Synthesis and Reactions of Isoquinoline Derivatives III.[1] Synthesis and Reactions of 3,4-Dihalogeno-1-phenylisoquinolines

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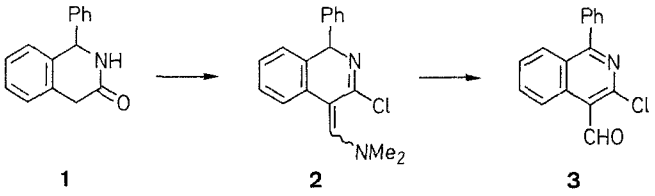
Dedicated to Prof. Edward C. Taylor on the occasion of his 65th birthday.

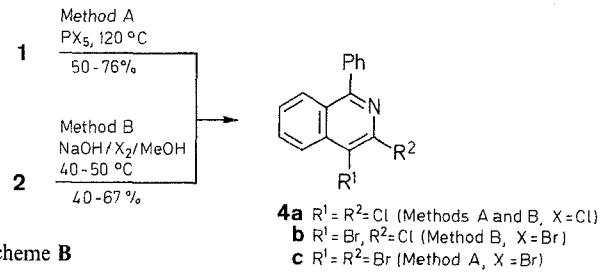
Reaction of 1-phenyl-1,4-dihydro-3(2*H*)isoquinolinone (**1**) with phosphorus pentahalides as well as a two-step procedure involving a Vilsmeier–Haack acylation of **1** followed by oxidative cleavage with sodium hypohalites make 3,4-dihalogeno-1-phenylisoquinolines easily available.

After a century of research on isoquinoline derivatives of natural and synthetic origin,[2,3] the present interest concentrates upon flexible synthetic routes to obtain special substitution patterns. During the past decade this approach has led to the development of several new compounds with interesting biological and pharmacological properties (e.g., see Refs. 4–7). In the preceding paper[1] we reported a new route to 3-chloro-1-phenylisoquinoline-4-aldehyde (**3**) starting from 1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone (**1**) by a Vilsmeier–Haack acylation reaction leading to 3-chloro-4-dimethylaminomethylene-1-phenyl-1,4-dihydroisoquinoline (**2**), followed by treatment with potassium permanganate in acidic solution (Scheme **A**).



Scheme **A**

During optimization trials, we tested the oxidation of **2** by aqueous sodium hypochlorite. Using phase-transfer conditions,[8] as well as homogenous reaction conditions[9] only small amounts of **3** can be isolated. Surprisingly, the main product in both cases is 3,4-dichloro-1-phenylisoquinoline (**4a**). Replacement of sodium hypochlorite by an aqueous solution of bromine in ice-cold sodium hydroxide yields 50% of the analogous 4-bromo-3-chloro compound (**4b**). Compound **4a** is formed in even better yield by the direct treatment of **1** with phosphorus pentachloride. Phosphorus pentabromide gives rise to the 3,4-dibromo derivative **4c** (Scheme **B**). The structure of the isoquinoline derivatives **4a–c** was proven by NMR double resonance decoupling experiments (Table). Similar results have been reported by a soviet group[10] while our work was still in progress.

