Synthesis of 6,6'-Diamino-2,2'-biquinoline and 2,2'-Bi-1,6-naphthyridine

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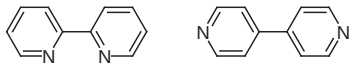
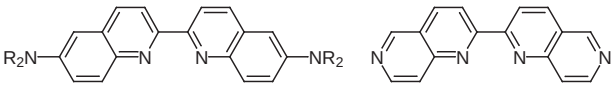
Abstract: High-yield synthesis and characterization of the new heterocycles 6,6'-diamino-2,2'-biquinoline (**3**), 6,6'-bis(*N*,*N*-dimethylamino)-2,2'-biquinoline (**4**), and 2,2'-bi-1,6-naphthyridine (**5**) are described. The preparation of **3** and **4** is based on the coupling of 2-amino-6-chloroquinoline and 2-chloro-6-dimethylaminoquinoline in the presence of $NiCl_2 \cdot 6H_2O/PPh_3$/Zn in DMF (NiCRA). Compound **5** was synthesized through a condensation reaction of 4-aminopyridine-3-carbaldehyde and butane-2,3-dione.

Key words: spacer ligands, coupling reactions, NiCRA, biquinoline, binaphthyridine

Chelating and bridging nitrogen ligands, such as 2,2'-bipyridine (**1**) or 4,4'-bipyridine (**2**) are of constant interest in transition metal coordination chemistry. Long spacer ligands are currently investigated as building blocks for supramolecular complexes and for the construction of (porous) metal frameworks.[1–3] The generation of such frameworks is a promising path in the search for stable microporous metal-organic networks that exhibit reversible guest exchange and possibly selective catalytic activity.[1,4]



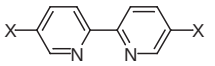
1 **2**



3 R = H
4 R = Me

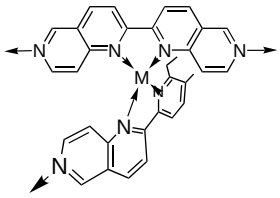
5

Multidentate ligands which combine chelating and bridging coordinative properties have so far been little investigated in the construction of metal coordination polymers. We report here on the synthesis of the long spacer and chelating ligands 6,6'-diamino- and 6,6'-bis(*N*,*N*'-dimethylamino)-2,2'-biquinoline (**3** and **4**) and 2,2'-bi-1,6-naphthyridine (**5**). This is a continuation of our recent investigations on the coordination behavior of modified 2,2'-bipyridine ligands such as ambidentate 5,5'-diamino-2,2'-bipyridine (**6a**),[5] 5,5'-dicyano-2,2'-bipyridine (**6b**)[6] or the 5,5'-diisothiocyanato-2,2'-bipyridine ligand (**6c**) as well as on modified and ambidentate tris(pyrazolyl)borate ligands.[7]



6a -X = $-NH_2$
6b -X = -CN
6c -X = -NCS

The idea behind the use of such functionalized bridging/chelating 2,2'-bipyridine-type ligands is to have cross-connecting blocks (tectons) for coordination polymers based on the *endo*-chelation of two ligands with an appropriate metal center as depicted in **7** or to supply functional donor atoms within the inner walls of a porous coordination polymer or other metallacyclic polyhedra[8] (Figure).



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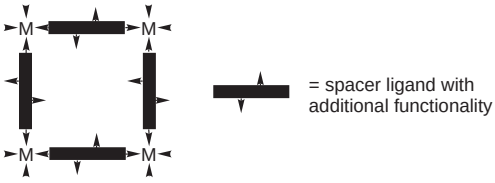
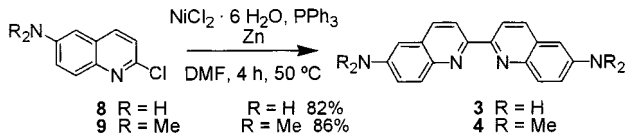


Figure. Schematic illustration of molecular boxes or coordination polymers built from spacer ligands such as **5** with additional functionalities

