A Convenient Synthesis of Mutagenic 3*H*-Imidazo[4,5-*f*]-quinolin-2-amines and Their 2-^{14}C-Labelled Analogues

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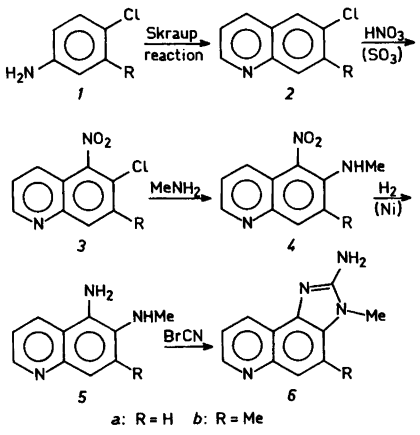
Several compounds, identified in meat or fish after heating, show high mutagenic activity. In Ames' test,[1] the title compounds *6a* ("IQ") and *6b* ("MeIQ") are among the most potent mutagens known for *Salmonella typhimurium* TA 98 after activation by liver S-9 fraction.[2] Both *6a*[3] and *6b*[4] have been synthesized. The last step in each synthesis is the introduction of the *N*-methyl group. The reaction yields a mixture of methyl derivatives, which is particularly regrettable when isotopically labelled *6a* or *6b* is needed (*e.g.*, in metabolic studies). This difficulty is avoided in the present syntheses of *6a* and *6b*, the last step being cyclization with cyanogen bromide, which is readily available in (^{13}C- or) ^{14}C-labelled form.[5]

The synthetic route is outlined in Scheme 1 and is based on work by Soviet scientists. This work includes the synthesis of *5a* essentially according to the scheme[6] and its cyclization to 3*H*-imidazo[4,5-*f*]quinolines other than *6*.[7] Among the apparently unknown intermediates *2b–5b*, *2b* was accompanied by its known[8] 5-methyl isomer and *3b* by a small amount of its 8-nitro isomer.



Scheme 1.

The unwanted isomers were readily removed by crystallization.

Experimental. All reactions and purifications were monitored by TLC on silica gel (Riedel-de Haën, SIF) or by GLC on a 25 m×0.24 mm i.d. capillary column coated with CP Sil 5 and heated from 100 to 250 °C at 10 °C/min. The TLC spots were visualized by UV irradiation. Column chromatography (CC) of unlabelled mixtures was performed by the "flash" technique.[9] Evaporations were performed at reduced pressure below 40 °C. Melting points are corrected. Mass spectra were recorded at 70 eV, using electron impact and direct insertion. ^{1}H NMR spectra were recorded at 90 MHz and *ca.* 30 °C.

*3-Methyl-3*H*-imidazo[4,5-*f*]quinolin-2-amine* (*6a*) was prepared from 6-chloroquinoline (*2a*)[10] exactly as described below for the sequence *2b–6b*, but the separation of isomers was, of course, superfluous.

Compound	*3a*	*4a*	*5a*	*6a*
Yield (%)	86	88	65	75
Cryst. from	CCl_4	Me_2CO	PhMe	C_5H_5N
M.p. (°C) obs.	129	194	168–169	>300
M.p. (°C) lit.	129[10]	190[6]	179–180[6]	>300[3]

Although the melting points of *4a* and *5a* differed from those reported,[6] the mass and ^{1}H NMR spectra completely confirmed their formulas. The product *6a* was identical (MS, ^{1}H NMR, UV) with a sample provided by T. Sugimura.[3]

