Directed *ortho*-Lithiation of Chloroquinolines. Application to Synthesis of 2,3-Disubstituted Quinolines

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2-, 3- and 4-Chloroquinolines were selectively lithiated at low temperature by lithium diisopropylamide at the more acidic C-3, C-4 and C-3 positions respectively. Reaction of 2-chloro-3-lithioquinoline with electrophiles led to various 2,3-disubstituted quinolines. The versatility of this functionalization methodology is enhanced by the C-2 halogen reactivity towards oxygen or nitrogen nucleophiles. So, a great variety of 2,3-disubstituted quinolines were synthesized, such as 2-chloro, 2-alkoxy, 2-aminoquinolines or 2-quinolones bearing an hydroxy, carbonyl (aldehyde, ketone or carboxylic acid), iodo, trimethylsilyl or boronic acid moiety at the C-3. Some of the resulting 2,3-disubstituted synthons were annelated to tetracyclic polyaromatics, which possess the xanthone or indole structure. This could be achieved *via* further functionalization of the quinoline ring either by SNAr2 or heteroaromatic cross-coupling reactions, after the first directed-lithiation step.

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Metalation [1] of *pi*-deficient heterocycles (pyridine, quinoline and diazines...) has grown in interest only during the last fifteen years. Today many DMGs (Directed Metalation Group), as well as selective strong bases are available for the lithiation of heterocycles [2], which are often difficult to functionalize by usual electrophilic routes. This metalation functionalization strategy has only been recently developed in the quinoline series [3], even if lithiation of 2-alkoxyquinolines has been reported long ago by Gilman [4] and Narasimhan [5]. As early as 1979, our laboratory [6] found that fluorine could induce selective *ortho*-lithiation of quinoline using lithium diisopropylamide. The poor nucleophilic character of this strong base avoid competitive nucleophilic attacks on the sensitive pyridine moiety. More recently, amino and hydroxyquinolines [3a] and [3b] were *ortho*-lithiated by us after activation of these functions respectively as pivaloylamino, carbamate or ureido groups.

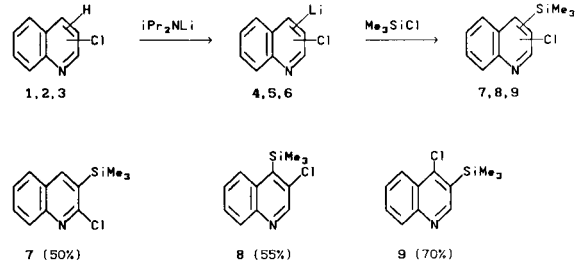
We wish to report here that 2-, 3- and 4-chloroquinolines could be lithiated by lithium diisopropylamide. Starting from the commercially available 2-chloroquinoline, numerous 2,3-disubstituted quinolines, as well as polycondensed heterocycles could be conveniently prepared.

Metalation Conditions and Application to Synthesis.

2-Chloro, 3-chloro and 4-chloroquinolines **1-3** were *ortho*-lithiated by lithium diisopropylamide (2 hours at −75° in tetrahydrofuran), and the resulting chlorolithioquinolines were characterized by reaction with chlorotrimethylsilane (Scheme I).

Ring deprotonation by lithium diisopropylamide is regioselectively directed by the chlorine atom, as shown by the ^{1}H-nmr spectra of the trimethylsilyl derivatives **7-9**. Unreacted material could be recovered aside from the lithiation derived trimethylsilyl compounds.

Scheme I



Reaction of 2-chloro-3-lithioquinoline (**4**) with electrophiles afforded 3-substituted 2-chloroquinolines **7**, **10-15**, in moderate to good yields (Scheme II) (Table I). A wide variety of substituents could be thus introduced at the C-3 position of 2-chloroquinoline, such as Me_3Si, I, CHAr-OH, CHO, CO_2H and $B(OH)_2$.

Scheme II

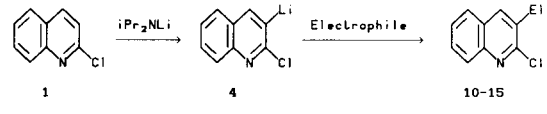


Table I

Electrophile	E1	Compound	Yield
Me_3Si-Cl	Me_3Si	7	50%
Ph-CHO	Ph-CHOH	10	55%
2-MeOPh-CHO	2-MeOPh-CHOH	11	60%
H-CO_2Et	CHO	12	45%
CO_2	CO_2H	13	67%
$B(OMe)_3$	$B(OH)_2$	14	85%
I_2	I	15	75%

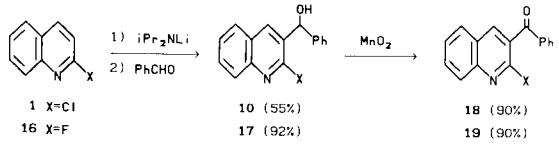
The lithiation directing abilities of fluorine and chlorine could be compared by reacting 2-chloroquinoline (**1**) or 2-fluoroquinoline (**16**) with lithium diisopropylamide (2 hours in tetrahydrofuran at −75°) and trapping the resulting lithiated species with benzaldehyde. This led to the corresponding (2-chloro or 2-fluoro-3-quinolyl)phenylmethanol, **10** or **17**, respectively in 55% and 92% yields (Scheme III).