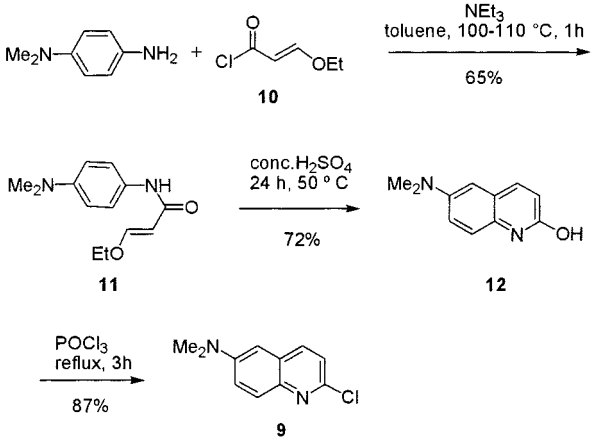
The biquinolines **3** and **4** are obtained through a Semmelhack coupling[9] of the 2-chloroquinolines **8** and **9** in 2–2.5 hours in yields of 82 and 86%, respectively (Scheme 1). A *ni*ckel-containing *c*omplex *r*educing *a*gent (NiCRA) consisting of $NiCl_2 \cdot 6H_2O/PPh_3$/Zn/DMF, i.e. with zinc as the reducing agent,[10] was best employed as a stoichiometric coupling reagent.[11]

The starting materials for the coupling reaction, the 6-amino- and 2-chloro-6-dimethylaminoquinoline (**8** and **9**), in turn, were prepared according to Effenberger and Hartmann[12] starting from aniline or 4-(dimethylamino)aniline, respectively, and 3-ethoxypropenoyl chloride



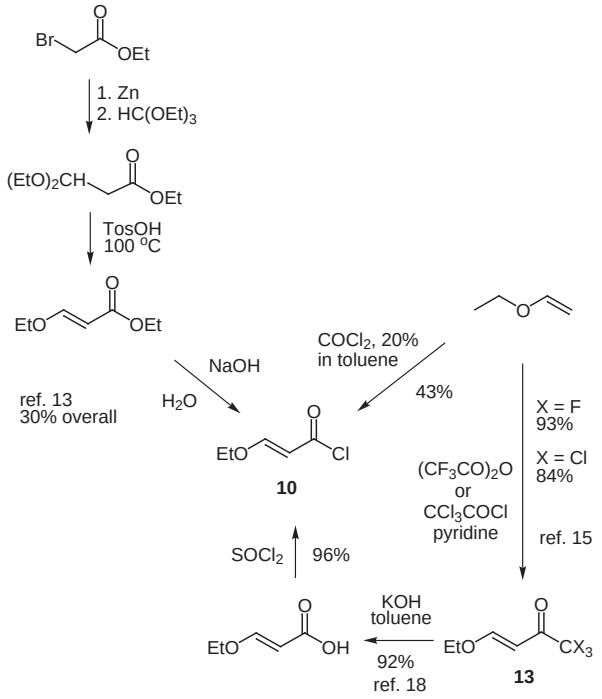
Scheme 1

(**10**) (Scheme 2). In the first step, 3-ethoxypropenoic amide (**11**) is obtained, which is then cyclized with mineral acids to the 2-hydroxyquinolines **12** in good yield. While the cyclization of the unsubstituted amide occurred at room temperature with concentrated HCl and was complete within 15 minutes, cyclization of the dimethylaminoanilide **11** required the use of warm concentrated H_2SO_4 and a reaction time of 24 hours. The decreased reactivity can be traced to the negative inductive effect of the protonated amino function which makes the electrophilic substitution on the aromatic ring more difficult. Even stronger electron-withdrawing substituents such as a nitro group would fully suppress the cyclization under moderate conditions. The 2-hydroxyquinoline **12** is transfered with phosphoryl chloride into the corresponding 2-haloquinoline **9**.