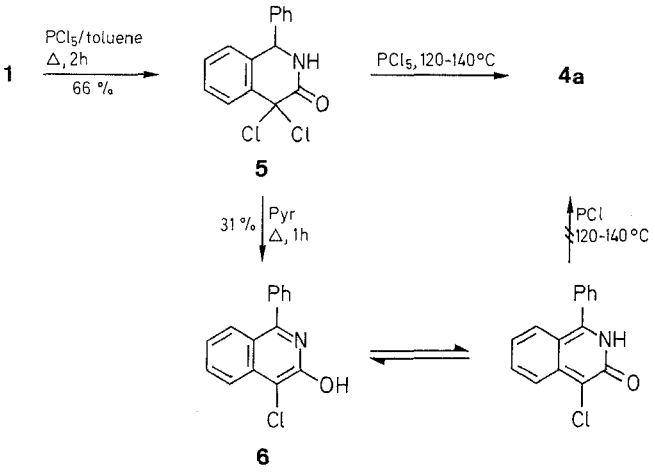


Scheme **B**

The direct conversion of **1** to **4a** by phosphorus pentachloride proceeds via the intermediate **5** which can be isolated under appropriate conditions (< 110 °C). Heating at 120–140 °C transforms **5** into **4a**. However, 4-chloro-1-phenylisoquinolin-3-ol (**6**), which is formed from **5** by heating in pyridine, does not react further to yield **4a** under the same conditions. (Scheme **C**). Compound **6** therefore, cannot be an intermediate in the reaction sequence **1** → **5** → **4a**. This is in agreement with

literature data which indicate quite drastic conditions for the substitution of hydroxy groups by chlorine in isoquinolin-3-ol derivatives.[11,12]

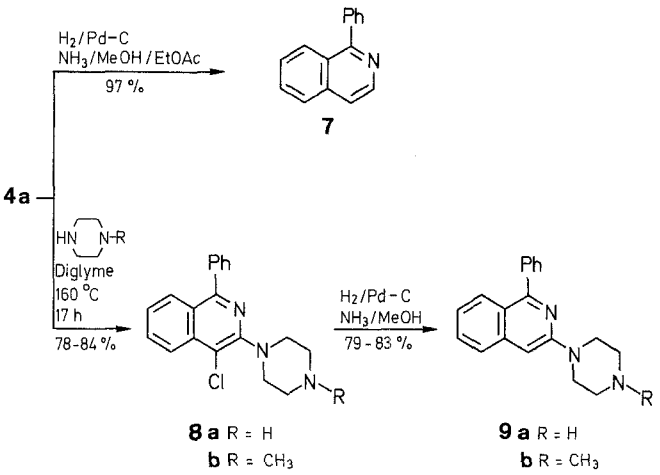
As is known for the corresponding halogen-free compound,[13] **6** exists in two tautomeric forms: The UV spectrum in ethanol shows two maxima at $\lambda = 344$ nm (lactim form) and $\nu = 426$ nm (lactam form), whereas in ether only the lactim absorption at $\lambda = 345$ nm can be observed.



Scheme **C**

The 3,4-dihalogeno-1-phenylisoquinoline derivatives **4a–c**, now easily accessible by our method, have high synthetic potential. For instance, dehydrohalogenation of **4a** with palladium on charcoal yields 1-phenylisoquinoline **7** quantitatively, thereby opening a very simple access to **7** from **1** in only two steps.

Regioselective substitution of the 3-chloro substituent in **4a** takes place by reaction with piperazine and *N*-methylpiperazine. The resulting 4-chloro-1-phenyl-3-piperazinoisoquinoline derivatives **8** can easily be transformed into the pharmacologically interesting 1-phenyl-3-piperazinoisoquinolines **9**[14] (**9a** = perafensine[5]) thus offering a new and improved synthesis of these compounds (Scheme **D**).



Scheme **D**

3,4-Dichloro-1-phenylisoquinoline (4a); Typical Procedures:

Method A: A mixture of 1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone (**1**;[15] 67 g, 0.3 mol) and PCl_5 (250 g, 1.2 mol) is stirred for 2 h at 115–120 °C and the mixture of $POCl_3$ and PCl_3 which is formed during the reaction is distilled off (*in vacuo* at the end, total volume 75 mL). After diluting with toluene (60 mL), MeOH (400 mL) is added, the mixture cooled to 0 °C and the precipitated product collected by filtration; yield 62.3 g (76 %), mp 162 °C.

Method B: To a solution of 3-chloro-4-dimethylaminomethylene-1,4-dihydroisoquinoline (**2**;[1] 29.7 g, 0.1 mol) in MeOH (1000 mL) at 40 °C aq. NaOCl (20 %, 140 mL) is added, the mixture stirred at 50 °C for 90 min, then cooled to 0 °C, the precipitate collected by filtration and washed well with water; yield: 21.1 g (**4a/3** = 97.5: 2.5). After recrystallization from acetone **4a** is obtained as pale yellow crystals; yield 18.4 g (67 %), mp 161–162 °C.