Synthesis of 2,3-Disubstituted Quinolines.

Some of the previously described 2-chloroquinolines could be further transformed into new synthons, either by modification of the 3-substituent or by halogen-substitution. 2-Halo, 2-hydroxy, 2-alkoxy and 2-aminoquinolines bearing a 3-carbonyl function have been thus prepared.

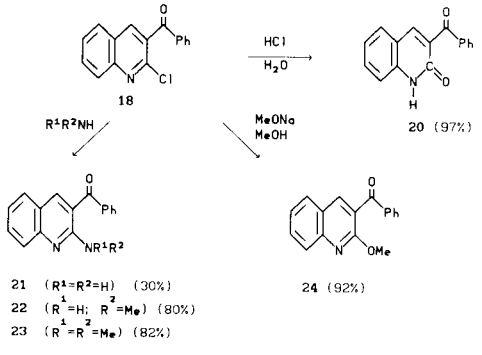
The secondary alcohols **10** and **17** were oxidized to the corresponding ketones **18** and **19** using activated manganese dioxide in refluxing toluene [7] (Scheme III).

Scheme III



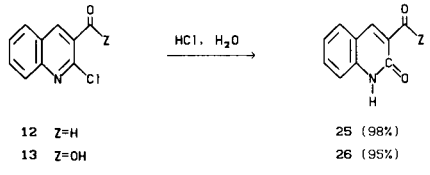
The 2-chloroketone **18** underwent nucleophilic substitutions by reaction with hydrochloric acid, sodium methylate, ammonia, methylamine or dimethylamine (Scheme IV).

Scheme IV



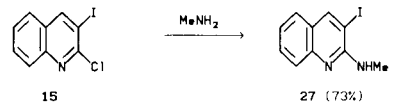
2-Chloroquinoline-3-carboxaldehyde (**12**) and 3-carboxylic acid **13** were hydrolyzed to the corresponding 2-quinolones **25** and **26** by treatment with hot hydrochloric acid (Scheme V).

Scheme V



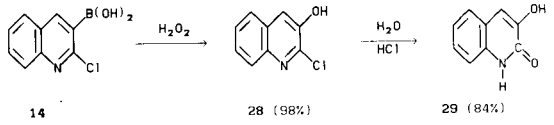
Methylamine reacted selectively at the C-2 position of 2-chloro-3-iodoquinoline (**15**), leading to 3-iodo-2-methylaminoquinoline (**27**) (Scheme VI).

Scheme VI



Oxidation of 2-chloroquinoline-3-boronic acid (**14**) using hydrogen peroxide, gave 2-chloro-3-hydroxyquinoline (**28**). The resulting 2-chloro compound **28** was then hydrolyzed to 3-hydroxy-2-quinolone (**29**) in a high overall yield (70% starting from 2-chloroquinoline in three steps) (Scheme VII).

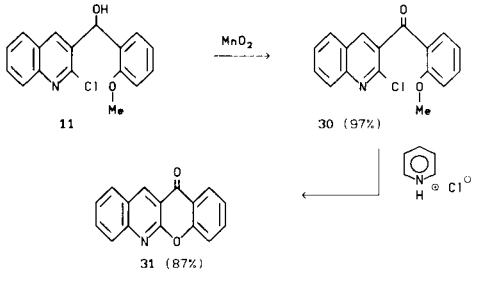
Scheme VII



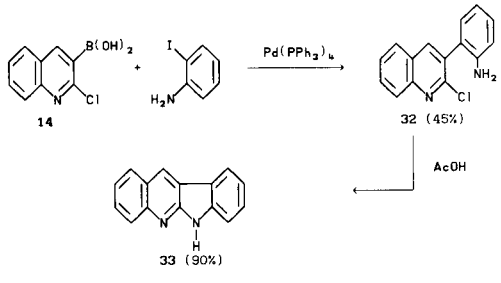
Synthesis of Polyheteroaromatics.

Some 3-substituted 2-chloroquinolines were cyclized into condensed polyheterocycles, taking advantage of the C-2 halogen reactivity under nucleophilic conditions. (2-Chloro-3-quinolyl)(2-methoxyphenyl)methanol (**11**) was oxidized by manganese dioxide to the corresponding ketone **30**, which could be later cyclized by treatment with boiling pyridinium chloride (Scheme VIII).