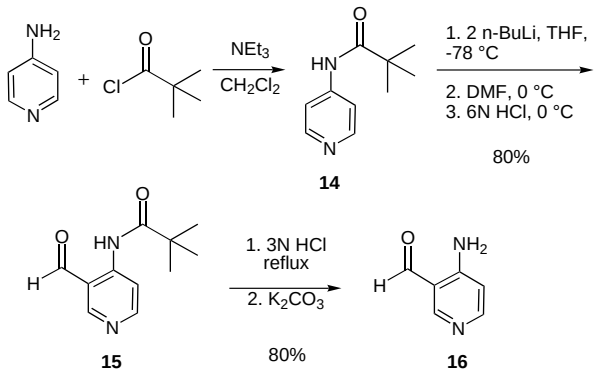
Scheme 2

3-Ethoxypropenoyl chloride (**10**) was derived both from ethyl bromoacetate according to Shaw and Warrener[13] (30% overall yield in 4 steps, Scheme 3) and from ethyl vinyl ether by the addition of phosgene according to Paul and Tchelicheff.[14] For the latter, the use of a 20% phosgene solution in toluene instead of liquid phosgene, as originally proposed, was found feasible here and **10** was obtained in 43% yield in a one-step reaction (Scheme 3). As an alternative to phosgene, the vinyl ether could also be acylated with trifluoroacetic anhydride or trichloroacetyl chloride in very high yield in the presence of pyridine.[15] For the mechanism of the addition of an acyl halide or anhydride to a vinyl ether see ref. 16. The trihalomethyl ketones **13** were then cleaved with wet KOH in toluene to the free acid as part of the haloform reaction. Although the relative reaction rate is considerably slower for the cleavage of a CF_3 group by a factor of 10^{10} versus a CCl_3 group,[17] the trifluoro derivative could still be cleaved within a few hours in good yield.[18] Aminolysis of the trifluoromethyl ketone **13** with *p*-(dimethylamino)aniline, to give **11** directly, was tried but found unsuccessful.



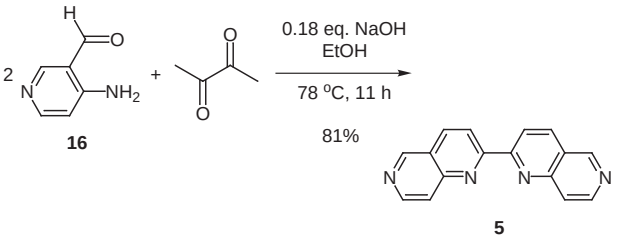
Scheme 3

A reductive coupling of 2-chloro-1,6-naphthyridine with a NiCRA in analogy to the above synthesis of **3** and **4** should have been a possibility, yet the sole known synthesis of 2-chloro-1,6-naphthyridine is low yielding.[19] Thus, a different strategy was chosen, in which the bond connecting the two naphthyridines was formed during the course of the ring closure reaction. The preparation of substituted quinolines[20] from 2-aminobenzaldehyde or of naphthyridine derivatives[21] from aminopyridinecarbaldehydes and methyl ketones has been investigated. Starting from 4-aminopyridine-3-carbaldehyde (**16**) some 1,6-naphthyridine derivatives have been described.[22] Compound **16** is obtained by acid hydrolysis of *N*-(3-formyl-4-pyridyl)-2,2-dimethylpropionamide (**15**). The latter is, in turn, synthesized from 4-aminopyridine, 2,2-dimethylpropionoyl chloride, and dimethylformamide via 2,2'-dimethyl-*N*-(4-pyridyl)propionamide (**14**) as indicated in Scheme 4. We found that the yield of **15** could be increased from 60 to 80% in comparison to the previous reports[23] if the product was worked up by distillation instead of recrystallization. In the case of **16**, twofold sublimation proved advantageous in comparison to the described recrystallization.



Scheme 4

4-Aminopyridine-3-carbaldehyde (**16**) is then condensed with butane-2,3-dione under basic conditions to give 2,2'-bi-1,6-naphthyridine (**5**) (Scheme 5). However, the experimental conditions required considerable optimization. When the base was added dropwise to the solution of both starting materials at room temperature, followed by heating to reflux, the yield was only 17%. In order to decrease the amount of homocondensation products of butane-2,3-dione, the base was reduced to 0.18 equivalent. Furthermore, a highly diluted solution of butane-2,3-dione was added dropwise to a solution of **16** and sodium hydroxide in ethanol. Comparative experiments also showed that addition under reflux gave a higher yield than addition at room temperature followed by reflux. At last, a slight excess of diacetyl could compensate for its loss due to self-condensation. Altogether, a maximum yield of 81% could be reached in the condensation reaction to form **5**. An overview on the optimization experiments is given in the Table.



Scheme 5

Solvents were dried according to standard procedures over potassium metal (Et_2O, THF), CaH_2 (DMF), distilled and stored under argon. $CHCl_3$, CH_2Cl_2 and toluene were purchased with a residual water content of less than 0.05% and used as such. All aniline starting materials were purified by vacuum distillation under argon prior to use. Commercial Ph_3P was dried for 24 h in vacuum at 50°C. Technical grade $POCl_3$ was distilled over a short Vigreux column under inert gas (bp 106°C) and stored under argon in the dark.