6-Chloro-7-methylquinoline (2b). 4-Chloro-*m*-toluidine (*1b*)[11] was subjected to the Skraup reaction as described for aniline.[12] GLC analysis of the product (yield *ca.* 80 %) showed almost only *2b* and its 5-methyl isomer, eluted in that order and with the relative peak heights 2:1. About half of the *2b* was isolated by crystallization from diethyl ether. The isomers in the mother liquor were readily separated by crystallization of their picrates from *N*,*N*-dimethylformamide. From the less soluble picrate, 1 M sodium hydroxide liberated *2b*. After crystallization from light petroleum (b.p. 40–60 °C), the total yield of *2b*, m.p. 82.5–83 °C, was 45–50 %. Anal. $C_{10}H_8ClN$: C, H, N. MS, *m/e* (rel. int.): 177 (100, M), 142 (98), 179 (31), 141 (30), 63 (19), 71 (17), 115 (16), 140 (15), 114 (15), 178 (14). ^{1}H NMR ($CDCl_3$): δ 2.59 (Me, d), 7.36 (3-H, dd), 7.83 (5-H, s), 7.97 (8-H, m), 8.05 (4-H, dm), 8.87 (2-H, dd); $|J|$ 0.85 (7,8), 1.65 (2,4), 4.2 (2,3), 8.3 (3,4) Hz.

6-Chloro-5-methylquinoline, m.p. 79.5–80 °C (lit.[8] 81–82 °C), was obtained from its picrate as described for *2b*. The ^{1}H NMR spectral data agreed with those reported.[8]

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6-Chloro-7-methyl-5-nitroquinoline (3b). Conc. sulfuric acid (3 ml) was added dropwise to *2b* (8.9 g, 50 mmol), stirred with a glass rod. After cooling, the resulting salt was stirred with more acid (30 ml) until completely dissolved. To the stirred and cooled solution was added fuming sulfuric acid (65 % SO_3, 9 ml) in one portion, followed by ≥96 % nitric acid (9 ml) added over 30 min below 20 °C. After another 10 min without cooling, the solution was poured on to ice (500 g), neutralized with ammonia and extracted with chloroform. The extract was washed with water, analysed by GLC and evaporated. The analysis showed almost only *3b* and its 8-nitro isomer, eluted in that order and with the relative peak heights 19:4. Crystallization of the residue from methanol yielded *3b* (8.4 g, 75 %), m.p. 127–127.5 °C. Anal. $C_{10}H_7ClN_2O_2$: C, H, N. MS, *m/e* (rel. int.): 141 (100), 222 (69, M), 140 (39), 164 (37), 192 (34), 176 (29), 114 (26), 63 (24), 224 (22), 113 (22). ^{1}H NMR ($CDCl_3$): δ 2.66 (Me, d), 7.52 (3-H, dd), 7.98 (4-H, ddd), 8.15 (8-H, m), 8.98 (2-H, dd); $|J|$ 0.85 (4,8), 0.95 (7,8), 1.65 (2,4), 4.2 (2,3), 8.7 (3,4) Hz.

6-Chloro-7-methyl-8-nitroquinoline, m.p. 213–213.5 °C, was obtained from the mother liquor by evaporation, CC ($CHCl_3$–EtOAc, 1:1 v/v) and crystallization from methanol. Anal. $C_{10}H_7ClN_2O_2$: C, H, N. MS, *m/e* (rel. int.): 141 (100), 222 (65, M), 205 (41), 140 (40), 192 (34), 63 (32), 114 (31), 113 (28), 128 (26), 129 (25). ^{1}H NMR ($CDCl_3$): δ 2.55 (Me, s), 7.51 (3-H, dd), 7.99 (5-H, s), 8.14 (4-H, dd), 8.97 (2-H, dd); $|J|$ 1.7 (2,4), 4.3 (2,3), 8.4 (3,4) Hz.