Scheme VIII



Scheme IX



Transition metal catalyzed cross-coupling reaction between 2-chloroquinoline-3-boronic acid (**14**) and 2-iodoaniline following the Suzuki's procedure [8] (3 mmole % tetrakis(triphenylphosphine)palladium, 2 *M* aqueous sodium carbonate, refluxing toluene) allowed the construction of the expected unsymetrical biaryl **32** in moderate yield. Cyclization of the resulting amine under acidic catalysis, afforded in good yield the unsubstituted indolo[2,3-*b*]-quinoline (**33**) (Scheme IX).

Discussion.

Metalation of 2-, 3- and 4-chloroquinolines is selectively directed by the halogen electron-withdrawing effect, and is chemoselectively achieved using lithium diisopropylamide at low temperature. *Ortho*-lithiation of 2-chloroquinoline proves to be a powerful and versatile strategy for the elaboration of various 2,3-difunctional quinolines, due to the peculiar reactivities of either the C-2 chlorine atom or the C-3 grafted function. Connection between directed *ortho*-lithiation and aromatic cross-coupling tactics significantly broadens the efficiency and the scope of each methodology for heterocyclic synthesis.

EXPERIMENTAL

The ^{1}H-nmr spectra were obtained using a Varian T-60 spectrometer and were recorded in ppm downfield from the internal standard of tetramethylsilane in deuteriochloroform or hexamethyldisiloxane in hexadeuteriodimethyl sulfoxide. The ir spectra were obtained either as thin films or potassium bromide pellets with a Perkin-Elmer R-12 spectrophotometer. Elemental analysis were performed on a Carlo Erba instrument.

Diethyl ether and tetrahydrofuran were distilled from benzophenone-sodium. Water content of the solvents was estimated by the modified Karl-Fisher method [9] (tetrahydrofuran and diethyl ether less than 45 and 10 ppm respectively). Diisopropylamine and chlorotrimethylsilane were distilled from calcium hydride and stored over calcium hydride. Metalations were performed under a dry argon atmosphere, and solvents and reagents were handled under argon with syringes through septa.

2-Chloroquinoline (**1**).

This compound was purified by vacuum distillation of the commercial reagent, bp = 140° (15 mm Hg); ^{1}H-nmr (deuteriochloroform): 7.30 (d, 1H, H-3), 7.65 (m, 4H, H-5, 6, 7, 8), 8.05 (d, 1H, H-4), J_{3-4} = 9 Hz.

3-Chloroquinoline (**2**).

3-Chloroquinoline was prepared by Sandmeyer diazotation [10] of 3-aminoquinoline [11] and purified by vacuum distillation, bp = 95° (2 mm Hg); ^{1}H-nmr (deuteriochloroform): 7.60 (m, 3H, H-5, 6, 7), 8.05 (d, 1H, H-4), 8.05 (dd, 1H, H-8), 8.75 (d, 1H, H-2), J_{2-4} = 2.5 Hz, J_{6-8} = 2 Hz, J_{7-8} = 8 Hz.

4-Chloroquinoline (**3**).

4-Chloroquinoline was obtained by neutralization of the corresponding commercial hydrochloride (aqueous sodium carbonate), followed by extraction by diethyl ether, drying over magnesium sulfate and evaporation of the solvent. The crude 4-chloroquinoline was stored in diethyl ether at 0°; ^{1}H-nmr (deuteriochloroform): 7.30 (d, 1H, H-3), 7.55 (m, 2H, H-6, 7), 8.00 (m, 2H, H-5, 8), 8.60 (d, 1H, H-2), J_{2-3} = 5 Hz.

2-Fluoroquinoline (**16**).

2-Fluoroquinoline was prepared *via* chlorine-fluorine exchange using potassium fluoride in dimethylsulfone [12] starting from 2-chloroquinoline (**1**) in 60% yield, bp = 109° (5 mm Hg); ^{1}H-nmr (deuteriochloroform): 6.85 (dd, 1H, H-3), 7.50 (m, 4H, H-5, 6, 7, 8), 8.00 (dd, 1H, H-4), J_{3-4} = 8 Hz, J_{3-F} = 2.5 Hz, J_{4-F} = 8 Hz.

General Procedure for the Metalation of Chloroquinolines.

Into a cold solution (−20°) of tetrahydrofuran (125 ml) and *n*-butyllithium (1.6 *M* in hexane, 31.5 ml, 0.05 mole) was added dropwise under stirring diisopropylamine (5.05 g, 0.05 mole) and the mixture was allowed to stand for 1 hour at 0°. Slow addition of chloroquinoline (8.2 g, 0.05 mole) in tetrahydrofuran (25 ml) solution was achieved at −75° and stirring was continued for 2 hours at −75°. The required electrophile (0.05 mole) in tetrahydrofuran (25 ml) solution was then slowly introduced and the reaction mixture was further stirred for 2 hours at −75°, before hydrolysis by aqueous tetrahydrofuran (2 ml of water in 10 ml of tetrahydrofuran). Water (150 ml) and diethyl ether (150 ml) were introduced at −10°, the aqueous layer was extracted with diethyl ether (3 x 150 ml) and the combined extract was dried over magnesium sulfate. Solvent removal under vacuum afforded a crude product, which was purified either by crystallization, vacuum distillation or flash-chromatography on silica.