NMR spectra were recorded on a Bruker ARX200 (200.1 MHz for ^1H, 50.3 MHz for ^{13}C) or a Varian O-300 instrument (300.0 MHz for ^1H, 75.4 MHz for ^{13}C) and calibrated against the solvent signal (DMSO-d_6: ^1H NMR 2.53 ppm, ^{13}C NMR 39.5 ppm; $CDCl_3$: ^1H NMR 7.26 ppm, ^{13}C NMR 77.0 ppm; C_6D_6:^1H NMR 7.19 ppm, ^{13}C NMR 128.0 ppm; 1,4-dioxane: ^1H NMR 3.58 ppm, ^{13}C NMR 66.5 ppm). IR-spectra were measured on a Perkin-Elmer 783 infrared spectrophotometer as KBr disks or nujol mulls. Mass spectra were obtained on a GC/MS Finnigan MAT in solid-probe EI mode at an ionization energy of 70 eV. Elemental analyses were carried out with a Perkin-Elmer Elemental Analyzer E 240 C.

6-Amino-2-chloroquinoline (8)

6-Amino-2-chloroquinoline (**8**) was prepared from aniline and 3-ethoxypropenoyl chloride (**10**) according to refs.12, 24 and 25. The hitherto unreported NMR data for **8** are given below.

^1H NMR ($CDCl_3$): δ = 4.00 (br s, 2 H, NH_2), 6.86 (d, 1 H, *J* = 2.7 Hz, H-5), 7.14 (dd, 1 H, *J* = 8.9, 2.7 Hz, H-7), 7.23 (d, 1 H, *J* = 8.5 Hz, H-3), 7.80 (d, 1 H, *J* = 8.9 Hz, H-8), 7.81 (d, 1 H, *J* = 8.5 Hz, H-4).

^{13}C NMR ($CDCl_3$): δ = 107.3 (C-5), 122.1, 122.3 (C-3,7), 128.3 (C-10), 129.5 (C-8), 136.6 (C-4), 142.6 (C-9), 145.1 (C-6), 146.6 (C-2).

6,6´-Diamino-2,2´-biquinoline (3), Typical Procedure

In a 250 mL three-necked flask were placed $NiCl_2 \cdot 6H_2O$ (6.20 g, 26 mmol) and Ph_3P (27.3 g, 104 mmol). The flask was evacuated and refilled three times with argon. Anhyd DMF (200 mL) was added under inert gas and the color of the solution turned rapidly to blue. After Ph_3P and $NiCl_2 \cdot 6H_2O$ had completely dissolved, zinc powder (1.80 g, 29 mmol) was added under inert gas at 50°C and the color of the solution turned slowly to brown-red. After stirring this mixture for 1 h, a solution of **8** (4.60 g, 26 mmol) in DMF (20 mL) was added dropwise into the mixture. Stirring was continued for 4 h at 50°C at which time the starting material could not be detected anymore by TLC (eluent EtOAc). The mixture was then concentrated in vacuum to half of its volume. After adding H_2O (500 mL) the mixture was carefully poured into conc ammonia (350 mL) and stirred for 18 h. The color of the solution turned blue because of the formation of hexaammine-nickel(II) complexes. The PPh_3 precipitate was removed by filtration and the filtrate was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were treated three times with half-concentrated HCl (100 mL each) to separate the diaminobiquinoline from Ph_3P. During this procedure strongly colored amine hydrochlorides were formed. The combined acidic aqueous phases were carefully neutralized with aq 10% Na_2CO_3 solution (30 mL). The product **3** separated as a yellow powder and was purified by recrystallization from DMSO/H_2O; yield: 3.0 g (82%); mp 309°C.

Table Reaction of **16** with Butane-2,3-dione (Scheme 5) Under Different Conditions

Reaction Conditions	Amount of Butane-2,3-dione (equiv)[a]	Yield of **5** (%)
NaOH added dropwise to **16** and butane-2,3-dione	1.00	17
Butane-2,3-dione added dropwise to **16** and NaOH at r.t.	1.00	48
Butane-2,3-dione added dropwise to **16** and NaOH at reflux	1.00	68
	1.10	71
	1.16	81
	1.30	68
	1.40	60

[a] Equivalents per stoichiometric molar amount.

^{1}H NMR (DMSO-d_6): δ = 5.70 (br s, 4 H, NH_2), 6.83 (d, 2 H, *J* = 2.4 Hz, H-5,5'), 7.18 (dd, 2 H, *J* = 9.0, 2.4 Hz, H-7,7'), 7.79 (d, 2 H, *J* = 9.0 Hz, H-8,8'), 8.02 (d, 2 H, *J* = 8.7 Hz, H-3,3'), 8.46 (d, 2 H , *J* = 8.6, H-4,4').

