

THE SYNTHESIS OF THREE ISOMERS OF THE FOOD CARCINOGEN IQ

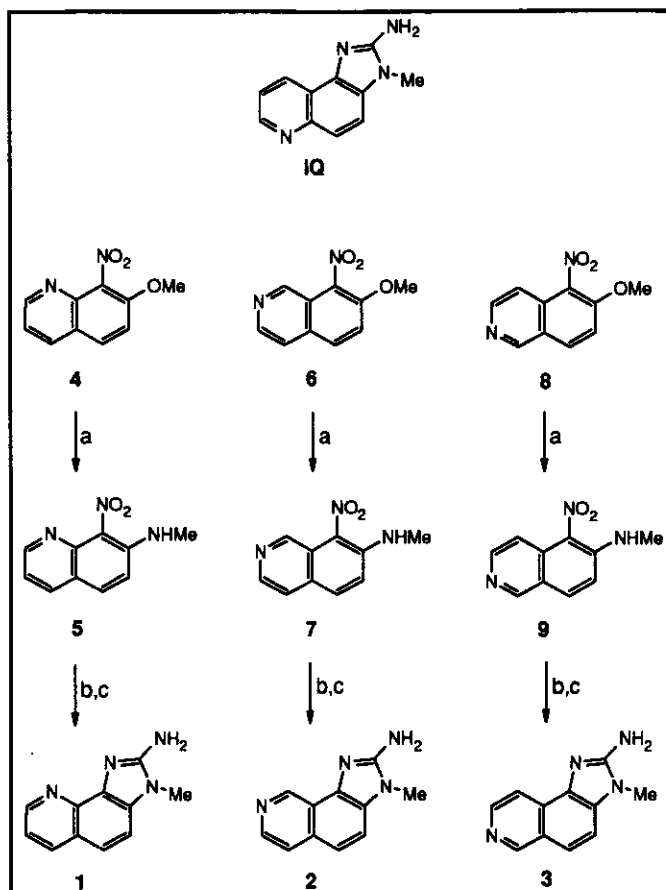
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Abstract - 2-Amino-3-methyl-3*H*-imidazo[4,5-*h*]quinoline, 2-amino-3-methyl-3*H*-imidazo[4,5-*f*]isoquinoline and 2-amino-3-methyl-3*H*-imidazo[4,5-*h*]isoquinoline were synthesized from 7-methoxyquinoline, 6- and 7-methoxyisoquinolines in 21-28 % overall yields.

The mutagenic 2-amino-3-methyl-3*H*-imidazo[4,5-*f*]quinoline (IQ, Scheme) and a number of related toxic heteroaromatic amines have been isolated from model reaction systems and broiled proteinaceous foods.¹ IQ itself was found to be carcinogenic in rodents and in nonhuman primates.² For reference purposes and for biological and structure-activity studies,³ we needed the closely related isomers (1-3). In contrast to previous syntheses of related heterocyclic amines,⁴ our method provides exclusively the desired *N*³-methyl isomer (*cf.* reference 5). This is of importance since apart from the difficulties encountered in separating the *N*¹- from the *N*³-methyl derivatives, the two isomers exhibit very different biological activities.⁴ Therefore, any contamination by the *N*¹-methyl isomer would lead to false activity results.

The Skraup reaction of 3-methoxyaniline afforded 5- and 7-methoxyquinolines⁶ in *ca.* 1:5 ratio (¹H nmr spectroscopy). Nitration of this mixture, followed by crystallization to remove unwanted isomers, afforded quinoline (4) in good yield. This has been previously synthesized from 7-chloro-8-nitroquinoline and methoxide.⁷ Treatment of 4 with methylamine yielded quinoline (5), which on reduction gave the air-sensitive 8-amino-7-methylaminoquinoline. Ring closure of the crude diamine with cyanogen bromide afforded the required IQ isomer (1) in 32 % overall yield from 4. In an analogous way, nitration of 7- and 6-methoxyisoquinolines⁸ afforded isoquinolines (6)⁹ and (8),¹⁰ respectively. Replacement of the methoxyl group by methylamine gave 7 and 9 in good yield. Subsequent reduction to 8-amino-7-methylamino- and 5-amino-6-methylaminoisoquinoline followed by treatment with cyanogen bromide afforded the desired isomers (2) and (3) in 26 % and 36 % overall yields from 6 and 8. The route offers a suitable method for the specific isotopic labelling of the IQ isomers (1-3) by employing labelled methylamine and/or cyanogen bromide, for example.