2-Chloro-3-trimethylsilylquinoline (**7**).

Metalation of 2-chloroquinoline (**1**) according to the general procedure and reaction with chlorotrimethylsilane afforded after vacuum distillation 50% of **7**, bp = 130° (1 mm Hg); ^{1}H-nmr (deuteriochloroform): 0.35 (s, 9H, CH_3), 7.30-8.10 (m, 4H, H-5, 6, 7, 8), 8.20 (s, 1H, H-4); ir (neat): 3070, 3040, 2970, 2930, 2910, 2860, 1625, 1570, 1490 cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}ClNSi$: C, 61.13; N, 5.94; H, 5.98. Found: C, 60.8; N, 5.95; H, 5.90.

3-Chloro-4-trimethylsilylquinoline (**8**).

Metalation of 3-chloroquinoline (**2**) according to the general procedure and reaction with chlorotrimethylsilane afforded after vacuum distillation 55% of **8** bp = 125° (2 mm Hg); ^{1}H-nmr (deuteriochloroform): 0.40 (s, 9H, CH_3), 7.40-7.80 (m, 2H, H-6, 7), 7.90-8.30 (m, 2H, H-5, 8), 8.70 (s, 1H, H-2); ir (neat): 3060, 3020, 2950, 2880, 1520, 1490 cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}ClNSi$: C, 61.13; N, 5.94; H, 5.98. Found: C, 61.2; N, 6.12; H, 6.18.

4-Chloro-3-trimethylsilylquinoline (**9**).

Metalation of 4-chloroquinoline (**3**) according to the general procedure and reaction with chlorotrimethylsilane afforded after vacuum distillation 70% of **9**, bp = 114° (0.5 mm Hg); ^{1}H-nmr (deuteriochloroform): 0.35 (s, 9H, CH_3), 7.40-7.80 (m, 2H, H-6, 7), 7.90-8.40 (m, 2H, H-5, 8), 8.85 (s, 1H, H-2); ir (neat): 3050, 3030, 2950, 2900, 1610, 1550, 1470 cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}ClNSi$: C, 61.13; N, 5.94; H, 5.98. Found: C, 61.1; N, 6.05; H, 6.10.

(2-Chloro-3-quinolyl)phenylmethanol (**10**).

Metalation of 2-chloroquinoline (**1**) according to the general procedure and reaction with benzaldehyde gave after flash-chromatography on silca (diethyl ether/hexane; 1/1) 55% of **10**, mp = 103°, bp = 240-250° (1 mm Hg); ^{1}H-nmr (deuteriochloroform): 4.05 (d, 1H, OH), 6.15 (d, 1H, CH), 7.10-8.00 (m, 9H, H-5, 6, 7, 8 and H-phenyl), 8.35 (s, 1H, H-4), $J_{CH=OH}$ = 3 Hz; ir (potassium bromide): 3360, 3080, 3060, 3030, 2920, 1620, 1590, 1565, 1490 cm^{-1}.

Anal. Calcd. for $C_{16}H_{12}ClNO$: C, 71.25; N, 5.19; H, 4.48. Found: C, 71.1; N, 5.10; H, 4.50.

(2-Chloro-3-quinolyl)-2-methoxyphenylmethanol (**11**).

Metalation of 2-chloroquinoline (**1**) according to the general procedure and reaction with *ortho*-anisaldehyde gave a crude product which was crystallized by addition of diethyl ether, yielding 60% of **11**, mp = 167°; ^{1}H-nmr (deuteriochloroform): 3.50 (d, 1H, OH), 3.80 (s, 3H, OCH_3), 6.50 (d, 1H, CH), 6.70-8.10 (m, 8H, H-5, 6, 7, 8 and H-phenyl), 8.30 (s, 1H, H-4), J_{CH-OH} = 4 Hz; ir (potassium bromide): 3220, 3060, 3010, 2960, 2940, 2910, 2840, 1620, 1605, 1590, 1570, 1490, 1460 cm^{-1}.

Anal. Calcd. for $C_{17}H_{14}ClNO_2$: C, 68.12; N, 4.67; H, 4.71. Found: C, 67.8; N, 4.59; H, 4.70.

2-Chloroquinoline-3-carboxaldehyde (**12**).

Metalation of 2-chloroquinoline (**1**) according to the general procedure and reaction of ethyl formate (0.2 mole) gave a crude product which was crystallized in a mixture of diethyl ether and ligroïn (1/1), yielding 45% of **12**, mp = 146° (lit 148° [13]); ^{1}H-nmr (deuteriochloroform): 7.50-8.20 (m, 4H, H-5, 6, 7, 8), 8.75 (s, 1H, H-4), 10.55 (s, 1H, CHO); ir (potassium bromide): 3060, 3040, 2870, 1685, 1615, 1580, 1490, 1455 cm^{-1}.

