SYNTHESIS OF IMIDAZONAPHTHYRIDINES AND -QUINOLINES

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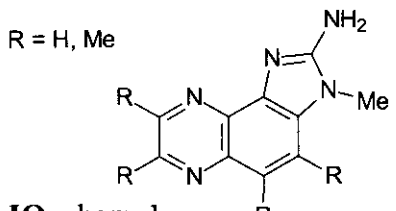
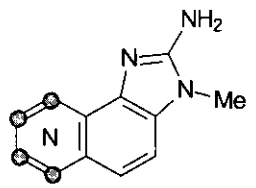
Abstract — Four 2-amino-3-methylimidazo[4,5-*b*][1,*x*]naphthyridines, $x = 5–8$ (**6–9**) have been obtained from aromatic aldehydes (**11–14**) and 2-amino-1-methyl-2-imidazolin-5-one (**15**) in one step. The N^1- and N^3-methyl isomers of 2-aminoimidazo-[4,5-*b*]quinoline (**5** and **10**) were prepared from 2-nitrobenzaldehyde *via* the isolated *E*-isomers of imidazolin-5-one (**17**) and imidazolin-4-one (**20**).

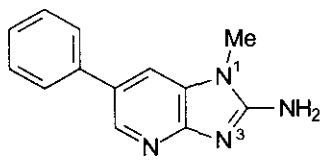
The imidazo[4,5-*f*]quinoxalines[1a] (**IQx** homologues), -quinolines[1b] (**IQ** isomers), imidazo[4,5-*b*]-pyridines[1c] (**PhIP** and **DMIP** isomers) and related linear compounds, such as **1–5**,[1d,e] belong to a group of mutagenic heterocyclic amines to which we are continuously exposed since they are present in airborne particles, cigarette smoke condensate, and in cooked food.[1,2] Some of them have been connected with cardiovascular diseases and found to be carcinogenic in rodents and nonhuman primates.[1,2]



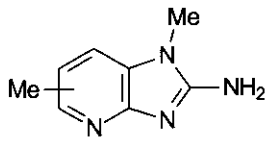
IQx homologues



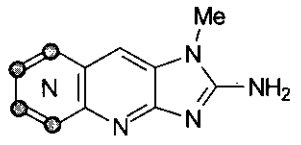
IQ isomers



PhIP



DMIP isomers



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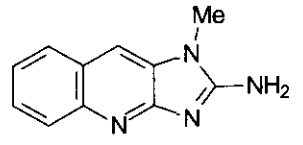

