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Synthesis of Mutagenic Heteroaromatics: 2-Aminoimidazo[4,5-*f*]quinolines

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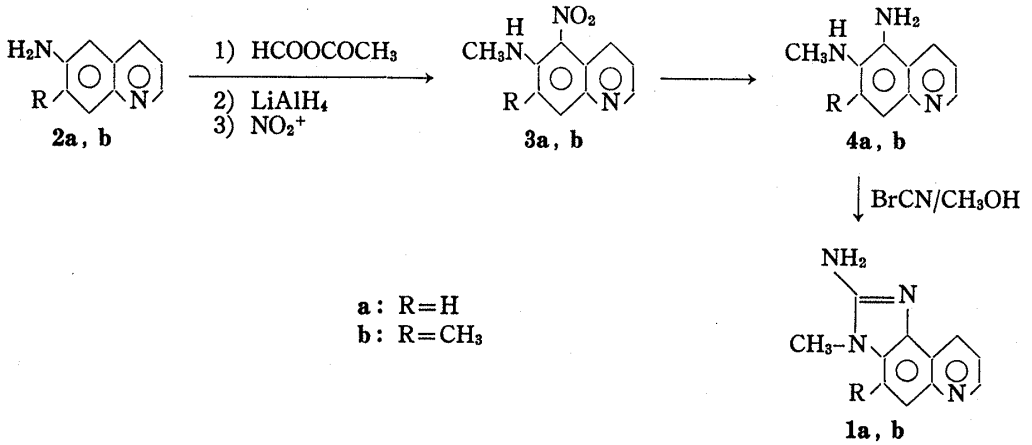
Two potent mutagens, 2-amino-3-methylimidazo[4,5-*f*]quinoline and 2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline, were synthesized.

Keywords——mutagen; 2-amino-3-methylimidazo[4,5-*f*]quinoline; 2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline; imidazo[4,5-*f*]quinoline; cyanogen bromide

Recent studies showed that pyrolysates of foods, proteins, and amino acids contain potent muta-carcinogens. Active compounds were isolated and their structures were determined.[1] For further studies, synthesis of these active compounds is essential. Previously, we established syntheses[2] of 3-amino-5*H*-pyrido[4,5-*b*]indoles (Trp-P) isolated from a pyrolysate of tryptophan,[1a] 2-aminodipyrido[1,2-*a*: 3′,2′-*d*]imidazoles (Glu-P)[3] isolated from a pyrolysate of glutamic acid,[1b] and 3,4-cyclopentenopyrido[3,2-*a*]carbazole (Lys-P-1)[4] isolated from a pyrolysate of lysine.[1c] Syntheses of alkylated derivatives of Trp-P and Glu-P were also completed.[5,6] More recently, two new potent heteroaromatic mutagens were isolated from broiled sardines, and their structures were determined as 2-amino-3-methylimidazo[4,5-*f*]-quinoline (IQ, **1a**) and 2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline (Me-IQ, **1b**).[7a] Syntheses of these mutagens were also reported.[7b] We here describe a simple and high yield synthesis of **1a** and **1b**.

1a and **1b** were synthesized in overall yields of 35% and 30%, respectively, from 6-aminoquinoline (**2a**) and 6-amino-7-methylquinoline (**2b**). **2a** is commercially available. **2b** was synthesized by means of the Skraup synthesis from 5-acetamido-2-nitrotoluene, which was obtained in good yield by nitration of *m*-acetyltoluidine. *N*-Methylation of **2a** and **2b** was performed by formylation with HCOOH–$(CH_3CO)_2O$ followed by reduction with $LiAlH_4$: yields were 77% and 91%, respectively. When similar reactions were applied to 6-amino-5-nitroquinolines, the yields of 6-methylamino derivatives were poor. 6-Methylamino- and 7-methyl-6-methylaminoquinoline were mono-nitrated in H_2SO_4–HNO_3 selectively at the 5-position of the quinolines in yields of 81% and 68%, respectively. For the reduction of the nitro group to an amino group, Pd-C-catalyzed reduction (for 6-methylamino-5-nitroquinoline;



