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Syntheses of 2-Amino-3,4-dimethyl-3*H*-imidazo[4,5-*f*]quinoline and Its Related Compounds

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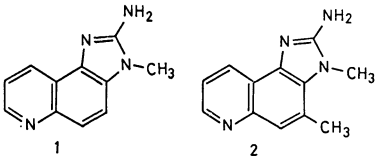
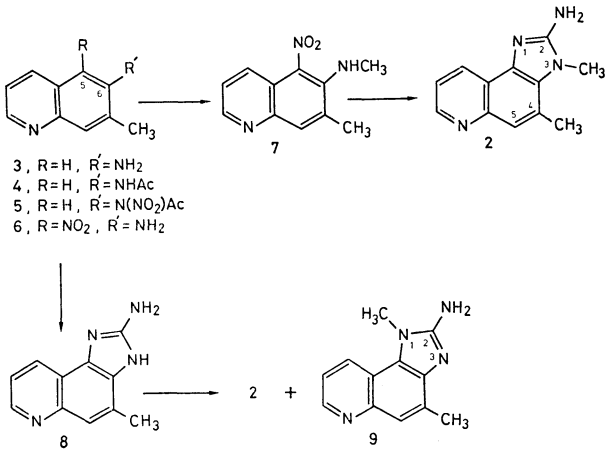
The strongly mutagenic compound, 2-amino-3,4-dimethyl-3*H*-imidazo[4,5-*f*]quinoline (Me-IQ), isolated from broiled sardines was synthesized from 6-amino-7-methylquinoline. Several structurally related compounds were also synthesized to clarify the structure-activity relationship. Some of them also showed strong mutagenic activity towards *Salmonella typhimurium* TA98.

We previously isolated two new potent mutagens from broiled fish (sardine) and identified them as 2-amino-3-methyl-3*H*-imidazo[4,5-*f*]quinoline (IQ, compound **1**)[1-4] and 2-amino-3,4-dimethyl-3*H*-imidazo-[4,5-*f*]quinoline (Me-IQ, compound **2**).[5] They are strongly mutagenic, especially towards *Salmonella typhimurium* TA98.[2,5] For final structure assignment of Me-IQ and for studies on structure-activity relationship of 2-aminoimidazo[4,5-*f*]quinoline derivatives, we synthesized compound **2** and its related compounds from 6-aminoquinoline derivatives. In this paper, we describe detailed data on syntheses of these new imidazo[4,5-*f*]quinoline derivatives. A preliminary account of this work has been published.[2,5]

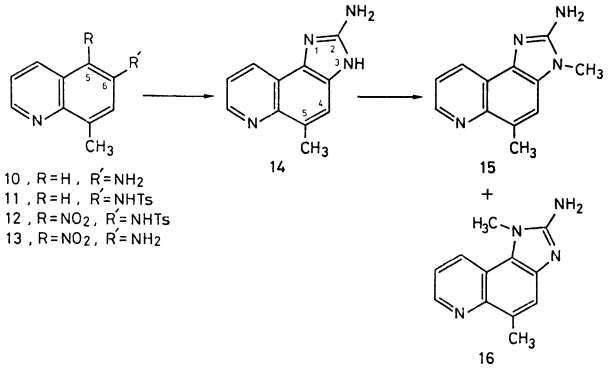


Results and Discussion

Compound **2** was synthesized from 6-amino-7-methylquinoline (**3**) as shown in Scheme 1. Compound **3** prepared by the method of Huisgen[6] was converted to the 6-acetamido derivative **4**. Nitration of compound **4** with KNO_3–H_2SO_4 mixture gave an *N*-nitro derivative **5**. Acid hydrolysis of compound **5** gave the 5-nitro derivative **6** with migration of the nitro group on nitrogen to the neighboring 5-C position of the quinoline nucleus. Compound **6** was treated with sodium hydride in *N*,*N*-dimethylformamide and methylated with methyl iodide to afford the *N*-methyl derivative **7**. Compound **7** was then reduced to the 6-methylamino-5-amino derivative with Fe/HCl mixture and the neutralized reaction mixture was treated with cyanogen bromide to afford compound **2**. Compound **2** was also prepared by methylation of compound **8**, which was obtained from compound **6**. In the latter reaction, the 1-methyl isomer, compound **9**, was also produced.