Anal. Calcd. for $C_{10}H_6ClNO$: C, 62.68; N, 7.31; H, 3.16. Found: C, 62.5; N, 7.19; H, 3.24.

2-Chloroquinoline-3-carboxylic Acid (**13**).

Metalation of 2-chloroquinoline (**1**) according to the general procedure and fast addition of a large excess of dry ice (0.5 mole) afforded a pale pink solution, which was hydrolyzed. The resulting aqueous layer was extracted with diethyl ether (2 x 150 ml), boiled with black carbon and filtered over asbestos. Acidification by concentrated hydrochloric acid to *p*H 1 gave 67% of **13**, which was dried in a vacuum stove, mp = 226° (lit 220° dec [14]); ^{1}H-nmr (DMSO-d_6): 7.40-8.20 (m, 4H, H-5, 6, 7, 8), 8.80 (s, 1H, H-4), 13.15 (broad s, 1H, CO_2H); ir (potassium bromide): 3070, 2820, 2770, 2560, 1730, 1615, 1575, 1560, 1485, 1445 cm^{-1}.

Anal. Calcd. for $C_{10}H_6ClNO_2$: C, 57.85; N, 6.75; H, 2.91. Found: C, 57.6; N, 6.62; H, 2.74.

2-Chloroquinoline-3-boronic Acid (**14**).

Metalation of 2-chloroquinoline (**1**) according to the general procedure and reaction with trimethyl borate afforded an aqueous layer, which was acidified to *p*H 4 by concentrated hydrochloric acid. Extraction with diethyl ether, drying over magnesium sulfate and evaporation to dryness gave 85% of **14**, as a pale yellow powder, mp >200° dec; ^{1}H-nmr (DMSO-d_6): 7.30-8.20 (m, 6H, H-5, 6, 7, 8 and OH), 8.50 (s, 1H, H-4); ir (potassium bromide): 3400, 3060, 3030, 1640, 1620, 1580, 1560, 1490, 1455 cm^{-1}.

Anal. Calcd. for $C_9H_7BClNO_2$: C, 52.12; N, 6.75; H, 3.40. Found: C, 51.8; N, 6.77; H, 3.19.

2-Chloro-3-iodoquinoline (**15**).

Metalation of 2-chloroquinoline (**1**) according to the general procedure and reaction with iodine afforded after hydrolysis a crude reaction mixture which was decolorized by solid sodium thiosulfate. Standard workup and vacuum distillation gave 75% of **15**, bp = 145° (1.5 mm Hg), mp = 145°; ^{1}H-nmr (deuteriochloroform): 7.30-7.90 (m, 4H, H-5, 6, 7, 8), 8.40 (s, 1H, H-4); ir (potassium bromide): 3050, 3030, 1610, 1575, 1560, 1545, 1485 cm^{-1}.

Anal. Calcd. for C_9H_5ClIN: C, 37.34; N, 4.84; H, 1.74. Found: C, 37.4; N, 4.84; H, 1.71.

(2-Fluoro-3-quinolyl)phenylmethanol (**17**).

Metalation of 2-fluoroquinoline (**16**) according to the general procedure and reaction with benzaldehyde afforded a crude product which was steam distilled. Subsequent standard workup and crystallization by addition of diethyl ether gave 92% of **17**, mp = 111°; ^{1}H-nmr (deuteriochloroform): 2.90 (s, 1H, OH), 6.10 (s, 1H, CH), 7.20-8.00 (m, 9H, H-5, 6, 7, 8 and H-phenyl), 8.40 (d, 1H, H-4), J_{4-F} = 9.5 Hz; ir (potassium bromide): 3300, 3060, 2870, 1620, 1580, 1500 cm^{-1}.

Anal. Calcd. for $C_{16}H_{12}FNO$: C, 75.88; N, 5.53; H, 4.78. Found: C, 75.6; N, 5.36; H, 4.65.

(2-Chloro-3-quinolyl) Phenyl Ketone (**18**).

Secondary alcohol **10** (13.5 g, 0.05 mole) was oxidized by manganese dioxide (43.5 g, 0.5 mole) in toluene (250 ml) at ebullition temperature using a Dean-Stark apparatus (reaction was monitored by ir-spectroscopy). Filtration of manganese oxides over asbestos, washing of the filtered cake by chloroform (3 x 150 ml), drying of the filtrate over magnesium sulfate and removal of the solvents under vacuum yielded 90% of **18**, mp = 96°; ^{1}H-nmr (deuteriochloroform): 7.20-7.90 (m, 9H, H-5, 6, 7, 8 and H-phenyl), 8.05 (s, 1H, H-4); ir (potassium bromide): 3070, 3010, 1665, 1580, 1560, 1500, 1490, 1460 cm^{-1}.