2a, b **3a, b** **4a, b** **1a, b**

a: R=H
b: R=CH_3

Chart 1

3a) or $SnCl_2$–HCl treatment (for 7-methyl-6-methylamino-5-nitroquinoline; **3b**) was successful. The Pd-C-catalyzed reduction in more acidic media (in CH_3CO_2H) gave a better result. Condensation of amines **4a** and **4b** with BrCN gave the desired aminoimidazoles in 72% and 70% yields, respectively. Recrystallization from solvents containing dilute hydrobromic acid gave the hydrobromides of **1a** and **1b**. Spectral data of the synthetic **1a** and **1b** as well as crystal data were consistent with those described for authentic samples isolated from broiled sardines.[7] The present synthesis of **1a** and **1b** is simple and unambiguous as regards the position of the *N*-methyl group. This made the synthesis of a metabolite[8] of **1a** possible.

Experimental

2-Amino-3-methylimidazo[4,5-*f*]quinoline (IQ, 1a)——A mixture of $(CH_3CO)_2O$ (4.4 g) and HCOOH (40 ml) was added to a solution of 6-aminoquinoline (**2a**, 3.96 g) in HCOOH (40 ml), and the whole was stirred at room temperature for 2 h. The reaction mixture was evaporated to dryness and the residue was washed with aqueous K_2CO_3 and recrystallized from AcOEt to give 4.12 g (87%) of 6-formamidoquinoline (mp 115°C, M^+ 172). Reduction of the formyl group (4.12 g) was performed with $LiAlH_4$ (1.5 g) in tetrahydrofurane (THF) (400 ml) at 0°C. The reaction mixture was acidified with conc. HCl and then basified with aqueous K_2CO_3. The organic layer was evaporated to dryness and the residue was recrystallized from AcOEt to give 3.05 g (80.3%) of 6-methylaminoquinoline (proton magnetic resonance (PMR) ($CDCl_3$); δ, 2.85 (s), 4.45 (s), 6.57 (d, $J=3$ Hz), 6.95 (dd, $J=8$ Hz, 3 Hz), 7.20 (dd, $J=5$ Hz, 10 Hz), 7.84 (d, $J=8$ Hz), 7.85 (dd, $J=10$ Hz, 2 Hz), 8.60 (dd, $J=5$ Hz, 2 Hz)). This amine (3.05 g) was nitrated with HNO_3–H_2SO_4 (10 ml–10 ml) at 0°C (10 min). The reaction mixture was basified with aqueous K_2CO_3 and extracted with CH_2Cl_2. The extract was concentrated, and recrystallization of the residue from CH_2Cl_2–*n*-C_6H_{14} gave 2.9 g (80.5%) of 6-methylamino-5-nitroquinoline (**3a**, mp 122—124°C, PMR ($CDCl_3$); δ, 3.50 (s), 3.75 (s), 7.63 (dd, $J=6$ Hz, 8 Hz), 7.65 (d, $J=9$ Hz), 8.21 (dd, $J=8$ Hz, 2 Hz), 8.35 (d, $J=9$ Hz), 8.97 (dd, $J=2$ Hz, 6 Hz)). Next, 5.5 g of **3a** was reduced in CH_3COOH (250 ml) with H_2 gas in the presence of 10% Pd-C (2 g) at room temperature for 7 h. The mixture was filtered, the filtrate was evaporated to dryness, and the residue was washed with aqueous K_2CO_3. Recrystallization from AcOEt gave 3.7 g (78%) of 5-amino-6-methylaminoquinoline (**4a**, PMR (DMSO-d_6); δ, 3.40 (s), 5.80 (s), 6.14 (s), 7.19—7.56 (m), 8.78 (dd, $J=9$ Hz, 2 Hz), 8.90 (dd, $J=5$ Hz, 2 Hz)). **4a** (3.7 g) was treated with 3 g of BrCN in MeOH (200 ml) at room temperature for 3 h. The mixture was then concentrated, and recrystallization of the residue from EtOH containing dilute HBr gave 3.1 g (72%) of **1a**·HBr·H_2O mp >300°C. (*Anal.* Calcd for $C_{11}H_{10}N_4$·HBr·H_2O: C, 44.46; H, 4.37; N, 18.86; Found: C, 44.32; H, 4.19; N, 18.79). To prepare free **1a**, **1a**·HBr·H_2O was subjected to silica gel column chromatography (AcOEt–MeOH–NH_4OH). Free **1a**, mp >300°C (83%) was obtained. The spectral data of **1a** thus obtained were identical with those reported for IQ isolated from broiled sardines.