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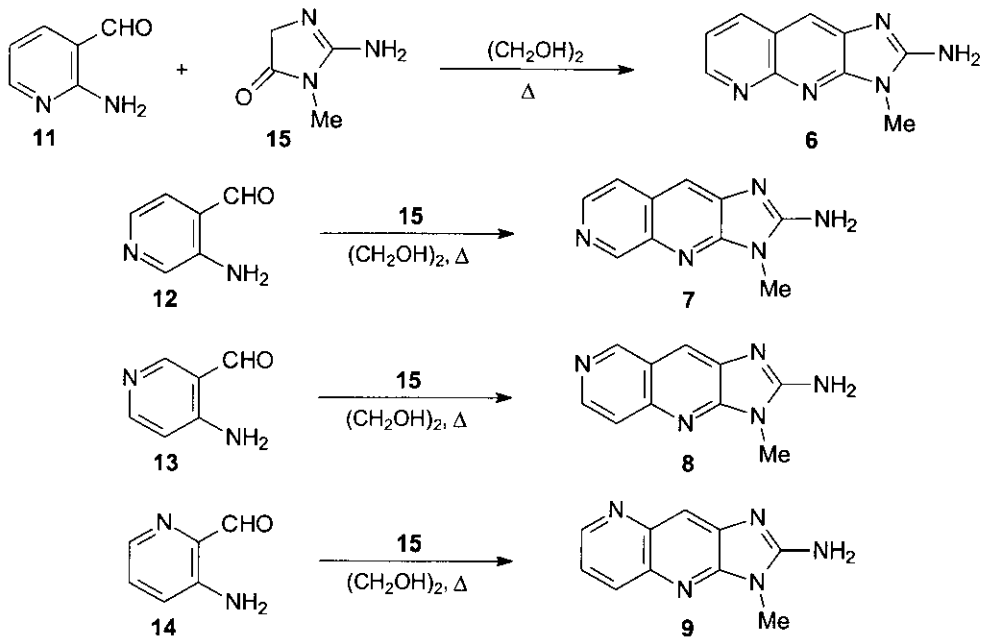
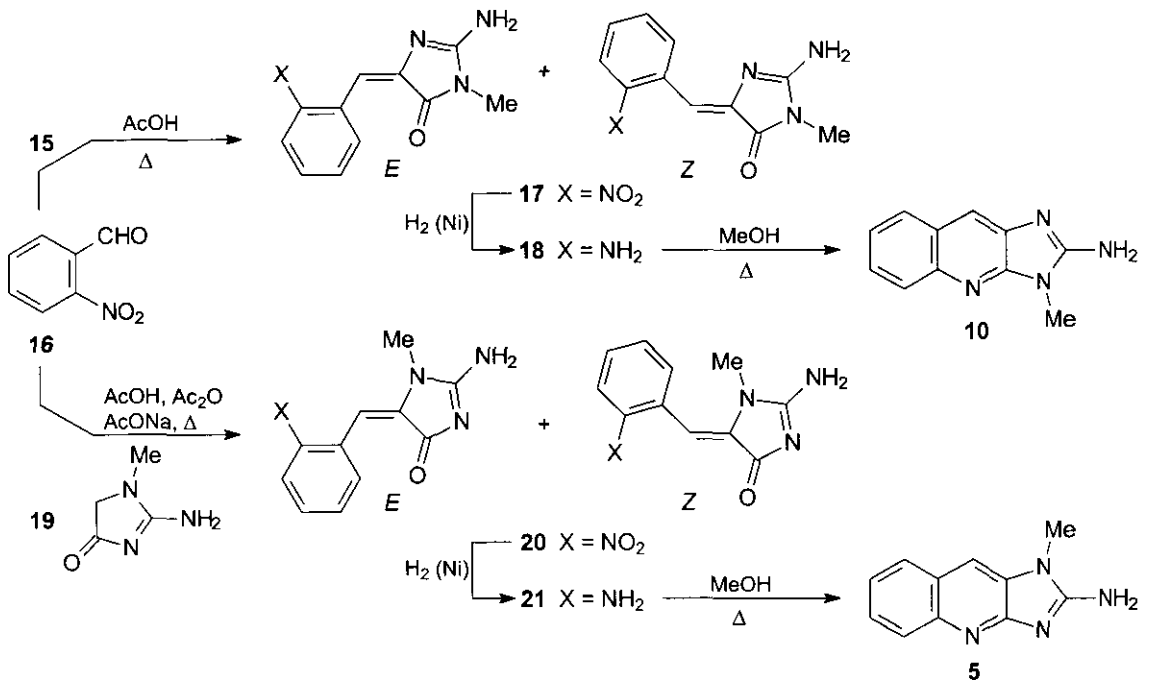
Methods that provide exclusively the N^1- and the N^3-methyl isomer are desirable because apart from the possible separation difficulties after a methylation step, the two compounds can have very different biological activities. For example, the 3-methyl isomer of **PhIP** was found to be much less active than **PhIP** itself in the Ames test.[1f] Thus, any contamination by the other isomer

would give wrong biological activity results. In connection with previous structure–activity studies[3] we needed the imidazonaphthyridines (**6–9**) and -quinoline (**10**). We also wished to compare the outcome of the condensation between isocreatinine[4] (**15**) and aromatic aldehydes (**11–14**) to that previously reported[1d] from the Friedländer reaction of creatinine (**19**) with these aldehydes. We now report that the desired **6–9** can be prepared in 35–45% yield by heating isocreatinine with **11–14** in ethylene glycol. Under similar conditions, their isomers (**1–4**) were obtained in 65–85% yield from **11–14** and creatinine.[1d] Thus, the N^1- and the N^3-methyl isomers of these imidazonaphthyridines can be prepared free from each other.