N,*7-Dimethyl-5-nitro-6-quinolinamine* (4b). 40 % aq. methylamine (17 g, 220 mmol) was added over 1 h to a refluxing solution of *3b* (8.0 g, 36 mmol) in 95 % ethanol (100 ml). After refluxing for another 4 h, GLC or TLC ($CHCl_3$–EtOAc, 1:1 v/v) showed no *3b*. The solution was then poured on to ice-water and extracted with chloroform. The extract was washed with water and evaporated. Crystallization of the residue from methanol yielded *4b* (6.6 g, 85 %), m.p. 161–162 °C. Anal. $C_{11}H_{11}N_3O_2$: C, H, N. MS, *m/e* (rel. int.): 217 (100, M), 142 (52), 143 (46), 170 (40), 156 (31), 144 (29), 141 (28), 172 (28), 200 (27), 115 (27). ^{1}H NMR ($CDCl_3$): δ 2.46 (7-Me, d), 3.00 (NMe, d), 5.2 (NH, broad s), 7.40 (3-H, dd), 7.88 (8-H, m), 8.18 (4-H, ddd), 8.69 (2-H, dd); $|J|$ 0.8 (4,8), 0.85 (7,8), 1.5 (2,4), 4.3 (2,3), 5.6 (*N,N*), 8.7 (3,4) Hz.

N^6,*7-Dimethyl-5,6-quinolinediamine* (5b). A vigorously stirred mixture of *4b* (3.26 g, 15.0 mmol), Raney nickel (3 teaspoons) and abs. ethanol (185 ml) was hydrogenated under ambient conditions. After *ca.* 90 min, the calculated amount (1.1 l) of hydrogen had been absorbed. The catalyst was then filtered off quickly and the filtrate evaporated. CC ($CHCl_3$–MeOH, 19:1 v/v) of the dark residue yielded *5b* (1.94 g, 69 %). After crystallization from toluene, *5b* melted at 131–132.5 °C. Anal. $C_{11}H_{13}N_3$: C, H, N. MS, *m/e* (rel. int.): 172 (100), 187 (92, M), 145 (60), 173 (13), 188 (12), 144 (12), 117 (10), 142 (9), 159 (8), 51 (8). ^{1}H NMR ($CDCl_3$): δ 2.48 (7-Me, d), 2.74 (NMe, s), 4.5 (NH, broad s), 7.23 (3-H, dd), 7.40 (8-H, m), 8.09 (4-H, ddd), 8.76 (2-H, dd); $|J|$ 0.85 (4,8), 0.95 (7,8), 1.65 (2,4), 4.2 (2,3), 8.5 (3,4) Hz.

*3,4-Dimethyl-3*H*-imidazo[4,5-f]quinolin-2-amine* (6b). Two procedures are given: *A* for unlabelled and *B* for labelled *6b*.

A. Cyanogen bromide (1.06 g, 10.0 mmol) and *5b* (1.87 g, 10.0 mmol) were dissolved in methanol (40 ml). The hydrobromide of *6b* separated gradually. After 4 h, conc. ammonia (1.0 ml) was added and the mixture evaporated. CC ($CHCl_3$–MeOH, 5:1 v/v) of the residue yielded *6b* (1.65 g, 78 %). After crystallization from 95 % ethanol, *6b* melted at 296–298 °C (sealed tube) and was identical (m.p., MS, ^{1}H NMR, UV) with a sample provided by T. Sugimura.[4]

B. Potassium cyanide (65 mg, 1.00 mmol), labelled with ^{13}C or ^{14}C, was dissolved in methanol (2 ml) and added over 20 min to a stirred solution of bromine (160 mg, 1.00 mmol) in methanol (2 ml), cooled in ice-water, *cf.* Ref. 5. Potassium bromide separated gradually. *5b* (187 mg, 1.00 mmol) was immediately dissolved in the colourless mixture. After 4 h at 20 °C, *6b* (165 mg, 78 %) was isolated as in *A*, but CC was performed at atmospheric pressure.

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Added in proof. In the last step (*5*→*6*), the reaction mixture should be kept at 0 °C overnight. The hydrobromide of *6* may then be collected, washed with cold methanol and dissolved in warm water (40 ml/g). Pure *6* separates from the solution on adding aqueous ammonia and cooling. A partly similar synthesis of *6a* and *6b* was published recently.[13]

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