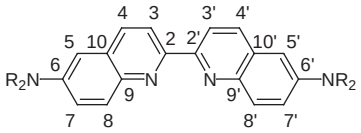
^{13}C NMR (DMSO-d_6): δ = 104.8 (C-5,5'), 118.3 (C-7,7'), 121.7 (C-3,3'), 129.7 (C-10,10'), 130.0 (C-8,8'), 133.5 (C-4,4'), 141.2 (C-9,9'), 147.5 (C-6,6'), 150.9 (C-2,2').

IR (KBr): ν = 3442 w, 3374 m, 3316 w, 3036 w, 1630 s, 1602 m, 1589 m, 1518 w, 1507 w , 1490 s, 1428 m, 1308 m, 1272 m, 1268 m, 1161 m, 1138 w, 1068 w, 1031 m, 962 w, 913 w, 868 w, 840 w, 728 w, 660 w, 600 w (br) , 556 w, 521 w, 422w cm^{-1}.

MS: *m*/*z* (%) = 286 (100, M^+), 143 (0.5, $M/2^+$).

Anal. $C_{18}H_{14}N_4$ (286.3): calcd. C 75.51, H 4.93, N 19.55; found C 75.30, H 5.33, N 19.37.

The numbering scheme for the NMR notation of **3** and **4** is as follows:



6,6´-Bis-(*N*,*N*-dimethylamino)-2,2´-biquinoline (4)

The synthetic route as given above for 6,6´-diamino-2,2´-biquinoline (**3**) was followed. Starting from **9** (0.80 g, 3.8 mmol), the biquinoline was obtained as a light-yellow powder; yield: 0.56 g (86%); mp 348°C.

^{1}H NMR ($CDCl_3$): δ = 3.15 (s, 12 H, CH_3)**,** 6.86 (d, 2 H, *J* = 2.7 Hz, H-5,5'), 7.38 (dd, 2 H, *J* = 9.4, 2.9 Hz, H-7,7'), 8.05 (d, 2 H, *J* = 9.2 Hz, H-.8,8'), 8.08 (d, 2 H, *J* = 8.4 Hz, H-3,3'), 8.63 (d, 2 H, *J* = 8.7 Hz, H-4,4').

^{13}C NMR ($CDCl_3$): δ = 105.1 (C-5,5'), 119.2, 119.5 (C-3,3',7,7'), 129.7 (C-10,10'), 130.4 (C-8,8'), 134.6 (C-4,4'), 141.9 (C-9,9'), 148.7 (C-6,6'), 152.8 (C-2,2').

IR (nujol): ν = 1695 w , 1594 m, 1542 m, 1495 s, 1492 s, 1382 s, 1369 m, 1358 w, 1292 w, 1280 w, 1268 w, 1220 w, 1182 w, 1175 w, 1152 w, 1130 w, 1076 w, 1061 m, 1004 w, 946 w, 880 w, 842 w, 760 w, 736 w cm^{-1}.

MS: *m*/*z* (%) = 342 (100, M^+), 326 (6, $M - CH_3^+$), 171 ($M/2^+$).

Anal. $C_{22}H_{22}N_4$ (342.4): calcd. C 77.16, H 6.47, N 16.36; found C 77.01, H 6.44, N 16.25.

2-Chloro-6-(*N*,*N*-dimethylamino)quinoline (9)
3-Ethoxypropenoyl Chloride (10)

Anhyd Et_3N (2.6 ml, 2.0 g, 20 mmol) was added to a 20% solution of phosgene in toluene (100 mL, 189 mmol) at –15°C. After stirring for 10 min, ethyl vinyl ether (18.1 mL, 13.6 g, 190 mmol) was added dropwise, such that the temperature never exceeded 0°C. When the addition was complete, the cooling bath was removed and stirring was continued for 48 h at r. t. The solvent and the 2-(chloroethyl) ethyl ether formed were distilled off. Vacuum distillation of the residue then gave **10** as a pale yellow oil; yield: 10.9 g (43%); bp 55°C/2.5 mbar (Lit.[14] bp 105 °C/35 Torr).

^{1}H NMR ($CDCl_3$): δ = 1.31 (t, 3 H, *J* = 7.0 Hz, CH_3), 4.02 (q, 2 H, *J* = 7.0 Hz, CH_2O), 5.46 (d, 1 H, *J* = 12.1 Hz, =CHCOCl), 7.74 (d, 1 H, *J* = 12.1 Hz, EtOCH=).

