6-Pyridylnicotine and Bis-6,6′-nicotine – New Chiral 2,2′-Bipyridines

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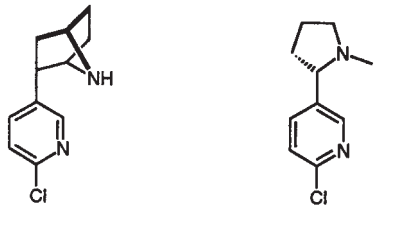
Starting from (–)-nicotine, two new 2,2'-bipyridine ligands **6** and **7** with chiral pyrrolidine side chains have been synthesized. The stoichiometric complexation by palladium(II) or mercury(II) ions gives the bipyridyl complexes **8** and **9.**

Over the last few years, the classical metal bipyridyl complexes have been developed into really interesting aggregates,[1–5] while new polybipyridyls have given access to the supramolecular systems of J.-M. Lehn and others. The alteration of pyridyl units, spacers and metals resulted in many new and fascinating supramolecules. In particular, optically active transition metal complexes of 2,2′-bipyridyls are of high interest, both for reversible optical data storage and enantioselective organic transformations. In spite of their potential for asymmetric induction in C–C bond formation[6] or oxidation processes, the number of publications describing enantiomerically pure species remained comparatively few. The most recent examples[7] were published by S. Sakaki, who is interested in copper(I) based chiral photosensitizers, and A. von Zelewsky, who coined the term: *super chiragens*. Using the *complexes as ligands* approach[8] a number of bipyridyls bearing additional amino functions allow controlled synthesis of heteropolynuclear complexes, resulting in both aesthetically pleasing assemblies and supramolecules with interesting redox and photochemical properties, In particular, helical assemblies attract attention, because bistable, nonracemic helices may[9] be useful as optical switches in information technology. The application as optical device is based on the helicity and its inversion by circular polarised light (CPL).

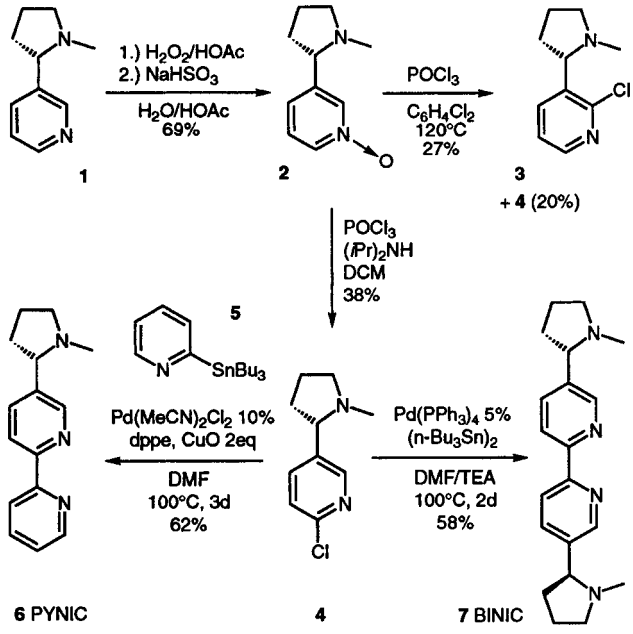
For these purposes we envisioned ligands with minimised, yet chiral, amino bearing side-chains. Moreover, we were interested in obtaining epibatidine[10-12] analogues for pharmacological testing. To avoid the obstacles of lengthy synthesis we focused on readily available natural starting materials and chose 6-chloronicotine[18] (**4**) for our ligand design, as the chirality and the first pyridyl unit are already implemented.