Anal. Calcd. for $C_{16}H_{10}ClNO$: C, 71.78; N, 5.23; H, 3.77. Found: C, 71.9; N, 5.13; H, 3.97.

(2-Fluoro-3-quinolyl) Phenyl Ketone (**19**).

Secondary alcohol **17** was oxidized according to the foregoing procedure to yield 90% of **19**, mp >250°; ^{1}H-nmr (deuteriochloroform): 7.20-7.80 (m, 9H, H-5, 6, 7, 8 and H-phenyl), 8.10 (s, 1H, H-4); ir (potassium bromide): 3070, 3010, 1660, 1560, 1400 cm^{-1}.

Anal. Calcd. for $C_{16}H_{10}FNO$: C, 76.49; N, 5.57; H, 4.01. Found: C, 76.5; N, 5.56; H, 4.08.

(2-Chloro-3-quinolyl) 2-Methoxyphenyl Ketone (**30**).

Secondary alcohol **11** was oxidized according to the foregoing procedure to yield 97% of **30**, mp = 124°; ^{1}H-nmr (deuteriochloroform): 3.55 (s, 3H, OCH_3), 6.80-8.10 (m, 8H, H-5, 6, 7, 8 and H-phenyl), 8.20 (s, 1H, H-4); ir (potassium bromide): 3070, 3040, 3010, 2980, 2940, 1665, 1615, 1595, 1575, 1560, 1485, 1460 cm^{-1}.

Anal. Calcd. for $C_{17}H_{12}ClNO_2$: C, 68.58; N, 4.70; H, 4.06. Found: C, 68.5; N, 4.72; H, 3.81.

3-Benzoyl-2-quinolone (**20**).

(2-Chloro-3-quinolyl) phenyl ketone (**18**) (1 g, 3.74 mmoles) was boiled for 6 hours in 6*N* hydrochloric acid (30 ml). Addition of water (50 ml), filtration, washing with water (2 x 25 ml) and drying in a vacuum stove yielded 97% of **20**, mp >250°; ^{1}H-nmr (DMSO-d_6): 7.00-8.00 (m, 10H, H-5, 6, 7, 8, NH and H-phenyl), 8.15 (s, 1H, H-4), 11.70 (s, 1H, CO_2H); ir (potassium bromide): 3160, 3100, 3060, 3000, 2950, 2890, 2850, 1660, 1620, 1580, 1565,

1500, 1490 cm^{-1}.

Anal. Calcd. for $C_{16}H_{11}NO_2$: C, 77.10; N, 5.62; H, 4.45. Found: C, 77.2; N, 5.38; H, 4.19.

(2-Amino-3-quinolyl) Phenyl Ketone (**21**).

(2-Chloro-3-quinolyl) phenyl ketone (**18**) (2 g, 7.48 mmoles) was reacted with concentrated aqueous ammonia (10 ml) in a sealed tube at 150° for 24 hours. The cooled aqueous mixture afforded a crude product, which was purified by flash chromatography on silica (diethyl ether/hexane; 3/10), yielding 30% of **21**, mp = 159°; ^{1}H-nmr (deuteriochloroform): 6.60 (s, 2H, NH_2), 7.20-7.80 (m, 9H, H-5, 6, 7, 8 and H-phenyl), 8.25 (s, 1H, H-4); ir (potassium bromide): 3440, 3410, 3300, 3130, 3050, 1645, 1620, 1560, 1510, 1480 cm^{-1}.

Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 77.40; N, 11.28; H, 4.87. Found: C, 77.1; N, 11.1; H, 4.81.

(2-Methylamino-3-quinolyl) Phenyl Ketone (**22**).

A mixture of (2-chloro-3-quinolyl) phenyl ketone (**18**) (1 g, 3.74 mmoles) and methylamine (40% aqueous solution, 10 ml) was warmed in a sealed tube at 140° for 20 hours. Extraction by chloroform (3 x 50 ml), drying over magnesium sulfate, removal of the solvent and addition of diethyl ethyl (50 ml) yielded 80% of **22**, mp = 113°; ^{1}H-nmr (deuteriochloroform): 3.20 (d, 3H, CH_3), 7.00-8.00 (m, 9H, H-5, 6, 7, 8 and H-phenyl), 8.10 (s, 1H, H-4); ir (potassium bromide): 3380, 3080, 3060, 3010, 2970, 2930, 2900, 2870, 1640, 1620, 1600, 1565, 1540, 1490 cm^{-1}.

Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.84; N, 10.68; H, 5.38. Found: C, 77.6; N, 10.8; H, 5.44.

(2-Dimethylamino-3-quinolyl) Phenyl Ketone (**23**).