4-Bromo-3-chloro-1-phenylisoquinoline (4b):

According to Method B, compound **2** (29.7 g, 0.1 mol) is dissolved in MeOH (1000 mL) and a solution of bromine (37 g, 0.2 mol) in ice-cold aq. NaOH (10 %, 200 mL) added dropwise. The crude product (18.5 g, **4b/3** = 92.5/7.5) is recrystallized from MeOH (2000 mL) to which a trace of H_2SO_4 (0.5 mL) has been added; yield: 12.8 g (40 %); mp 162 °C; colorless needles.

3,4-Dibromo-1-phenylisoquinoline (4c):

According to Method A, compound **1** (6.7 g, 0.03 mol) is treated with PBr_5 (52 g, 0.12 mol) without distillation of the volatile reaction prod-

Table. Physical Data of New Compounds Prepared

Product	Yield (%)	mp (°C)	Molecular Formula[a]	^{1}H-NMR ($CDCl_3$/TMS)[b] δ, J(Hz)
4a	76	162	$C_{15}H_9Cl_2N$ (274.1)	7.47–7.58 (m, 3H, $Ph_{m,p}$); 7.595 (ddd, 1H, H-6); 7.63–7.72 (m, 2H, Ph_o); 7.83 (ddd, 1H, H-7); 8.105 (ddd, 1H, H-5); 8.29 (ddd, 1H, H-8)[c]
4b	40	162	$C_{15}H_9BrClN$ (318.6)	7.50–7.58 (m, 3H, $Ph_{m,p}$); 7.595 (ddd, 1H, H-6); 7.63–7.71 (m, 2H, Ph_o); 7.83 (ddd, 1H, H-7); 8.11 (ddd, 1H, H-5); 8.29 (ddd, 1H, H-8)[c]
4c	50	168–168.5	$C_{15}H_9Br_2N$ (363.1)	7.49–7.56 (m, 3H, $Ph_{m,p}$); 7.605 (ddd, 1H, H-6); 7.62–7.70 (m, 2H, Ph_o); 7.805 (ddd, 1H, H-7); 8.075 (ddd, 1H, H-5); 8.305 (ddd, 1H, H-8)[c]
5	66	171–172	$C_{15}H_{11}Cl_2NO$ (291.2)	5.77 (s, 1H, CHPh); 6.65 (br s, 1H, NH); 6.68–6.98 (m, 1H, H-6); 7.13–7.75 (m, $7H_{arom}$); 7.95–8.25 (m, 1H, H-8)
6	31	248–249	$C_{15}H_{10}ClNO$ (255.7)	7.23–8.17 (m, $9H_{arom}$); 11.8 (br s, 1H, OH)[d]
8a	84	119	$C_{19}H_{18}ClN_3$ (323.8)	1.65 (br s, 1H, NH); 2.90–3.27 (m, 4H, CH_2NHCH_2); 3.27–3.63 (m, 4H, CH_2NCH_2); 7.18–7.80 (m, $7H_{arom}$); 7.90–8.33 (m, 2H, H-5, H-8)
8b	78	96.5	$C_{20}H_{20}ClN_3$ (337.8)	2.40 (s, 3H, CH_3); 2.50–2.80 [m, 4H, $CH_2N(CH_3)CH_2$]; 3.20–3.70 (m, 4H, CH_2NCH_2); 7.12–7.83 (m, $7H_{arom}$); 7.90–8.33 (m, 2H, H-5, H-8)

[a] Satisfactory microanalyses obtained: C ±0.37, H ±0.25, Cl ±0.08; (exceptions: C −0.45 for **6**; Cl −0.46 for **4a**, +0.44 for **6**). Br −0.21 for **4e** (exception: Br −0.48 for **4b**).

[b] Recorded on a Varian T60 or Bruker WP 60 spectrometer at 60 MHz, unless otherwise noted.