The synthetic task was thus reduced to the regioselective attachment of a second 2-pyridyl unit or a dimerisation to give PYNIC (**6**) and BINIC (**7**) as depicted. Such syntheses of bipyridyls from halopyridines and metallated pyridines by palladium(0) catalysed cross-coupling reactions[14,15,20] are well established. (–)-Nicotine was converted into its pyridine *N*-oxide[13] using H_2O_2 and acetic acid for oxidation of both nitrogens and subsequent chemoselective reduction of the pyrrolidine *N*-oxide by $NaHSO_3$. The crystalline pyridine *N*-oxide was treated with 10 equivalents of phosphoryl chloride at room temperature, leading to two isomeric chloronicotines **3** (27%) and **4** (20%). However, addition of 3.4 equivalents of diisopropylamine[14] suppresses the formation of the undesired 2-chloronicotine beyond observation (<1%), raising the yield of the desired isomer to 38%. Replacement of diisopropylamine by other secondary amines, such as piperidine and pyrrolidine, met with no success. The formation of the sterically more demanding **3** is explained by directing effects of the pyrrolidine nitrogen. An undefined ammonium phosphoryl species holds the chloride in place, ready for the Boekelheide[15, 16] reaction at the 2-position. The competition of secondary amines for phosphoryl chloride makes the substitution at the more accessible 6-position the major reaction pathway. Palladium-catalysed coupling of the chloronicotine **4** and 2-(tributylstannyl)pyridine[19] (**5**) gave the 2,2′-bipyridine **6** (PYNIC) in 52% yield with an enantiomeric excess greater than 90% as determined by ^{1}H NMR spectroscopy of the 1:1 salts with D(–)-tartaric acid and L-(+)-tartaric acid in MeOH-d_4. Additional copper oxide (2 equivalents) raised the



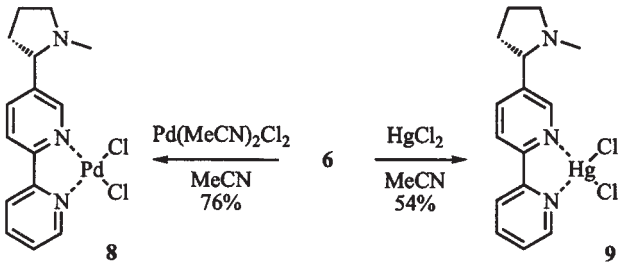
Epibatidine 6-Chloronicotine **4**

Scheme 1



Scheme 2

yield to 62%. The formal dimerisation[17] of (–)-nicotine to BINIC (**7**) was achieved by heating **4** in the presence of palladium and hexabutylditin in 58% yield, which was not improved by additional copper oxide. A potential epimerisation of the benzylic position by palladium(II) mediated processes can be excluded for the formation of BINIC (**7**), as no *meso* compound was observed.



Scheme 3

The pale yellow palladium dichloro complex **8** (76%) was obtained in moderate yield by mixing stoichiometric amounts of dihalide and ligand in acetonitrile, and precipitation followed by recrystallisation. The maximum in the UV spectrum of the free ligand at 242 nm (log ε = 5,458) is shifted upon complexation by palladium(II) to 308 and 303 nm (log ε = 6.151, 6.090) [λ_{max} $Pd(MeCN)_2Cl_2$ in MeCN: 230 nm (log ε = 5.387)]. The off-white mercury dichloro complex **9** was obtained by the same method, although in poorer yield (54%). The metal complexes of PYNIC (**6**) and BINIC (**7**) with a variety of cations are currently under further investigation.

Melting points (uncorrected): open glass capillaries. Büchi apparatus. ^1H and ^{13}C NMR spectra: Bruker WP 200, Bruker AM 400 at 200 (50.3) MHz and 400 (100,58) MHz. Chemica1 shifts are reported as δ values (ppm) downfield from TMS. IR spectra: Perkin Elmer 1710 FT and Bruker IFS 25, recorded in $\nu_{max.}$(cm^{-1}). Mass spectroscopy: Finnigan MAT 312, VG Autospec (FAB. HRMS). Elemental analysis: Elementar Vario EL, Heraeus Elementaranalysator CHN Rapid. UV/VIS spectra: Beckmann 3600, Optical activity: Perkin–Elmer 241, λ = 589 nm. Column chromatography: Baker silica gel 60 (40–60 μm) and Sephadex LH 20, using Et_2O, EtOAc, PE (light petroleum, bp 40–60°C), or $CHCl_3$. TLC was carried out using aluminium sheets precoated with silica gel 60 F_{254} (0.2 mm, E, Merck). Spots were visualised by UV and/or spraying with an acidic, ethanolic solution of *p*-anisaldehyde, $KMnO_4$ in acetone or an ethanolic solution of ninhydrin, followed by heating. DMF, DMSO, $CHCl_3$ and CH_2Cl_2 were stored over 3Å molecular sieves.