Scheme 1.



Scheme 2.

Compound **15** was synthesized from 6-amino-8-methylquinoline (**10**) as shown in Scheme 2. This method is practically the same as that reported for the synthesis of compound **1**.[2] Namely, the tosyl derivative **11**, prepared from compound **10**,[7] was converted to the nitro derivative **12** by treatment with 61% HNO_3. Compound **12** was then hydrolyzed with concentrated H_2SO_4, resulting in formation of 6-amino-5-nitro-8-methylquinoline (**13**). Compound **13** was converted to the diamine derivative by reduction with Fe/HCl mixture. The reaction mixture was neutralized, and then treated with cyanogen bromide to yield the cyclized derivative **14**. The 3-methyl derivative **15** was finally obtained as a major product by heating the tetramethylammonium salt of compound **14** in vacuum.[2,3,8] In this reaction 1-methyl derivative **16** was also obtained as a minor product.

The mass, UV, and ^{1}H-NMR spectra of compound **2**, isolated from broiled fish were exactly the same as those of the synthetic compound **2**, but different from those of compounds **9**, **15**, and **16**. Therefore, compound **2** was unambiguously identified as 2-amino-3,4-dimethyl-3*H*-imidazo[4,5-*f*]quinoline (**2**). Compounds **2**, **9**, **15**, and **16** showed strong mutagenic activity towards the *S. typhimurium* TA98 strain by

metabolic activation with microsomal enzymes. However compounds **8** and **14** showed almost no mutagenic activity.[9] Quantitative measurements of compounds **1** and **2** in various cooked foods by G.C.-mass spectrometry are in progress in this laboratory.

Experimental

Spectral Measurements. ^{1}H-NMR (270 MHz) spectra were recorded in a Bruker WH 270 spectrometer at 23 °C in $CDCl_3$ or CD_3OD. Chemical shifts were measured relative to the residual $CHCl_3$ signal (δ 7.25) or CHD_2OD signal (δ 3.40). Mass spectra were obtained by a Varian MAT-44 instrument. UV spectra were obtained using a Shimadzu UV-300 spectrophotometer.

*6-Acetamido-7-methylquinoline (**4**).* 6-Amino-7-methylquinoline (**3**)[6] (130 mg) was dissolved in acetic anhydride (1 ml) and the solution was allowed to stand at room temperature for 10 min. Then, cold water (6 ml) was added, and the solution was adjusted to pH 10 by adding NaOH solution. The product was extracted with ethyl acetate (3×10 ml) and crystallized from ethanol. Yield, 110 mg; mp 176—177 °C; MS: 200 (M^+), 158 (M^+-Ac).

*6-(N-Nitroacetamido)-7-methylquinoline (**5**).* Compound **4** (1.2 g) was dissolved in concentrated H_2SO_4 (5 ml), and KNO_3 (1.5 g) was added with vigorous stirring at 0 °C. Stirring was continued for 30 min at room temperature and then the reaction mixture was poured onto ice, neutralized with NaOH solution and extracted with ethyl acetate. The crude product was purified on a column of silica gel (3 cm×50 cm) with methanol–chloroform (3:97, v/v) as solvent. Compound **5** was crystallized from methanol. Yield, 500 mg; mp 240—242 °C; MS: 245 (M^+), 203 (M^+-Ac), 199 (M^+-NO_2): NMR ($CDCl_3$): δ=8.96 (1H, dd, J=4.2, 1.5 Hz, 2-H), 8.20 (1H, dd, J=8.6, 1.5 Hz, 4-H), 8.18 (1H, s, 8-H), 7.67 (1H, br s, 5-H), 7.51 (1H, dd, J=8.6, 4.2 Hz, 3-H), 2.52 (3H, s, 7-Me), 2.25 (3H, s, Ac).