[c] Recorded on a Bruker HX 270 spectrometer at 270 MHz; for all three spectra the following coupling constants were found: $J_{5,6} = \sim 8.5$ Hz, $J_{5,7} = \sim 1$ Hz, $J_{5,8} = \sim 1$ Hz, $J_{6,7} = \sim 7$ Hz, $J_{6,8} = \sim 1$ Hz, $J_{7,8} = 8.5$ Hz.

[d] Recorded in DMSO-d_6.

ucts. After dilution with toluene (10 mL), the product is precipitated by addition of cold MeOH (55 mL); yield: 6.1 g (50%); mp 168–168.5 °C; colorless needles.

4,4-Dichloro-1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone (5):
A solution of **1** (67 g, 0.3 mol) and PCl_5 (250 g, 1.2 mol) in toluene (600 mL) is refluxed for 2 h. Then a mixture of toluene/$POCl_3$/PCl_3 (450 mL) is distilled off at 20 mbar. MeOH (300 mL) is added to the residue and the precipitate formed on cooling to −5 °C is collected by filtration (64.3 g). The crude product is stirred vigorously in methylcyclohexane (500 mL) at 90 °C for 30 min and again collected by filtration; yield: 57.6 g (66%); mp 171–172 °C, pale yellow crystals.

4-Chloro-1-phenylisoquinolin-3-ol (6):
A solution of **6** (11.7 g, 0.04 mol) in pyridine (80 mL) is refluxed for 1 h. The solvent is removed by evaporation and the oily residue stirred with MeOH (40 mL) at 0 °C. The crude brownish precipitate is purified by chromatography on silica (EtOAc); yield: 3.2 g (31%); mp 248–249 °C; dark yellow crystals.

UV (EtOH): λ_{max} = 344 (4875), 426 (1500) nm.

UV (ether): λ_{max} = 345 (6250) nm.

1-Phenylisoquinoline (7):
A solution of **4a** (34.6 g, 0.136 mol) in a mixture of EtOAc (1000 mL) and sat. methanolic ammonia (250 mL) is hydrogenated with Pd/C (10%, 2 g) at room temperature at 1 bar of hydrogen pressure during 2.5 h. After filtration, the solution is evaporated *in vacuo*, the crystalline residue stirred with water and collected by filtration; yield: 27.2 g (97%); mp 92–95 °C (Lit.[16] mp 97 °C); colorless crystals.

4-Chloro-1-phenyl-3-piperazinoisoquinoline (8a):
A solution of **4a** (8.3 g, 0.03 mol) and piperazine (26 g, 0.3 mol) in diglyme (50 mL) is stirred at 160 °C for 17 h. After cooling the mixture is diluted with toluene (100 mL) and washed with brine (50 mL), and water (3 × 50 mL), dried ($MgSO_4$), and evaporated. The oily yellow residue (11.4 g) is treated with diisopropyl ether (75 mL), cooled to 0 °C and the precipitate collected by filtration; yield: 8.2 g (84%); mp 119 °C; yellow crystals.

4-Chloro-3-(4-methylpiperazino)-1-phenylisoquinoline (8b):
The compound **8b** is obtained from **4a** (8.2 g, 0.03 mol) and *N*-methylpiperazine (30 g, 0.3 mol) as described above for the synthesis of **8a**. The crude product (11.3 g) is recrystallized from diisopropyl ether; yield: 7.9 g (78%); mp 96.5 °C; pale yellow needles.

1-Phenyl-3-piperazinoisoquinoline Hydrochloride (9a); Typical Procedure:
A solution of **4a** (6.5 g, 0.02 mole) in a mixture of MeOH (100 mL) and methanolic ammonia (15%, 30 mL) is hydrogenated with Pd/C (10%, 3 g) at room temperature under 1 bar of hydrogen pressure for 12 h. After filtration the solution is evaporated and the crude product stirred vigorously with acetone (40 mL); yield: 5.4 g (83%) mp 285 °C (Lit.[14] mp 284–287 °C); pale yellow crystals.

9b: HCl; yield: 79%; mp 281 °C (Lit.[14] mp 278–282 °C); light green-yellowish crystals.

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