(–)-Nicotine *N*-Oxide (2):
Prepared on a 42 mmol scale according to the literature[13] replacing gaseous SO_2 by 40% $NaHSO_3$ solution (15 mL). HOAc (18 mL) and H_2O (10 mL) at 0°C. The reduction was stopped after 30 min by evaporation under reduced pressure. Solid Na_2CO_3 was added until pH 9. Extraction with $CHCl_3$ gave a red oil after drying and concentration, which was purified by column filtration on silica gel (EtOH/$CHCl_3$ 1:3) to give a red crystalline mass (5.16 g, 29.0 mmol, 69%): mp 5–10°C.
^1H NMR (200 MHz, $CDCl_3$, TMS, 25 °C): δ = 1.6–2.0 (m, 3H), 2.15–2.40 (m, 5H), 3.09 (t, 1H, *J* = 8 Hz), 3.16–3.27 (m, 1H), 7.20–7.30 (m, 2H), 8.12 (dt, 1H, *J* = 5.5 Hz, *J* = 2 Hz). 8.15–8.20 (m, H-2).
FT-IR: ν = 2972s, 2784m, 1604s, 1440s, 1268s, 1136s cm^{-1}.
MS: *m/z* (%) = 179 (2), 178 (12, M^+), 85 (100),

(–)-6-Chloronicotine (4), (–)-2-Chloronicotine[18] (3):
A solution of nicotine *N*-oxide (2) (356 mg, 2.00 mmol) in anhyd CH_2Cl_2 (3 mL) was treated with $POCl_3$ (1.0 mL, 10.92 mmol) under N_2 at 0°C. Additional $POCl_3$ (1.0 mL, 10.92 mmol) and $(i\text{Pr})_2NH$ (0.98 mL, 6.93 mmol) was added over 2 h, Stirring was continued at r.t. for 1 h, prior to solvent removal. The oily residue was poured on ice water, adjusted to pH 9 by solid Na_2CO_3 (ca. 30 g) and extracted by EtOAc (3 x 30 mL). The dried, concentrated organic phases were purified by gradient column chromatography (PE/$CHCl_3$) to give **4** as a pink liquid (143.1 mg, 37%); R_f = 0.64 ($CHCl_3$/EtOH 1:1). In the absence of $(i\text{Pr})_2NH$ both isomers were isolated in a ratio **3/4** 1.4:1. Separation on deactivated Alox (1% H_2O, PE/$CHCl_3$ 10:1) gave pure **4** (78 mg, 0.40 mmol, 20%) and **3** (106 mg, 0.54 mmol, 27%),

4: $[\alpha]_D^{23}$–56.2 (c = 1.47, $CHCl_3$).
^1H NMR (200 MHz. $CDCl_3$, TMS, 25 °C): δ = 1.57–2.05 (m, 3H), 2.16 (s, 3H, NCH_3), 2.03–2.40 (m, 2H), 3.08 (t, *J* = 8 Hz, 1′-H), 3.23 (ddd, 1H, *J* = 2 Hz. *J* = 8 Hz, *J* = 1 Hz, H-4′), 7.30 (d, 1H, *J* = 8 Hz, H-5), 7.69 (dd, ^4J = 2 Hz, ^3J = 8 Hz, H-4), 8.31 (d, ^4J = 2 Hz, H-2).
^{13}C NMR (50 MHz, $CDCl_3$, TMS, 25 °C, APT): δ = 22.6 (t, 3′), 35.3 (t, 2′), 40.3 (q, CH3), 56.9 (t. 4′), 69.0 (d,1′), 124.3 (d, 5), 137.9 (d, 4), 138.1 (s, 3), 149.3 (d, 2), 150.0 (s, 6).
FT-IR: ν = 2972s, 2948s, 2876m, 2780s, 1456s, 1104s cm^{-1}.
MS: *m/z* (%) = 198 (M^{+37}[Cl], 8), 196 (M^{+35}[Cl], 20), 167 (M^{+35}[Cl]-NCH_3, 12), 84 ($C_5H_{10}N$, 100).
HRMS: *m/z* 196.0695137 ([$C_{10}H_{13}N_2{}^{35}Cl$] calcd 196.0767193).