A mixture of (2-chloro-3-quinolyl) phenyl ketone (**18**) (1 g, 3.74 mmoles) and dimethylamine (30% aqueous solution, 30 ml) was warmed in a sealed tube at 140° for 20 hours. Extraction by chloroform (3 x 50 ml), drying over magnesium sulfate, removal of the solvent and addition of diethylether (50 ml) yielded 82% of **23**, mp = 117°; ^{1}H-nmr (deuteriochloroform): 3.00 (s, 6H, CH_3), 7.00-7.90 (m, 9H, H-5, 6, 7, 8 and H-phenyl), 7.95 (s, 1H, H-4); ir (potassium bromide): 3050, 3030, 2980, 2930, 2880, 1660, 1620, 1595, 1555, 1515, 1485 cm^{-1}.

Anal. Calcd. for $C_{18}H_{16}N_2O$: C, 78.24; N, 10.14; H, 5.84. Found: C, 78.1, N, 10.0; H, 5.95.

(2-Methoxy-3-quinolyl) Phenyl Ketone (**24**).

(2-Chloro-3-quinolyl) phenyl ketone (**18**) (1 g, 3.74 mmoles) was refluxed in a solution of sodium methylate (0.5 g of sodium, 22 mmoles) in methanol (25 ml) for 2 hours. Addition of water (25 ml) induced crystallization of 92% of **24** mp = 94°; ^{1}H-nmr (deuteriochloroform): 4.05 (s, 3H, OCH_3), 7.20-8.00 (m, 9H, H-5, 6, 7, 8 and H-phenyl), 8.10 (s, 1H, H-4); ir (potassium bromide): 3080, 3030, 2990, 2950, 2900, 2860, 1665, 1620, 1605, 1575, 1500, 1475 cm^{-1}.

Anal. Calcd. for $C_{17}H_{13}NO_2$: C, 77.55; N, 5.31; H, 4.98. Found: C, 77.5; N, 5.26; H, 4.83.

3-Formyl-2-quinolone (**25**) [15].

2-Chloroquinoline-3-carboxaldehyde (**12**) (1 g, 5.22 mmoles) was boiled with hydrochloric acid (6*N* aqueous solution, 50 ml) for 4 hours. Alkalinisation to *p*H 9 (solid sodium carbonate) filtration and washing with water (50 ml) yielded 98% of **25**, mp >250° (sublimes); ^{1}H-nmr (DMSO-d_6): 7.00-7.90 (m, 4H, H-5, 6, 7, 8), 8.40 (s, 1H, H-4), 10.15 (s, 1H, CHO), 12.05 (s, 1H, NH); ir (potassium bromide): 3420, 3260, 3150, 3090, 3060, 3000, 2940, 2870, 1690, 1675, 1620, 1500, 1490, 1475 cm^{-1}.

Anal. Calcd. for $C_{10}H_7NO_2$: C, 69.36; N, 8.09; H, 4.07. Found: C, 69.4; N, 8.04; H, 3.89.

2-Oxo-1,2-dihydroquinoline-3-carboxylic Acid (**26**) [16].

2-Chloro-3-quinolinecarboxylic acid (**13**) (1.15 g, 5.5 mmoles) was boiled with hydrochloric acid (6*N* aqueous solution, 50 ml) for 4 hours. Addition of water (50 ml), filtration and drying in a vacuum stove yielded 95% of **26**, mp >270°; ^{1}H-nmr (DMSO-d_6): 7.10-8.00 (m, 4H, H-5, 6, 7, 8), 8.80 (s, 1H, H-4), 13.50 (broad s, 2H, NH and CO_2H); ir (potassium bromide): 3170, 3090, 3070, 3030, 1720, 1650, 1595, 1550, 1505, 1480 cm^{-1}.

Anal. Calcd. for $C_{10}H_7NO_3$: C, 63.49; N, 7.40; H, 3.73. Found: C 63.2; N, 7.47; H, 3.66.

2-Methylamino-3-iodoquinoline (**27**).

2-Chloro-3-iodoquinoline (**15**) (1.4 g, 4.84 mmoles) was heated at 130° for 20 hours in a sealed tube with a mixture of methylamine (40% aqueous solution, 10 ml) and ethanol (10 ml). Addition of water (20 ml), filtration and drying under vacuum yielded 73% of **27**, mp = 84°; ^{1}H-nmr (deuteriochloroform): 3.15 (d, 3H, CH_3), 5.25 (m, 1H, NH), 7.00-7.85 (m, 4H, H-5, 6, 7, 8), 8.30 (s, 1H, H-4); ir (potassium bromide): 3420, 3040, 2990, 2950, 2900, 1615, 1595, 1555, 1525 cm^{-1}.

Anal. Calcd. for $C_{10}H_9IN_2$: C, 42.28; N, 9.86; H, 3.19. Found: C, 42.3; N, 9.68; H, 3.07.

2-Chloro-3-hydroxyquinoline (**28**).