*6-Amino-7-methyl-5-nitroquinoline (**6**).* Compound **5** (500 mg) was suspended in concentrated H_2SO_4 (2 ml) and heated at 70 °C for 30 min. The reaction mixture was poured onto ice and neutralized with NH_4OH. The precipitate was collected by filtration, washed with a small amount of water and dried. The crude product was crystallized from ethanol. Yield, 360 mg; mp 171—172 °C; MS: 203 (M^+), 157 (M^+-NO_2); NMR ($CDCl_3$): δ=8.98 (1H, ddd, J=8.8, 1.3, 1.0 Hz, 4-H), 8.68 (1H, dd, J=4.2, 1.3 Hz, 2-H), 7.95 (1H, dd, J=1.0, 0.8 Hz, 8-H), 7.46 (1H, dd, J=8.8, 4.2 Hz, 3-H), 6.72 (2H, br s, NH_2), 2.44 (3H, d, J=0.8 Hz, Me).

*7-Methyl-6-methylamino-5-nitroquinoline (**7**).* Compound **6** (27 mg) was dissolved in *N,N*-dimethylformamide (0.2 ml). Sodium hydride (7.8 mg, 50% oil suspension) was added and the reaction mixture was stirred for 30 min at room temperature. Then methyl iodide (10 μl) was added during 1 h and stirring was continued for 1 h at room temperature. After cold water (1 ml) was added, the reaction mixture was neutralized with NaOH solution and the product was extracted with ethyl acetate (3×1.5 ml). The crude product thus obtained was purified on a column of silica gel (1 cm×30 cm) with methanol–chloroform (5:95, v/v) as solvent. Yield, 4.3 mg; powder; MS: 217 (M^+), 170 (M^+-H-NO_2), 156 (M^+-NO_2-Me); NMR ($CDCl_3$): δ=8.69 (1H, dd, J=4.3, 1.5 Hz, 2-H), 8.18 (1H, ddd, J=8.6, 1.5, 0.7 Hz, 4-H), 7.86 (1H, dd, J=0.7, 0.7 Hz, 8-H), 7.40 (1H, dd, J=8.6, 4.3 Hz, 3-H), 5.17 (1H, d, J=5.5 Hz, NH), 3.00 (3H, d, J=5.5 Hz, N-Me), 2.47 (3H, d, J=0.7 Hz, 7-C-Me).

*2-Amino-3,4-dimethyl-3H-imidazo[4,5-f]quinoline (**2**).* Compound **7** (4 mg) was dissolved in concentrated HCl (0.1 ml) and reduced by adding Fe powder (10 mg). After 20 min, the reaction mixture was filtered and washed with water. The filtrate was neutralized with KOH solution, aqueous BrCN (12 mg, 0.2 ml) was added during 3 h with stirring, and stirring was coninued for 4 h. The reaction mixture was made alkaline with KOH solution and extracted with ethyl acetate (5×1 ml). The crude product thus obtained was purified by HPLC [Shimadzu LC-3A; μBondapak C_{18} (Waters); 30% methanol–0.04% formic acid]. Yield, 2.2 mg; mp 295—297 °C; MS: 212 (M^+), 197 ($M^+-H-HCN$); UV (MeOH): $\lambda(\varepsilon)$=219 (29000), 265 (48000), and 332 nm (4000); NMR ($CDCl_3$): δ=8.80 (1H, dd, J=4.2, 1.7 Hz, 7-H), 8.66 (1H, ddd, J=8.3, 1.7, 0.7 Hz 9-H), 7.53 (1H, dd, J=0.9, 0.7 Hz, 5-H), 7.36 (1H, dd, J=8.3, 4.2 Hz, 8-H), 4.51 (2H, br s, NH_2), 3.88 (3H, s, N-Me), 2.83 (3H, d, J=0.9 Hz, 4-C-Me), NOE (N-Me→4-C-Me) 3%±1%.