For the synthesis of the imidazoquinoline (**5**)[1e] and its isomer (**10**) a different approach was employed. Treatment of both isocreatinine (**15**) and creatinine (**19**) with 2-nitrobenzaldehyde (**16**) in ethylene glycol[1d,e] or piperidine,[5] produced neither **17** nor **20**. Condensation of isocreatinine with **16** under Perkin conditions[6] i.e., reflux in a mixture of sodium acetate, acetic acid and its anhydride, gave *N*-acetylated products. However, their reaction in acetic acid alone afforded the expected **17** in 13% yield. On the other hand, reaction of creatinine with **16** under Perkin conditions did furnish **20** (24%) with no formation of *N*-acetylated products. Flash chromatography of the geometrical isomers on silica gel, reduction (H_2/Raney Ni) of (*E*)-**17** to **18** and of (*E*)-**20** to **21**, and subsequent cyclization of the crude amines by heating in methanol afforded **10** in 50% yield from (*E*)-**17**, and **5** in 75% yield from (*E*)-**20**. The condensation of creatinine with **16** in acetic acid gave no **20**. Similarly, treatment of both isocreatinine and creatinine with **16** in acetic anhydride gave no **17** or **20**. Interestingly, upon standing at 8 °C in the presence of moisture, (*Z*)-**20** was converted into the 2-hydroxy analogue (**22**, not shown). No such spontaneous hydrolysis of **17** or (*E*)-**20** could be detected.



Numerous *E*- and *Z*-isomers of arylideneimidazolinones and -imidazolidinediones have been synthesized and distinguished by X-Ray crystallography, UV-, IR-, and NMR spectroscopy.[5,7] One of the most unambiguous, general and efficient differentiation methods is to look at the long range ($^3J_{CH}$) coupling between the carbonyl carbon and the olefinic hydrogen, since the *E*-isomers have a $^3J_{CH}$ which can be twice as large as that of the *Z* isomers,[7,8] (see experimental part).

EXPERIMENTAL

Organic solvents were of analytical grade and used as purchased. Evaporations were performed at reduced pressure below 40 °C. The reactions and purifications were monitored by TLC (UV detection) on aluminium sheets coated with silica gel 60 F_{254} (Merck); solvent mixtures A: $CHCl_3$–MeOH–aq. 25% NH_3, 4:1:0.03 and B: $CHCl_3$–MeOH–aq. 25% NH_3, 7:1:0.03 by volume ratios. Flash and 'dry flash' chromatography[9] were performed on silica gel (35–60 μ, Grace). Melting points (uncorrected) were determined on a Mettler FP62. EI mass spectra (direct insertion, 70 eV) were obtained on a Jeol JMS-SX/SX102A. All ^{1}H and ^{13}C NMR spectra were recorded in [$^2H_6$]DMSO on a Bruker DRX 400 at 30 °C and referenced to the solvent (δ 2.50 and 39.5) unless otherwise stated. Assignments were done using HMBC and HMQC experiments; the $^3J_{CH}$ constants for differentiation of the geometrical isomers were obtained by HMBC experiments. FTIR (KBr) spectra were recorded on a Perkin Elmer 1760X.

Materials.—Compounds (**11**–**14**) were prepared as previously reported[1d] and **15** *via* methylation of glycocyamidine.[4]

2-Amino-1-methylimidazo[*4,5*-b]*quinoline* (**5**).—Compound (*E*)-**20** (100 mg, 0.41 mmol) was dissolved in methanol (30 mL) and ethyl acetate (40 mL). Raney nickel (*ca.* 1.5 mL) was added, and the mixture was hydrogenated under ambient conditions for 15 min (TLC: A). The catalyst was filtered off on a celite bed and the solvents removed. The crude **21** [δ_H 3.18 (Me, s), 5.1 (2 NH_2, br s), 6.06 (H-6, s), 6.45 (H-4', app. t, *J* 7.4), 6.63 (H-3', app. d, *J* 8.0), 6.95 (H-5', app. t, *J* 7.6), 7.78 (H-6', app. d, *J* 7.9)] was immediately dissolved in methanol (70 mL) and heated at reflux overnight, under nitrogen and in the presence of molecular sieves. After removal of the solvent the residue was recrystallized from aqueous ethanol to give **5** (60 mg; 75% from (*E*)-**20**) which was identical with an authentic sample;[1e] δ_C 28.7 (Me), 109.1 (C-9), 122.3 (C-7), 124.3 (C-8a), 125.7 (C-6), 127.2 (C-5), 127.5 (C-8), 129.5 (C-3a), 144.6 (C-4a), 158.8 (C-9a), 161.5 (C-2).