^{13}C NMR ($CDCl_3$): δ = 14.2 (CH_3), 68.7 (CH_2O), 102.7 (=*C*HCO), 164.5 (C=O), 168.1 (EtO*C*H=).

3-Ethoxypropenoyl-4-(*N*,*N*-dimethylamino)anilide (11)

To a solution of *p*-(*N*,*N*-dimethylamino)aniline (4.00 g, 29.4 mmol) in anhyd toluene (100 mL) was added anhyd Et_3N (5 mL, 3.77 g, 37.3 mmol). After warming this mixture to about 100°C, a solution of **10** (3.93 g, 29.2 mmol) in anhyd toluene (20 mL) was added dropwise to give a yellow slurry. After complete addition, the mixture was refluxed for 1 h, then the solvent was removed in vacuum. The remaining solid was extracted with THF (100 mL) and the solution filtered off from the insoluble Et_3N·HCl. Solvent removal from the filtrate yielded a brown solid, which was recrystallized from $CHCl_3$ to give **11** as light-yellow crystals; yield: 4.45 g (65%); mp 151°C.

^{1} H NMR ($CDCl_3$): δ = 1.26 (t, 3 H, *J* = 7.0 Hz, OCH_2CH_3), 2.87 [s, 6 H, $N(CH_3)_2$], 3.81 (q, 2 H, *J* = 7.0 Hz, OCH_2CH_3), 5.31 (d, 1 H, *J* = 12.1 Hz, =C*H*CONH), 6.64 (dt, 1 H, *J* = 6.0, 2.3 Hz, arom. *m*-CH), 7.33 (br s, 2 H, arom. *o*-CH), 7.46 (br s, 1 H, CON*H*), 7.54 (d, 1 H, *J* = 12.1 Hz, =C*H*OEt).

^{13}C NMR ($CDCl_3$): δ = 14.5 (CH_3), 40.9 [$N(CH_3)_2$], 66.9 (OCH_2), 99.3 (=*C*HCO), 113.0 (arom. C-3,5), 121.7 (arom. C-2,6), 128.5 (arom. C-1), 147.8 (arom. C-4), 160.0 (NHCO), 165.1 (=*C*HOEt).

IR (nujol): ν = 3295 m, 3252 m, 3195 w, 3040 w, 1658 s, 1622 m, 1612 m, 1598 m, 1527 s, 1518 s, 1468 s, 1421 w, 1408 w, 1395 w, 1367 w, 1344 m, 1322 w, 1294 w, 1252 m, 1238 m, 1194 w, 1153 s, 1108 w, 1062 w, 1012 w, 962 w, 948 w, 925 w, 860 w, 842 w, 818 w, 810 w, 786 w, 758 w, 738 w, 712 w cm^{-1}.

MS: *m*/*z* (%) = 234 (75, M^+), 136 [100, $(Me_2N - C_6H_4 - NH)+H]^+$], 135 [40, $(Me_2N - C_6H_4 - NH)^+$], 121 (9, $(Me_2N - C_6H_4)+H^+$], 108 [7, $(Me_2N - C_6H_4 - NH) - HCN^+$], 99 (10, $HC{=}CHOEt^+$).

Anal. $C_{13}H_{18}N_2O_2$ (234.3): calcd. C 66.64, H 7.74, N 11.96; found C 66.23, H 7.96, N 11.52.

2-Hydroxy-6-(dimethylamino)quinolone (12)

To concd H_2SO_4 (30 mL) cooled to –10°C was added **11** (8.00 g, 34.2 mmol) in small portions. A clear yellow solution was produced after 5 min which was then warmed to 50°C and the reaction was monitored by TLC [1 drop of the reaction mixture was neutralized with aq satd $NaHCO_3$ solution (2 mL) and brought onto the TLC-plate with the starting material as reference; eluent: EtOAc]. The reaction was complete after 24 h. The mixture was poured onto ice (200 g) and the pH was carefully raised with 5 M NaOH up to 12–13. The precipitate was separated by filtration, dissolved in $CHCl_3$, filtered again, the solvent removed and the product recrystallized from acetone to give bright-yellow needle-shaped crystals; yield: 4.60 g (72%).