Scheme Reagents: a, MeNH₂; b, H₂/Ni; c, BrCN

EXPERIMENTAL

Since IQ and some related heterocyclic amines are carcinogenic,² contact with the reaction mixture should be avoided in the last step. These precautions may be unnecessary in the earlier steps, since the 2-amino-3-methylimidazole part of the molecule seems to be responsible for the mutagenic activity.³ Melting points (uncorrected) were determined on a Mettler FP5 or FP62 instrument. ¹H Nmr spectra were obtained on a Varian VXR-400 spectrometer at 20 °C, and referenced to the solvent [CDCl₃, 7.26 ppm] or [(CD₃)₂SO, 2.49 ppm]. Coupling constants are given in Hz. The mass spectra (70 eV, direct insertion) were obtained on a Finnigan 4021 instrument with electron impact ionization and an ion source temperature of 200 °C. Flash liquid chromatography was performed on silica gel (230-400 mesh ASTM, Merck). All reactions and purifications were monitored by tlc (uv detection) on aluminium sheets coated with silica gel 60 F₂₅₄

(Merck). Compositions of tlc solvent systems refer to volumes. Evaporations were performed under reduced pressure at 40 °C. Organic solvents were of p.a. quality or were freshly distilled.

7-Methoxy-8-nitroquinoline (4). A mixture of 7- and 5-methoxyquinoline⁶ (ca. 5:1, 1 g, 6.29 mmol) was dissolved in cold concentrated sulfuric acid (5 ml). To the cooled solution, potassium nitrate (1 g, 10 mmol) was added in one portion. After stirring for 24 h at 20 °C (tlc: EtOAc-CHCl₃-AcOH, 10:10:1) the mixture was poured onto ice and neutralized with 25 % ammonia. The filtered product was washed with water and recrystallized from ethanol-water to yield 4 (0.86 g, 80 %) as light yellow needles. mp 178-179 °C (lit.,⁷ 178-178.5 °C). Ms, *m/z* (% rel. int.): 204 (100, M⁺), 174 (58), 146 (74), 128 (47), 115 (58). ¹H Nmr (CDCl₃): δ 8.95 (2-H, dd, *J* 4.3 and 1.6), 8.16 (4-H, dd, *J* 8.3 and 1.6), 7.94 (5-H, d, *J* 9.2), 7.42 (6-H, d, *J* 9.2), 7.40 (3-H, dd, *J* 8.3 and 4.3), 4.07 (O-Me, s).

7-Methoxy-8-nitroisoquinoline (6). Yield: 84 %, mp 164-165 °C (lit.,⁹ 164-165 °C). Ms, *m/z* (% rel. int.): 204 (42, M⁺), 159 (7), 146 (17), 128 (48), 116 (39), 62 (100). ¹H Nmr (CDCl₃): δ 9.19 (1-H, s), 8.57 (3-H, d, *J* 5.6), 8.00 (5-H, d, *J* 9.0), 7.67 (4-H, d, *J* 6.3), 7.59 (6-H, d, *J* 9.2), 4.08 (O-Me, s).

6-Methoxy-5-nitroisoquinoline (8). Yield: 75 %, mp 151-152 °C (lit.,¹⁰ 135-137 °C). Ms, *m/z* (% rel. int.): 204 (37, M⁺), 174(2), 146 (12), 128 (20), 115 (32), 62 (100). ¹H Nmr (CDCl₃): δ 9.23 (1-H, s), 8.60 (3-H, d, *J* 6.1), 8.15 (8-H, dd, *J* 9.1 and 0.9), 7.55 (4-H, dd, *J* 6.1 and 0.9), 7.47 (7-H, d, *J* 9.1), 4.11 (O-Me, s).

7-Methylamino-8-nitroquinoline (5) was prepared from 4 and 40 % aq. methylamine as described for 7-methyl-6-methylamino-5-nitroquinoline.⁵ Yield: 68 %, mp 156-157 °C. Anal. Calcd for C₁₀H₉N₃O₂: C, 59.1; H, 4.5; N, 20.7. Found: C, 59.4; H, 4.5; N, 20.4. Ms, *m/z* (% rel. int.): 203 (100, M⁺), 186 (14), 169 (28), 156 (74), 142 (66), 128 (91). ¹H Nmr (CDCl₃): δ 8.91 (2-H, dd, *J* 4.4 and 1.8), 7.98 (4-H, dd, *J* 8.1 and 1.8), 7.76 (5-H, d, *J* 9.3), 7.24 (3-H, dd, *J* 8.6 and 4.4), 7.1 (N-H, bs), 7.14 (6-H, d, *J* 9.3), 3.10 (N-Me, d, *J* 5.1).