3:
^1H NMR (200 MHz, $CDCl_3$, TMS, 25 °C): δ = 1.42–l.95 (m), 1.75–2.95 (m, 2H). 2.12 (s, 3H, Me), 2.2–2.45 (m, 2H). 3.32 (ddd, *J* = 8.5 Hz. *J* = 6 Hz, *J* = 1.5 Hz, H-1′), 3.55 (bt, *J* = 8 Hz, H-4′), 7,25 (ddd, *3J* = 8 Hz, ^3J = 4,5 Hz, *J* = 0.25 Hz, H-5), 7.97 (ddd, ^3J = 8 Hz, *J* = 2 Hz, *J* = 0.5 Hz, H-4), 8.25 (dd, ^3J = 4.5 Hz, ^4J = 2 Hz, H-6).
^{13}C NMR (100 MHz, $CDCl_3$, TMS, 25 °C): δ = 22.7 (t, 3′), 33.2 (t, 2′), 40.5 (q, CH_3), 56.7 (t, 4′), 66.2 (d. 1′), 122.8 (d, 5), 136.7 (d, 4), 147.4 (d, 6), 150.7 (s, 2).
FT-IR: ν = 2972s, 2784s, 1564s, 1408s, 11 16s, 1072s, 804s cm^{-1}.
MS: *m/z* (%) = 198 (M^{+37}[Cl], 4), 196 (M^{+35}[Cl], 14), 84 ($C_5H_{10}N$, 100).
HRMS: *m/z* 196.0710596 ([$C_{10}H_{13}N_2{}^{35}Cl$] calcd 196.0767193).

(–)-6-(2-Pyridyl)nicotine (6):
6-Chloronicotine (392 mg, 2.00 mmol), $Pd(MeCN)_2Cl_2$ (51.9 mg, 0.200 mmol), dppe (79.7 mg, 0.200 mmol), LiCl (127 m, 3.00 mmol), CuO (636 mg, 8.00 mmol). 2-(tributylstannyl)pyridine[19] (1.47 g, 4,00 mmol) and anhyd DMF (6 mL) were heated under N_2 to 100°C for 3 d. The solvent was removed *in vacuo*. The mixture was diluted by CH_2Cl_2 (30 mL) and extracted by 1 N HCl (3 × 10 mL). The aqueous extracts were treated with NaOH (1.6 g, 40 mmol) and extracted by CH_2Cl_2 (5 × 20 mL). The dried ($MgSO_4$) and concentrated extracts left a crude oil, which was purified by gradient column chromatography on deactivated Alox N (PE/$CHCl_3$ 1:1, $CHCl_3$/EtOH 5:1) to give **6** as yellow oil (292 mg, 62%); $[\alpha]_D^{20}$ –2.98 (*c* = 0.265, EtOH). The enantiomeric excess was higher than 90% as determined by ^1H NMR spectroscopy of the 1:1 salts with D(–)-tartaric acid and L-(+)-tartaric acid in MeOH-d_4.
^1H NMR (400 MHz, $CDCl_3$, TMS, 25 °C): δ = 0.9 (m), 1.7–1.9 (m, 2H), 2.0–2.1 (m), 2.2–2.4 (m), 3.2 (t), 3.3 (t), 7.3 (ddd, *J* = 1.1 Hz, *J* = 4.8 Hz, *J* = 7.9 Hz. H-5′), 7.81 (ddd, *J* = 1.8 Hz, *J* = 7.5 Hz, *J* = 7.9 Hz, H-4′). 7.81 (dd. *J* = 2.0 Hz, *J* = 8.1 Hz, H-4), 8.37 (d, *J* = 7.9 Hz, H-3), 8.38 (ddd, *J* = 1.1 Hz, *J* = 1. 1 Hz, *J* = 7.9 Hz, H-3), 8.60 (d, *J* = 1.8 Hz, H-6), 8.68 (ddd, *J* = 0.9 Hz, *J* = 1.8 Hz, *J* = 4.8 Hz, H-6′).
^{13}C NMR (100 MHz, $CDCl_3$, TMS, 25 °C): δ = 22.6 (t, 4″), 35.2 (t, 3″), 40.4 (q, l″, N-CH_3), 57.0 (t, 5″), 68.7 (d, 2″), 120.9 (d, 3), 121.0 (d, 6′), 123.4 (d, 4′), 135.8 (d, 4), 136.8 (d, 5′), 138.9 (s, 5), 149.1 (d, 3′), 149.8 (d, 6), 155.2 (s, 2), 156.2 (s, 2′).
FT-IR: ν = 2972s, 2780m, 1588m, 1460s, 1252m cm^{-1}.
MS: *m/z* (%) = 239 (M^+, 19), 224 (M^+-CH_3, 2), 210 (M^+-NCH_3, 18), 84 [($C_5H_{10}N$), 100].
HRMS: *m/z* 239.1422100 ([$C_{15}H_{17}N_3$], calcd 239.1422378).
UV-VIS (MeCN): λ_{max} (log ε) = 280 (5.607), 242 (5.458), 233 (5.482) nm.