*2-Amino-4-methyl-3H-imidazo[4,5-f]quinoline (**8**).* Compound **6** (100 mg) was dissolved in concentrated HCl (1.5 ml) and reduced by adding Fe powder (200 mg). The reaction mixture was filtered and washed with water. The filtrate was neutralized with KOH solution, and aqueous BrCN (300 mg, 6 ml) was added during 1 h with stirring. Stirring was further continued for 2 h. Then the solution was made alkaline with KOH solution, and the crude product was extracted with ethyl acetate (5×100 ml). The ethyl acetate layer was evaporated to dryness, and the residue was fractionated on a column of silica gel (1.5 cm×30 cm) with methanol–chloroform (15:85, v/v) as solvent to isolate compound **8**. Yield, 36 mg; mp 280—290 °C (decomp): MS: 198 (M^+), 170 ($M^+-H-HCN$); NMR (CD_3OD): δ=8.81 (1H, dd, J=4.5, 1.6 Hz, 7-H), 8.73 (1H, ddd, J=8.4, 1.6, 0.8 Hz, 9-H), 7.67 (1H, dd, J=1.0, 0.8 Hz, 5-H), 7.60 (1H, dd, J=8.4, 4.5 Hz, 8-H), 2.74 (3H, d, J=1.0 Hz, Me).

*2-Amino-1,4-dimethyl-1H-imidazo[4,5-f]quinoline (**9**).* Compound **8** (16 mg) was dissolved in dimethyl sulfoxide (0.45 ml) and methylated with methyl iodide (20 μl) in the presence of K_2CO_3 (32 mg). The reaction was continued for 1 h at room temperature. In this reaction, compounds **2** and **9** were produced in approximately equal proportions. Compound **9** was separated from compound **2** by HPLC using the same conditions as those described above for purification of synthetic compound **2**. Yield, 3.5 mg; powder; MS: 212 (M^+), 197 (M^+-Me), 184 ($M^+-H-HCN$); NMR ($CDCl_3$): δ=8.81 (1H, d, J=4.0 Hz, 7-H), 8.54 (1H, d, J=8.5 Hz, 9-H), 7.76 (1H, s, 5-H), 7.39 (1H, dd, J=8.5, 4.0 Hz, 8-H), 5.98 (2H, br s, NH_2,), 4.02 (3H, s, N-Me), 2.72 (3H, s, 4-C-Me), NOE (N-Me→9-H)17%± 4%. UV (MeOH): $\lambda(\varepsilon)$=216 (26600), 276 (46500), and 344 nm (2400).

*8-Methyl-6-(p-tolylsulfonylamino) quinoline (**11**).* 6-Amino-8-methylquinoline (**10**)[7] (10 g), *p*-toluenesulfonyl chloride (12.1 g), and potassium acetate (6.2 g) were suspended in ethanol (200 ml) and refluxed for 2.5 h. The hot mixture was then filtered, and the filtrate was evaporated to dryness. The crude product was purified on a column of silica gel (5 cm×60 cm) with chloroform as solvent. Yield, 19 g; oil; MS: 312 (M^+), 248 (M^+-SO_2); NMR ($CDCl_3$): δ=8.84 (1H, dd, J=4.3, 1.7 Hz, 2-H), 8.01 (1H, dd, J=8.3, 1.7 Hz, 4-H), 7.73 (2H, d, J=8.1 Hz, tosyl-H_o), 7.42 (1H, d, J=2.4 Hz, 5-H), 7.35 (1H, dd, J=8.3, 4.3 Hz, 3-H), 7.29 (1H, dd, J=2.4, 0.9 Hz, 7-H), 7.18 (2H, d, J=8.1 Hz, tosyl-H_m), 2.67 (3H, d, J=0.9 Hz, 8-Me), 2.31 (3H, s, tosyl-Me).

8-Methyl-5-nitro-6-(p-tolylsulfonylamino) quinoline (12). Compound **11** (18.5 g) was nitrated with 61% HNO_3 (6.9 ml) at 70—80 °C for 1 h. The solution was poured onto ice, and the solid material formed was collected by filtration. The crude product was purified by crystallization from ethanol. Yield 16.6 g; mp 204—205 °C; MS: 357 (M^+), 246 ($M^+-SO_2-NO_2-H$); NMR ($CDCl_3$): δ=9.05 (1H, dd, J=4.4, 1.5 Hz, 2-H), 8.61 (1H, dd, J=8.9, 1.5 Hz, 4-H), 8.11 (1H, d, J=0.8 Hz, 7-H), 7.70 (2H, d, J=8.2 Hz, tosyl-H_o), 7.67 (1H, dd, J=8.9, 4.4 Hz, 3-H), 7.25 (2H, d, J=8.2 Hz, tosyl-H_m), 2.87 (3H, d, J=0.8 Hz, 8-Me), 2.37 (3H, s, tosyl-Me).