7-Methylamino-8-nitroisoquinoline (7) was prepared from 6 and 40 % aq. methylamine as described above for 7-methyl-6-methylamino-5-nitroquinoline.⁵ Yield: 85 %, mp 220-221 °C. Anal. Calcd for C₁₀H₉N₃O₂: C, 59.1; H, 4.5; N, 20.7. Found: C, 58.8; H, 4.5; N, 20.5. Ms, *m/z* (% rel. int.): 203 (100, M⁺), 186 (10), 168

(9), 156 (31), 142 (23), 128 (57). ^1H Nmr (CDCl_3): δ 10.17 (1-H, s), 9.1 (N-H, bs), 8.50 (3-H, d, J 5.3), 7.83 (5-H, d, J 9.4), 7.51 (4-H, d, J 5.3), 7.33 (6-H, d, J 9.4), 3.21 (N-Me, d, J 5.2).

6-Methylamino-5-nitroisoquinoline (9) was prepared from 8 and 40 % aq. methylamine as described for 7-methyl-6-methylamino-5-nitroquinoline.⁵ Yield: 85 %, mp 209-210 °C. *Anal.* Calcd for $\text{C}_{10}\text{H}_9\text{N}_3\text{O}_2$: C, 59.1; H, 4.5; N, 20.7. Found: C, 58.6; H, 4.4; N, 20.5. *Ms, m/z* (% rel. int.): 203 (100, M^+), 186 (11), 170 (8), 156 (47), 146 (24), 128 (54). ^1H Nmr (CDCl_3): δ 9.3 (N-H, bs.), 8.97 (1-H, s), 8.60 (3- and 4-H, m), 7.94 (8-H, d, J 9.3), 7.19 (7-H, d, J 9.3), 3.22 (N-Me, d, J 5.2).

2-Amino-3-methyl-3H-imidazo[4,5-h]quinoline (1). *Caution! See Experimental.* Compound (1) was prepared from the crude diamine as described for IQ.⁵ The ring closure was performed with a 5 M solution of cyanogen bromide in acetonitrile under nitrogen atmosphere. Ethanol-chloroform was used for recrystallization. Yield: 47 %, mp >300 °C. *Anal.* Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_4$: C, 66.6; H, 5.1; N, 28.3. Found: C, 66.5; H, 5.1; N, 28.3. *Ms, m/z* (% rel. int.): 198 (100, M^+), 183 (6), 170 (34), 156 (9), 142 (11), 129 (15). ^1H Nmr [$(\text{CD}_3)_2\text{SO}$]: δ 8.85 (8-H, dd, J 4.2 and 1.4), 8.36 (7-H, dd, J 8.3 and 1.4), 7.71 (5-H, d, J 8.7), 7.63 (4-H, d, J 8.7), 7.43 (7-H, dd, J 8.3 and 4.2).

2-Amino-3-methyl-3H-imidazo[4,5-h]isoquinoline (2). *Caution! See Experimental.* Compound (2) was prepared from the crude diamine as described above for 1. Yield: 31 %, mp >300 °C. *Anal.* Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_4$: C, 66.6; H, 5.1; N, 28.3. Found: C, 67.4; H, 5.1; N, 28.8. *Ms, m/z* (% rel. int.): 198 (100, M^+), 183 (28), 170 (19), 156 (19), 142 (3), 129 (12). ^1H Nmr [$(\text{CD}_3)_2\text{SO}$]: δ 9.74 (9-H, s), 8.48 (7-H, d, J 5.9), 8.1 (NH₂, bs), 8.09 (5-H, d, J 8.8), 8.07 (6-H, d, J 5.9), 7.85 (4-H, d, J 8.8), 3.74 (N-Me, s).

2-Amino-3-methyl-3H-imidazo[4,5-f]isoquinoline (3). *Caution! See Experimental.* Compound (3) was prepared from the crude diamine as described above for 1. Yield: 42 %, mp >300 °C. *Anal.* Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_4$: C, 66.6; H, 5.1; N, 28.3. Found: C, 67.1; H, 5.1; N, 28.6. *Ms, m/z* (% rel. int.): 198 (100, M^+), 183 (23), 170 (20), 156 (23), 142 (4), 129 (9). ^1H Nmr [$(\text{CD}_3)_2\text{SO}$]: δ 9.46 (1-H, s), 8.51 (3-H, d, J 6.1), 8.21 (4-H, d, J 6.1), 7.98 (8-H, d, J 8.7), 7.91 (7-H, d, J 8.7), 7.70 (NH₂, bs), 3.72 (N-Me, s).

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