Condensation of **11–14** *with* **15**.—The appropriate aldehyde (100 mg, 0.82 mmol) and **15** (140 mg, 1.24 mmol) in ethylene glycol (1 mL) were heated at 140 °C under nitrogen. After a few min the mixture became clear and within 1.5 h the reaction was complete (TLC: B). The solvent was removed, and the crude product was flash chromatographed on silica gel (B). Recrystallization (aq. MeOH) gave pure product.

2-Amino-3-methylimidazo[*4,5*-b][*1,8*]*naphthyridine* (**6**): yield 40%; mp >300 °C. *Anal.* Calcd for $C_{10}H_9N_5$: C, 60.3; H, 4.6; N, 35.2. Found: C, 60.2; H, 4.6; N, 35.1; MS, *m/z* 199 (M^+, 100%); δ_H 3.63 (Me, s), 7.38 (H-7, dd, *J* 8.1 and 4.3), 7.5 (NH_2, br s), 7.80 (H-9, s), 8.32 (H-8, dd, *J* 8.1 and 1.9), 8.75 (H-6, dd, *J* 4.0 and 1.6); δ_C 27.2 (Me), 115.5 (C-9), 118.7 (C-7), 120.8 (C-8a), 136.4 (C-8), 137.0 (C-9a), 148.1 (C-6), 150.8 (C-4a), 152.6 (C-3a), 159.5 (C-2).

2-Amino-3-methylimidazo[*4,5*-b][*1,7*]*naphthyridine* (**7**): yield 36%; mp >300 °C. *Anal.* Calcd for $C_{10}H_9N_5$: C, 60.3; H, 4.6; N, 35.2. Found: C, 60.1; H, 4.5; N, 35.2; MS, *m/z* 199 (M^+, 100%); δ_H 3.61 (Me, s), 7.63 (H-8, d, *J* 5.9), 7.8 (NH_2, br s), 7.91 (H-9, s), 8.42 (H-7, d, *J* 5.8), 9.12 (H-5, s); δ_C 28.2 (Me), 107.7 (C-9), 120.1 (C-8), 122.1 (C-8a), 130.8 (C-9a), 142.9 (C-7), 147.8 (C-4a), 150.5 (C-5), 151.5 (C-3a), 163.1 (C-2).

2-Amino-3-methylimidazo[*4,5*-b][*1,6*]*naphthyridine* (**8**): yield 43%; mp >300 °C. *Anal.* Calcd for $C_{10}H_9N_5$: C, 60.3; H, 4.6; N, 35.2. Found: C, 60.3; H, 4.5; N, 35.0; MS, *m/z* 199 (M^+, 100%); δ_H 3.61 (Me, s), 7.5 (NH_2, br s), 7.72 (H-5, d, *J* 5.8), 7.89 (H-9, s), 8.42 (H-6, d, *J* 5.7), 9.18 (H-8, s); δ_C 27.9 (Me), 115.1 (C-9), 120.1 (C-5), 143.3 (C-6), 145.1 (C-8a), 145.4 (C-4a), 152.0 (C-8), 152.3 (C-9a), 153.9 (C-3a), 160.3 (C-2); MS, *m/z* 199 (M^+, 100%).

2-Amino-3-methylimidazo[*4,5*-b][*1,5*]*naphthyridine* (**9**): yield 45%; mp >300 °C. *Anal.* Calcd for $C_{10}H_9N_5$: C, 60.3; H, 4.6; N, 35.2. Found: C, 60.1; H, 4.6; N, 35.1; MS, *m/z* 199 (M^+, 100%); δ_H 3.63 (Me, s), 7.37 (H-6, dd, *J* 8.0 and 4.2), 7.4 (NH_2, br s), 7.79 (H-9, s), 8.30 (H-5, dd, *J* 8.1 and 1.9), 8.73 (H-7, dd, *J* 4.2 and 1.9); δ_C 27.2 (Me), 115.6 (C-9), 118.7 (C-6), 120.9 (C-8a), 136.4 (C-9a), 137.3 (C-5), 148.2 (C-7), 150.8 (C-4a), 152.7 (C-3a), 159.7 (C-2).