Anal. calcd for $C_{15}H_{17}N_3$ (239.323): C 75.28, H 7.16, N 17.56; found: C 74.47, H 7.16, N 16.8.

(–)-Bis-6,6′-nicotine (7):
(–)-6-Chloronicotine (686 mg, 3.50 mmol), $Pd(PPh_3)_4$ (202 mg, 0.175 mmol), hexabutylditin (875 μL, 1.75 mmol), Et_3N (100 μL. 0.72 mmol) and DMF (10 mL) were heated under N_2 to 100°C for 2 d. The mixture was diluted by CH_2Cl_2 (50 mL) and extracted by 1N HCl (3 × 10 mL). The aqueous extracts were treated by NaOH (1.6 g, 40 mmol) and extracted by CH_2Cl_2 (5 × 30 mL). The dried ($MgSO_4$) and concentrated extracts were purified by column chromatography ($CHCl_3$) on 10 g silica gel deactivated by 30% NH_3 (1 mL) to give **7** as colorless needles (329 mg, 58%); mp 122°C; $[\alpha]_D^{21.5}$ –22.2 (*c* = 0,69, EtOH).
^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 °C): 1.7–1.9 (m. 4H), 2.0–2.1 (m, 2H), 2.2 (s, 6H, CH_3), 2.2–2.3 (m, 2H), 2.3–2.4 (m), 3.2 (t, 2H), 3.3 (t, 2H), 7.85 (dd, 2H, *J* = 2.0 Hz, *J* = 8.3 Hz, H-4/4′), 8.35 (dd, 2H, *J* = 8.3 Hz, *J* = 0.3 Hz, H-5/5′), 8.6 (d, 2H, *J* = 1.8 Hz, H-2/2′).
^{13}C NMR (100 MHz, $CDCl_3$, TMS, 25 °C): 27.7 (t, 4′), 35.3 (t, 3′), 40.6 (q, 1, N-CH_3), 57.4 (t, 5′), 69.2 (d, 2′), 121.6 (d, 3), 136.6 (d, 4), 139.5 (s, 5), 149.8 (d, 6), 156.3 (s, 2).
FT-IR: ν = 2972s, 2780s, 1596m, 1464s, 1252m cm^{-1}.
FAB-MS: *m/z* = 323 ($C_{15}H_{18}N_3$).
UV-VIS (CH_2Cl_2): λ_{max} (log ε) = 290 (5.990), 244 (5.827) nm.
Anal. calcd for $C_{20}H_{26}N_4$ (322.45): C 74.498. H 8.127, N 17.375; found: C 74.17, H 8.12, N 17.20.

