THE SYNTHESIS OF THREE ISOMERS OF THE FOOD CARCINOGEN IQ

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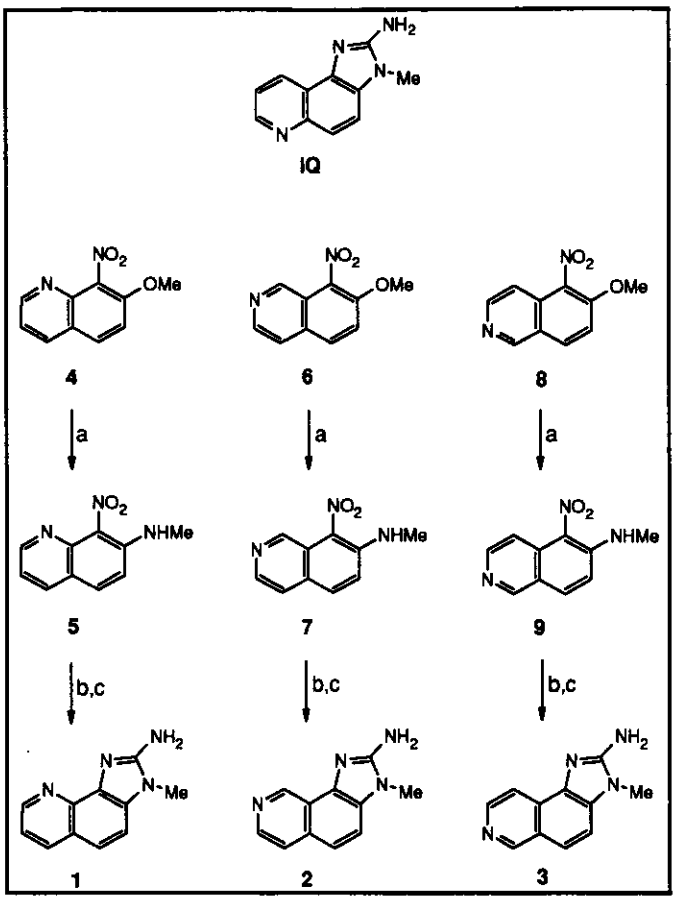
Abstract - 2-Amino-3-methyl-3*H*-imidazo[4,5-*h*]quinoline, 2-amino-3-methyl-3*H*-imidazo[4,5-*f*]isoquinoline and 2-amino-3-methyl-3*H*-imidazo[4,5-*h*]isoquinoline were synthesized from 7-methoxyquinoline, 6- and 7-methoxyisoquinolines in 21-28 % overall yields.

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-methoxyquinolines[6] in *ca.* 1:5 ratio (^{1}H 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-methoxyisoquinolines[8] 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, $MeNH_2$; b, H_2/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. ^{1}H Nmr spectra were obtained on a Varian VXR-400 spectrometer at 20 °C, and referenced to the solvent [$CDCl_3$, 7.26 ppm] or [$(CD_3)_2SO$, 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 F_{254}

(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-methoxyquinoline[6] (*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-$CHCl_3$-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 ($CDCl_3$): 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 ($CDCl_3$): 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 ($CDCl_3$): 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 $C_{10}H_9N_3O_2$: 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 ($CDCl_3$): 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 $C_{10}H_9N_3O_2$: 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). ^{1}H 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 $C_{10}H_9N_3O_2$: 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). ^{1}H 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-3*H*-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 $C_{11}H_{10}N_4$: 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). ^{1}H Nmr [$(CD_3)_2SO$]: 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-3*H*-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 $C_{11}H_{10}N_4$: 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). ^{1}H Nmr [$(CD_3)_2SO$]: δ 9.74 (9-H, s), 8.48 (7-H, d, *J* 5.9), 8.1 (NH_2, 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-3*H*-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 $C_{11}H_{10}N_4$: 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). ^{1}H Nmr [$(CD_3)_2SO$]: 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 (NH_2, bs), 3.72 (N-Me, s).

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REFERENCES

1. M. Jägerstad, K. Skog, S. Grivas, and K. Olsson, *Mutat. Res.*, 1991, **259**, 219; J. S. Felton and M. G. Knize, *ibid.*, 205.
2. H. Ohgaki, S. Takayama, and T. Sugimura, *ibid.*, 399.
3. S. Grivas, *J. Chem. Res. (S)*, 1988, 84; M. Jägerstad and S. Grivas, *Mutat. Res.*, 1985, **144**,131; S. Grivas and M. Jägerstad, *ibid.*, 1984, **137**, 29.
4. J. Ziv, S. Knapp, and J. D. Rosen, *Synth. Commun.*, 1988, **18**, 973; G. Kaiser, D. Harnasch, M. T. King, and D. Wild, *Chem. Biol. Interactions*, 1986, **57**, 97; H. Kasai and S. Nishimura, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 2223.
5. L. Adolfsson and K. Olsson, *Acta Chem. Scand. Ser. B*, 1983, **37**, 157.
6. M. H. Palmer, *J. Chem. Soc.*, 1962, 3645.
7. S. M. Daluge and P. M. Skonezny, *Eur. Pat. 51879* (Chem. Abstr., 1982, **97**, 127652x).
8. J. B. Hendrickson and C. Rodriguez, *J. Org. Chem.*, 1983, **48**, 3344.
9. M. Kulka, *J. Am. Chem. Soc.*, 1953, **75**, 3597.
10. D. Deprez, D. Farge, J. J. Hucherot, and C. Moutonnier, *Ger. Offen. 2916577* (Chem. Abstr., 1980, **92**, 111013a).

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