2-Amino-3-methylimidazo[*4,5*-b]*quinoline* (**10**).—Reduction of (*E*)-**17** as described under compound **5** afforded crude **18** [δ_H 2.99 (Me, s), 5.9 (2 NH_2, br s), 6.21 (H-6, s), 6.46 (H-4', app. t, *J* 7.0), 6.58 (H-3', app. d, 7.9), 6.86 (H-5', td, *J* 6.9 and 1.2), 7.79 (H-6', app. d, *J* 7.5)] which on cyclization afforded **10** in 50% yield (mp >300 °C) from (*E*)-**17**. *Anal.* Calcd for $C_{11}H_{10}N_4$: C, 66.6; H, 5.1; N, 28.3. Found: C, 66.6; H, 5.1; N, 28.2; MS, *m/z* 198 (M^+, 100%); δ_H 3.71 (Me, s),

7.41 (H-7, ddd, *J* 8.1, 6.9 and 1.2), 7.54 (H-6, ddd, *J* 8.5, 6.9 and 1.5), 7.83 (H-9, s), 7.88 (H-8, dd, *J* 8.2 and 1.4), 7.96 (H-5, dt, *J* 8.5 and 0.5); δ_C ([$^2H_4$]methanol) 27.4 (Me), 118.9 (C-9), 123.5 (C-8a), 124.5 (C-7), 127.4 (C-6), 127.5 (C-5), 128.7 (C-8), 142.8 (C-4a), 144.2 (C-9a), 150.5 (C-3a), 159.6 (C-2).

2-Amino-1-methyl-4-(2-nitrobenzylidene)-2-imidazolin-5-one (**17**).—Compounds (**15**) (550 mg, 4.9 mmol) and (**16**) (680 mg, 4.5 mmol) in acetic acid (6.5 mL) were heated under nitrogen at 100 °C for 60 min. The solvent was removed and the residue was 'dry flash' chromatographed on silica gel (B). Fractions containing each isomer were then flash chromatographed on silica gel (A). Recrystallization (aq. MeOH) yielded pure isomers.

(*E*)-**17**: yield 5%; mp 228–230 °C. *Anal.* Calcd for $C_{11}H_{10}N_4O_3$: C, 53.6; H, 4.1; N, 22.8; O, 19.5. Found: C, 53.5; H, 4.0; N, 22.7; MS, *m/z* 246 (M^+, 14%); δ_H 3.13 (Me, s), 6.61 (H-6, s), 7.48 (H-4', app. dd, *J* 7.8 and 1.3), 7.73 (H-5', app. t, *J* 7.4), 7.96 (H-3', app. dd, *J* 8.1 and 1.1), 8.0 (NH_2, br s), 8.98 (H-6', dd, *J* 8.1 and 1.2); δ_C 26.9 (Me), 103.3 (C-6), 125.3 (C-3'), 128.5 (C-4'), 130.7 (C-1'), 132.7 (C-6'), 133.5 (C-5'), 145.9 (C-4), 149.4 (C-2'), 162.8 (C-2), 170.6 (C-5, $^3J_{CH-6}$ 8.6).

(*Z*)-**17**: yield 8%; mp 212.0–213.5 °C. *Anal.* Calcd for $C_{11}H_{10}N_4O_3$: C, 53.6; H, 4.1; N, 22.8; O, 19.5. Found: C, 53.5; H, 4.1; N, 22.6; MS, *m/z* 246 (M^+, 16%); δ_H 3.07 (Me, s), 6.55 (H-6, s), 7.41 (H-4', app. dd, *J* 7.2 and 1.3), 7.66 (H-5', app. t, *J* 7.4), 7.90 (H-3', dd, *J* 8.2 and 1.3), 8.0 (NH_2, br s), 8.91 (H-6', dd, *J* 8.0 and 1.3); δ_C 25.7 (Me), 102.1 (C-6), 124.1 (C-3'), 127.3 (C-4'), 129.6 (C-1'), 131.5 (C-6'), 132.3 (C-5'), 144.5 (C-4), 148.2 (C-2'), 161.6 (C-2), 169.4 (C-5, $^3J_{CH-6}$ 4.5).