[(–)-6-(2-Pyridyl)nicotine]palladium Dichloride (8):
$Pd(MeCN)_2Cl_2$ (20.0 mg, 77 μmol) was dissolved in anhyd MeCN (3 mL). A solution of 6-(2-pyridyl)nicotine (170 μmol) in cyclohexane (1.20 mL) was layered carefully over the MeCN phase. After an initial growing period of 30 min, the mixture was stirred for 1 h. The yellow precipitate was digested by MeCN (2 × 3 mL) at 50°C for 2 h. The solvent was decanted; prolonged drying in vacuo gave the pale yellow complex **8** (41 mg, 76%).
^{1}H NMR (400 MHz, DMSO-d_6, TMS, 25 °C): δ = 0.7–0.8 (m), 0.9–1.05 (m, 2H), 1.2 (s), 1.28 (s, 3H), 1.35–l.5 (m, 2H), 2.3–2.4 (m), 6.93 (ddd, *J* = 1.1 Hz, *J* = 4 Hz, *J* = 7.2 Hz, H-5′), 7.41 (dd, *J* = l.7 Hz, *J* = 8.1 Hz, H-4), 7.48 (ddd, *J* = 1.7 Hz, *J* = 7.9 Hz, *J* = 7.9 Hz, H-4′), 7.68 (d, *J* = 7.9 Hz, H-3), 7.70 (bd, H-3′), 8.24 (d, 2H, *J* = 4 Hz, H-6/6′).
FT-IR (KBr): ν = 2940m, 2872m, 2780m, 1464s, 1444s cm^{-1}.
FAB-MS: *m/z* = 380 ($C_{15}H_{17}N_3{}^{106}Pd_{35}Cl$).
UV-VIS (MeCN): λ_{max} (log ε) = 318 (6.205), 308 (6.151), 303 (6.090), 262 (6.248), 252 (6.235) nm.
Anal. calcd for $C_{15}H_{17}N_3PdCl_2$ (416.83): C 43.24, H 4.11, N 10.09; found C 41.99, H 4.12, N 9.18.

[(–)-6-(2-Pyridyl)nicotine]mercury Dichloride (9):
$HgCl_2$ (43 mg, 0.158 mmol) was dissolved in abs MeCN (2.0 mL) and added to 6-(2-pyridyl)nicotine (74 mg, 0.31 mmol) under Ar resulting in the immediate formation of an off-white precipitate. The suspension was stirred at 50°C for 18 h and cooled to r.t. to complete precipitation. The solvent was decanted and the residue was washed by MeCN (3 × 4 mL), dried in vacuo to give **9** (42 mg, 54%).
^{1}H NMR (200 MHz, $CDCl_3$, TMS, 25 °C): δ = 1.7–2.1 (m, 4H), 2.2 (s, 3H), 2.2–2.4 (m), 3.3 (t, 2H), 7.63 (ddd, *J* = 1.2 Hz, *J* = 5.2 Hz, *J* = 7.5 Hz, H-5′), 8.03 (ddd, *J* = 1.7 Hz, *J* = 7.5 Hz, *J* = 8.32 Hz, H-4′), 8.06 (dd, *J* = 2 Hz, *J* = 8.23 Hz, H-4), 8.19 (ddd, *J* = 0.5 Hz, *J* = 0.5 Hz, *J* = 8.2 Hz, H-3). 8.21 (ddd, *J* = 0.9 Hz, *J* = 0.9 Hz, *J* = 8.0 Hz, H-3′), 8.67 (d, *J* = 1.5 Hz, H-6), 8.74 (ddd, *J* = 0.9 Hz, *J* = 1.7 Hz, *J* = 5.2 Hz. H-6′).
FT-IR (KBr): ν = 2964m, 2872w, 2776m, 1592s, 1472s, 1436s, 764s cm^{-1}.
MS (95°C): *m/z* = 511 ($C_{15}H_{17}N_3{}^{202}Hg^{35}Cl_2$, 4%, 461 ($C_{14}H_{14}N_3{}^{202}Hg^{35}Cl$, 6%).
UV-VIS (MeCN): $\lambda^m{}_{ax}$ (log ε) = 281 (5.777), 240 (5.993), 236 (5.938), 210 (5,789) nm.
Anal. calcd for $C_{15}{}^{202}H_{17}N_3HgCl_2$ (510.82): C 35.27, H 3.35, N 8.23; found C 34.87, H 3.26, N 8.04.

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