2-Chloroquinoline-3-boronic acid (**14**) (1 g, 5 mmoles) in diethyl ether (20 ml) was stirred with a solution of ammonium chloride (0.5 g) in water (20 ml). Hydrogen peroxide (30% aqueous solution, 5 ml) was added dropwise and stirring was pursued for 4 hours. Filtration, washing with water (20 ml) and drying in a vacuum stove afforded 98% of **28**, mp >210°; ^{1}H-nmr (DMSO-d_6): 7.40-8.00 (m, 5H, H-4, 5, 6, 7, 8), 11.05 (s, 1H, OH); ir potassium bromide): 3420, 3060, 2990, 2950, 2920, 2870, 2800, 2750, 2720, 2680, 2600, 2520, 1620, 1600, 1585, 1510 cm^{-1}.

Anal. Calcd. for C_9H_6ClNO: C, 60.19; N, 7.80; H, 3.37. Found: C, 60.2; N, 7.82; H, 3.24.

3-Hydroxy-2-quinolone (**29**).

2-Chloro-3-hydroxyquinoline (**28**) (0.6 g, 3.34 mmoles) was boiled for 24 hours in hydrochloric acid (6*N* aqueous solution, 10 ml). Filtration, washing with water (10 ml) and drying in a vacuum stove yielded 84% of **29**, mp >220° (sublimes); ^{1}H-nmr (DMSO-d_6): 6.90-7.65 (m, 5H, H-4, 5, 6, 7, 8), 9.50 (s, 1H, OH), 12.10 (s, 1H, NH); ir (potassium bromide): 3270, 3160, 3050, 3000, 1655, 1625, 1610, 1575, 1505 cm^{-1}.

Anal. Calcd. for $C_9H_7NO_2$: C, 67.08; N, 8.69; H, 4.38. Found: C, 66.9; N, 8.54; H, 4.27.

12-Oxo-12*H*-benzopyranno[2,3-*b*]quinoline (**31**).

Chloroketone **30** (1.5 g, 5.0 mmoles) was boiled for 15 minutes with pyridinium chloride (50 ml) and the resulting hot mixture was poured on ice (80 g). Extraction with chloroform, drying over magnesium sulfate and evaporation to dryness afforded a crude product, which was purified by sublimation (0.076 mm Hg) to yield 87% of **31**, mp = 242°; ^{1}H-nmr (deuteriochloroform): 7.35-8.45 (m, 8H, H-1, 2, 3, 4, 7, 8, 9, 10), 9.30 (s, 1H, H-11); ir (potassium bromide): 3060, 3010, 1675, 1620, 1605, 1570, 1495, 1470

cm^{-1}.

Anal. Calcd. for $C_{16}H_9NO_2$: C, 77.72; N, 5.66; H, 3.67. Found: C, 77.6; N, 5.65; H, 3.39.

3-(2-Aminophenyl)-2-chloroquinoline (**32**).

2-Chloroquinoline-3-boronic acid (**14**) (1 g, 5.0 mmoles) and 2-iodoaniline (1 g, 5.0 mmoles) in a mixture of benzene (20 ml) and aqueous sodium carbonate (2*N* aqueous solution, 10 ml), were boiled under argon after addition of tetrakistriphenylphosphinopalladium (0) (0.1 g, 0.3 mmole). Reaction was monitored by thin layer chromatography (silicagel) using a mixture of diethyl ether and hexane (2/8). Warming was stopped after 7 hours and the aqueous layer was extracted with chloroform (2 x 20 ml). Drying over magnesium sulfate, solvent removal and purification by flash-chromatography on silica (diethyl ether/cyclohexane, 4/10) yielded 45% of **32**, mp = 152°; ^{1}H-nmr (DMSO-d_6); 4.85 (s, 2H, NH_2), 6.35-8.15 (m, 8H, H-5, 6, 7, 8 and H-phenyl), 8.25 (s, 1H, H-4); ir (potassium bromide): 3440, 3420, 3320, 3210, 3060, 3020, 1630, 1585, 1575, 1560, 1500, 1490 cm^{-1}.

Anal. Calcd. for $C_{15}H_{11}ClN_2$: C, 70.73; N, 11.00; H, 4.35. Found: C, 70.8; N, 11.0; H, 4.36.

Indolo[2,3-*b*]quinoline (**33**).

3-(2-Aminophenyl)-2-chloroquinoline (**32**) was reflux for 2 hours in acetic acid (10 ml). Addition of water (10 ml), filtration, washing with water (20 ml) and drying under vacuum yielded 90% of **33**, mp > 250° (sublimes); ^{1}H-nmr (DMSO-d_6): 7.00-8.30 (m, 8H, H-1, 2, 3, 4, 7, 8, 9, 10), 8.95 (s, 1H, H-11); 11.55 (broad s, 1H, NH); ir (potassium bromide): 3300, 2600, 1640, 1615, 1580, 1515, 1490, 1480, 1460 cm^{-1}.

Anal. Calcd. for $C_{15}H_{10}N_2$: C, 82.55; N, 12.83; H, 4.62. Found: C, 82.7; N, 12.8; H, 4.54.

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