2-Amino-1-methyl-5-(2-nitrobenzylidene)-2-imidazolin-4-one (**20**).—Compounds (**16**) (1.95 g, 12.9 mmol) and (**19**) (1.55 g, 13.72 mmol) in a mixture of acetic acid (15 mL), acetic anhydride (4.6 mL) and sodium acetate (5.12 g) were heated at reflux under nitrogen for 60 min (TLC: B). The mixture was poured on ice-water and the precipitate was filtered off. This was crystallized (aq. MeOH) to give (*E*)-**20**. The solvents of the first mother liquor were removed and the residue was crystallized (MeOH) to yield (*Z*)-**20**.

(*E*)-**20**: yield 11%; mp 258–259 °C. *Anal.* Calcd for $C_{11}H_{10}N_4O_3$: C, 53.6; H, 4.1; N, 22.8; O, 19.5. Found: C, 53.5; H, 4.1; N, 22.7; MS, *m/z* 246 (M^+, 27%); δ_H 3.18 (Me, s), 6.41 (H-6, s), 7.51 (H-4', td, *J* 7.9 and 1.4), 7.63 (H-5', td, *J* 7.5 and 1.2), 7.76 (H-3', dd, *J* 8.0 and 0.6), 7.9 (NH, br s), 8.01 (H-6', dd, *J* 8.2 and 1.2), 8.4 (NH, br s); δ_C 28.7 (Me), 107.2 (C-6), 124.8 (C-6'), 129.3 (C-1'), 129.9 (C-4'), 133.3 (C-5'), 133.9 (C-3'), 136.6 (C-5), 148.8 (C-2'), 168.3 (C-2), 175.2 (C-4, $^3J_{CH-6}$ 7.8).

(*Z*)-**20**: yield 13%; mp 263–264 °C. *Anal.* Calcd for $C_{11}H_{10}N_4O_3$: C, 53.6; H, 4.1; N, 22.8; O, 19.5. Found: C, 53.5; H, 4.1; N, 22.6; MS, *m/z* 246 (M^+, 30%); δ_H 3.08 (Me, s), 6.63 (H-6, s), 7.57 (H-4', td, *J* 7.3 and 1.1), 7.69 (H-5', td, *J* 7.4 and 1.1), 7.72 (H-3', d, *J* 7.1), 8.07 (H-6', d, *J* 8.2), 8.1 (NH, br s); δ_C 25.8 (Me), 108.7 (C-6), 124.2 (C-6'), 128.4 (C-1'), 129.0 (C-4'), 131.3 (C-5), 132.3 (C-5'), 132.8 (C-3'), 147.6 (C-2'), 153.5 (C-4, $^3J_{CH-6}$ 3.8), 162.4 (C-2).

2-Hydroxy-1-methyl-5-(2-nitrobenzylidene)-2-imidazolin-4-one (**22**): mp 258.5–260.5 °C. *Anal.* Calcd for $C_{11}H_9N_3O_4$: C, 53.4; H, 3.7; N, 17.0; O, 25.9. Found: C, 53.3; H, 3.7; N, 16.9; MS, *m/z* 247 (M^+, 21%); δ_H 3.08 (Me, s), 6.62 (H-6, s), 7.56 (H-4', app. t, *J* 7.4), 7.65–7.75 (H'-5 and H-6', m), 8.07 (H-3', d, *J* 8.1), 11.3 (OH, br s); δ_C 25.8 (Me), 108.8 (C-6), 124.2 (C-3'), 128.9 (C-1'),

129.2 (C-4'), 131.5 (C-5), 132.8 (C-5' or C-6'), 132.9 (C-6' or C-5'), 147.7 (C-2'), 153.6 (C-2), 162.5 (C-4); FTIR (KBr): 3203, 3076, 1764, 1728, 1650, 1519, 1439, 1365, 1337, 1121, 1066 cm^{-1}.

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