^{1}H NMR ($CDCl_3$): δ = 2.97 (s, 6 H, CH_3), 6.68 (d, 1 H, *J* = 9.4 Hz, H-3), 6.78 (d, 1 H, *J* = 2.6 Hz, H 5), 7.08 (dd, 1 H, *J* = 9.0, 2.7 Hz, H-7), 7.38 (d, 1 H, *J* = 9.0 Hz, H-8), 7.73 (d, 1 H, *J* = 9.5 Hz, H-4), 12.84 (br s, 1 H, OH).

^{13}C NMR ($CDCl_3$): δ = 41.1 (CH_3), 108.9 (C-5), 117.0 (C-7), 118.5 (C-3), 120.8 (C-10), 121.3 (C-8), 130.9 (C-9), 140.6 (C-4), 146.7 (C-6), 164.0 (C-2).

IR (nujol): ν = 3400 w (br), 3140 w, 2724 w, 1658 s, 1621 s, 1565 w, 1512 w, 1468 s, 1428 m, 1418 m , 1384 w, 1368 m, 1340 w, 1284 w, 1270 w, 1242 w, 1200 w, 1162 w, 1158 w, 1118 s, 1069 w, 1030 w (br) , 972 w, 968 w, 953 w, 946 w, 925 w, 905 w, 842 s, 813 m, 753 w, 686 w cm^{-1}.

MS: *m*/*z* (%) = 189 (100, M^+), 188 (18, $M - H^+$), 173 [15, $(M - OH)+H^+$], 172 (32, $M - OH^+$), 159 (8, $[M - OH - HCN^+$), 145 (11, $M - NMe_2^+$), 128 (18, $M - OH - NMe_2^+$), 116 (11, $[M - NMe_2 - CO - H^+$).

Anal. $C_{11}H_{12}N_2O$ (188.2) calcd. C 70.20, H 6.38, N 14.90; found C 70.43, H 5.78, N 15.08.

Reaction of $POCl_3$ with 12 to form 9

Compound **12** (1.0 g, 5.3 mmol) was suspended in $POCl_3$ (15 mL) and heated to reflux for 3 h. After removal of excess $POCl_3$ by distillation, the semi-solid residue was poured onto ice (100 g), made alkaline to a pH of 8–9 with aq 10% Na_2CO_3 solution and the precipitate filtered. After drying in vacuum, the product was purified by sublimation at 140°C/0.2 mbar to give **9** as yellow crystals; yield: 0.95 g (87%); mp 75°C.

^{1}H NMR ($CDCl_3$): δ = 3.06 (br s, CH_3), 7.08 (d, 1 H, *J* = 2.5 Hz, H-5), 7.23 (d, 1 H, *J* = 9.4 Hz, H-3), 7.40 (dd, 1 H, *J* = 8.6, 2.5 Hz, H-7), 7.85 (d, 1-H, *J* = 8.6 Hz, H-8), 7.92 (d, 1-H, *J* = 9.4 Hz, H-4).

^{13}C NMR ($CDCl_3$): δ = 41.9 (CH_3), 108.3 (C-5), 120.2 (C-7), 122.7 (C-3), 128.0 (C-10), 129.6 (C-8), 137.5 (C-4), 147.0 (C-2); no signals were found for the quartenary carbon atoms 6 and 9.

IR (KBr): ν = 2930 m, 2890 m, 2818 m, 1653 s, 1580 s, 1560 m, 1518 s, 1453 m, 1427 m, 1372 s, 1197 m, 1156 m, 1138 m, 1099 s, 1021 m, 941 s, 848 m, 816 s, 806 m, 712 m, 642 m cm^{-1}.

Anal. $C_{11}H_{11}ClN_2$ (206.7) calcd. C 64.00, H 5.33, N 13.55; found C 64.11, H 5.22, N 12.33%.

***N*-(3-Formyl-4-pyridyl)-2,2-dimethylpropionamide (15)**

2,2'-Dimethyl-*N*-(4-pyridyl)propionamide (**14**; 22.0 g, 123 mmol) (prepared according to ref. 23) was dissolved in anhyd THF (400 mL) under an inert atmosphere and cooled to –78°C. Within 1 h, a 1.6 M hexane solution of BuLi (200 mL, 0.32 mol) was added dropwise. Then, the orange solution was warmed to 0°C, stirred for 3 h, and anhyd DMF (27.0 g, 0.38 mol) in anhyd THF (100 mL) was added. Subsequently, the solution was warmed to r.t. and stirred for an additional 45 min. The mixture was poured onto a mixture of 6 N HCl (250 mL) and ice (250 g). After stirring for 5 min, the solution was neutralized with K_2CO_3 (190 g, 1.4 mol) and extracted with Et_2O (3 × 200 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed in vacuum. The brown residue was distilled over an angular tube in a liquid nitrogen cooled flask (130°C bath temperature/0.1 mbar) to give a light yellow solid; yield: 20.3 g (80%); mp 59–63°C (Lit.[23] mp 60–63°C).

