2H, CH_2O), 3.25 (br. s, 1H, OH), 2.87 (t, J = 7.7 Hz, 2H, Pyr-CH_2), 1.86 (m, 2H, CH_2), 1.67 (m, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$): δ = 160.8 (quart. C), 147.3 (Pyr-CH), 137.7 (quart. C), 135.0 (Pyr-CH), 134.1 (quart. C), 129.0 (2C, aromat. CH), 127.9 (aromat. CH), 126.9 (2C, aromat. CH), 122.8 (Pyr-CH), 62.0 (CH_2O), 37.1 (CH_2), 32.2 (CH_2), 26.0 (CH_2) ppm.

7-Phenyl-1,2,3,4-tetrahydrochinolizidinium Chloride (*Clathryimine B*, **2a**, $C_{15}H_{16}ClN$)

0.94 g (4.14 mmol) Pyridyl-butanol **23** were dissolved in 50 cm^3 anhydrous $CHCl_3$ and treated with 1.29 g (12.75 mmol) Et_3N and 0.93 g (8.12 mmol) mesyl chloride and stirred at room temperature. After completion of the reaction (tlc control) 100 cm^3 brine was added to the mixture, followed by NaOH solution to reach *pH* 12. The volatile organic solvents were removed by distillation. The remaining aqueous layer was washed with diethyl ether, saturated with NaCl and extracted with $CHCl_3/CH_2Cl_2$ (1:1). The organic extract was dried over $CaCl_2$ and evaporated. The residue was

crystallised from $CHCl_3$/diethyl ether to give 0.26 g (24%) **2a** as white crystals. Mp 164°C (Ref. [5]: brown viscous oil); MS (FAB, NBA, pos.): m/z (%) = 210 (100, M^+); IR (KBr): $\bar{\nu}$ = 3055, 2955, 2928, 2853, 1628, 1449, 772, 702 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 9.88 (s, 1H, Pyr-CH), 8.48 (d, J = 7.9 Hz, 1H, Pyr-CH), 7.97 (d, J = 7.9 Hz, 1H, Pyr-CH), 7.89 (d, J = 7.4 Hz, 2H, aromat. CH), 7.45 (m, 3H, aromat. CH), 5.12 (br. s, 2H, N-CH_2), 3.31 (t, J = 6.4 Hz, 2H, Pyr-CH_2), 2.17 (br. s. 2H, CH_2), 2.03 (t, J = 6.4 Hz, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$): δ = 153.7 (quart. C), 143.4 (Pyr-CH), 141.6 (Pyr-CH), 138.1 (quart. C), 132.7 (quart. C), 130.0 (Pyr-CH), 129.5 (2C, aromat. CH), 128.7 (aromat. CH), 127.4 (2C, aromat. CH), 56.1 (N-CH_2), 28.3 (Pyr-CH_2), 21.2 (CH_2), 17.6 (CH_2) ppm.

Acknowledgement

We thank the *Fonds der Chemischen Industrie* for financial support.

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