6-Amino-8-methyl-5-nitroquinoline (13). Compound **12** (16 g) was suspended in concentrated H_2SO_4 (20 ml) and heated for 1 h at 95 °C. The hydrolyzate was neutralized with NH_4OH. The precipitate was collected by filtration and dried. The crude product was purified by crystallization from toluene and then recrystallized from ethanol. Yield, 3 g; mp 161—162 °C; MS: 203 (M^+), 157 (M^+-NO_2); NMR ($CDCl_3$): δ=9.15 (1H, dd, J=8.8, 1.7 Hz, 4-H), 8.70 (1H, dd, J=4.2, 1.7 Hz, 2-H), 7.50 (1H, dd, J=8.8, 4.2 Hz, 3-H), 6.99 (1H, d, J=1.0 Hz, 7-H), 6.67 (2H, br s, NH_2), 2.71 (3H, d, J=1.0 Hz, Me).

2-Amino-5-methyl-3H-imidazo[4,5-f]quinoline (14). Compound **14** was synthesized and purified by the procedure used for preparation of compound **8**. Yield, 15%; mp 246—248 °C (decomp); MS: 198 (M^+), 170 ($M^+-H-HCN$); NMR ($CDCl_3$): δ=8.88 (1H, dd, J=4.1, 1.7 Hz, 7-H), 8.61 (1H, dd, J=8.4, 1.7 Hz, 9-H), 7.53 (1H, d, J=0.7 Hz, 4-H), 7.43 (1H, dd, J=8.4, 4.1 Hz, 8-H), 4.59 (2H, br s, NH_2), 2.84 (3H, d, J=0.7 Hz, Me).

2-Amino-3,5-dimethyl-3H-imidazo[4,5-f]quinoline (15) and 2-Amino-1,5-dimethyl-1H-imidazo[4,5-f]quinoline (16). An aqueous solution of compound **14** (135 mg) and tetramethylammonium hydroxide (62.3 mg) was lyophilized in a sublimation apparatus and heated slowly to 200 °C under vacuum pressure (3 mmHg†). At this temperature the sublimate began to collect on the condenser. The crude product thus obtained was purified on a column of silica gel (3 cm × 30 cm) with methanol–chloroform (10:90, v/v) as solvent. Compound **15** was crystallized from aqueous ethanol. Yield, 34 mg; mp >300 °C; MS: 212 (M^+), 184 (M^+), UV (MeOH): $\lambda(\varepsilon)$=213 (24900), 265 (45600), 354 nm (3600). NMR ($CDCl_3$): δ=8.91 (1H, d, J=4.0 Hz, 7-H), 8.67 (1H, d, J=8.2 Hz, 9-H), 7.48 (1H, dd, J=8.2, 4.0 Hz, 8-H), 7.44 (1H, s, 4-H), 6.07 (2H, br s, NH_2), 3.67 (3H, s, N-Me), 2.87 (3H, s, C-Me).

During purification by the silica gel column chromatography, compound **16** was also obtained as a minor component. Yield, 3 mg; powder; MS: 212 (M^+), 197 (M^+-Me), 184 ($M^+-H-HCN$); NMR ($CDCl_3$): δ=8.85 (1H, dd, J=4.2, 1.6 Hz, 7-H), 8.56 (1H, dd, J=8.6, 1.6 Hz, 9-H), 7.74 (1H, d, J=0.7 Hz, 4-H), 7.41 (1H, dd, J=8.6, 4.6 Hz, 8-H), 4.50 (2H, br s, NH_2), 4.00 (3H, s, N-Me), 2.84 (3H, d, J=0.7 Hz, C-Me).

† 1 mmHg≈133.322 Pa.

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