^{1}H NMR ($CDCl_3$): δ = 1.37 (s, 9 H, CH_3), 8.60 (s, 2 H, H-2,6), 8.82 (s, 1 H, H-5), 10.01 (s, 1 H, CHO), 11.23 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 28.9 (CH_3), 40.6 (*C*Me_3), 113.8 (C-5), 117.7 (C-3), 147.1 (C-4), 166.1 (C-6), 167.7 (C-2), 179.5 (NC=O), 194.4 (CHO).

4-Aminopyridine-3-carbaldehyde (16)

Compound **15** (20.0 g, 97 mmol) was dissolved in 3 N HCl (200 mL) and heated to reflux for 8 h. During this time, the initially yellow solution turned brown. The mixture was extracted with Et_2O (3 × 200 mL each). The aqueous phase was made alkalic with K_2CO_3 (95 g, 0.7 mol) and extracted with $CHCl_3$ (3 × 200 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was removed in vacuum. The yellow-brown residue was sublimed twice (115°C bath temperature/0.1 mbar) and eventually recrystallized from methylcyclohexane to give a colorless solid; yield: 9.5 g (80%); mp 115–116°C (Lit.[23] mp 114–116°C).

^{1}H NMR ($CDCl_3$): δ = 6.47 (d, 1 H, *J* = 5.8 Hz, H-5), 6.53 (br s, 2 H, NH_2), 8.15 (d, 1 H, *J* = 5.8 Hz, H-6), 8.50 (s, 1 H, H-2), 9.86 (s, 1 H, CHO).

^{13}C NMR ($CDCl_3$): δ = 110.4 (C-5), 115.7 (C-3), 152.7 (C-6), 157.4 (C-2), 193.3 (CHO).

2,2'-Bi-1,6-naphthyridine (5)

4-Aminopyridine-3-carbaldehyde (**16**; 2.44 g, 20 mmol) was dissolved in absolute EtOH (40 mL) and combined with an aqueous solution of NaOH (70.0 mg, 1.75 mmol, 2 mL). The mixture was heated to reflux and a solution of butane-2,3-dione (1.00 g, 11.6 mmol) in absolute EtOH (50 mL) was added dropwise within 3 h. The initially yellow solution turned brown and a colorless precipitate occurred. After complete addition, the mixture was refluxed for another 8 h. The precipitate was filtered, washed with EtOH (3×10 mL), with acetone (10 mL) and recrystallized from 1,4-dioxane (300 mL) to give the product as a faint brown solid; yield: 2.10 g (81%); mp. >300°C.

^{1}H NMR (dioxane-d_8): δ = 7.97 (d, 2 H, *J* = 5.9 Hz, H-3,3'), 8.40 (d, 2 H, *J* = 8.8 Hz, H-8,8'), 8.76 (d, 2 H, *J* = 5.9 Hz, H-4,4'), 8.92 (d, 2 H, *J* = 8.5 Hz, H-7,7'), 9.29 (s, 2 H, H-5,5').

^{13}C NMR (dioxane-d_8) = δ = 121.4 (C-8,8'), 122.6 (C-3,3'), 124.7 (C-10,10'), 137.4 (C-4,4'), 148.3 (C-7,7'), 150.9 (C-2,2'), 153.8 (C-5,5'), 159.9 (C-9,9').

IR (KBr): ν = 3045 w, 3010 w, 1618 s, 1593 m, 1550 w, 1480 w, 1450 m, 1395 m, 1375 w, 1307 w, 1255 w, 1212 w, 1168 w, 1070 w, 950 m, 855 m, 845 s, 788 w, 660 w, 640 m, 520 m cm^{-1}.

MS: *m*/*z* (%) = 258 (100, M^+), 129 (16, $M - C_8H_5N_2^+ = M/2^+$), 102 (12, $M/2 - HCN^+$).

Anal. $C_{16}H_{10}N_4$ (258.3) calcd. C 74.40, H 3.90, N 21.69; found C 74.03, H 3.78, N 21.41%.

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