2-Amino-3,4-dimethylimidazo[4,5-*f*]quinoline (Me-IQ, 1b)——A mixture of HNO_3 and H_2SO_4 (1.5ml–5 ml) was added dropwise to an ice-cooled solution of *m*-*N*-acetyltoluidine (5 g) in conc. H_2SO_4 (35 ml). Stirring was continued for 30 min. The reaction mixture was poured into ice-water, and precipitates were filtered off. Recrystallization from AcOEt–$CHCl_3$ gave 4.89 g (75%) of 5-acetamido-2-nitrotoluene (PMR ($CDCl_3$); δ, 2.37 (s), 2.56 (s), 7.48—7.64 (m)), 7.97 (d, $J=8$ Hz)). Next, 10.7 g of 3 was heated in a mixture of glycerol (20 g), H_2SO_4 (15 g), and arsenic acid (8 g) at 130°C for 18 h. The mixture was then basified with aqueous NH_4OH and precipitates were collected. The precipitates were dissolved in EtOH (250 ml) and reduced with H_2 gas in the presence of 2 g of 10% Pd-C for 7 d. The reaction mixture was filtered and the filtrate was concentrated. The residue was subjected to silica gel column chromatography to give 7-methyl-6-aminoquinoline (**2b**, mp 137—138°C, PMR ($CDCl_3$); δ, 2.40 (s), 6.99 (s), 7.27 (dd, $J=6$ Hz, 8 Hz), 7.66 (s), 7.98 (dd, $J=2$ Hz, 8 Hz), 8.42 (dd, $J=2$ Hz, 6 Hz)) in a yield of 65%. A mixture of $(CH_3CO)_2O$–HCOOH (3 g–5 ml) was added to a solution of **2b** (0.93 g)) in HCOOH (20 ml). The mixture was stirred for 2 h at room temperature, basified with aqueous NH_4OH, concentrated and extracted with CH_2Cl_2. The extract was concentrated, and recrystallization of the residue from benzene–$CHCl_3$ gave 1.46 g (90%) of 7-methyl-6-formamidoquinoline (mp 154—156°C). The amide (1.15 g) was reduced with $LiAlH_4$ (0.47 g) in THF (10 ml). The mixture was acidified with conc. HCl, then basified with aqueous NH_4OH and extracted with AcOEt. The organic layer was evaporated to dryness and the residue was recrystallized from $CHCl_3$–*n*-C_6H_{14} to give the 6-methylaminoquinoline (0.96 g, 90%, PMR ($CDCl_3$); δ, 2.35 (s), 2.96 (s), 6.70 (s), 7.26 (dd, $J=4$ Hz, 8 Hz), 7.62 (s), 8.04 (d, $J=4$ Hz)), 8.40 (d, $J=4$ Hz)). The methylaminoquinoline (0.836 g) was dissolved in H_2SO_4 (10 ml) and cooled to 0°C. Next, 0.5 ml of HNO_3 was added and the mixture was stirred for 1 h. The reaction mixture was basified with NH_4OH and extracted with AcOEt. The organic layer was evaporated to dryness and the residue was subjected to silica gel column chromatography. Recrystallization from benzene–*n*-C_6H_{14} gave 0.72 g (68%) of 7-methyl-6-methylamino-5-nitroquinoline (**3b**, PMR ($CDCl_3$); δ, 2.57 (s), 3.78 (s), 7.76 (dd, $J=6$ Hz, 8 Hz), 8.32 (s), 8.35 (dd, $J=2$ Hz, 8 Hz), 9.10 (dd, $J=2$ Hz, 6 Hz)). Reduction of **3b** (0.72 g) was performed in HCl with $SnCl_2$ (2 g). The reaction mixture was heated for 1 h on a boiling water bath, then cooled to room temperature, and H_2S gas was bubbled through it. The mixture

was basified with NaOH and extracted with AcOEt. The extract was concentrated, and recrystallization of the residue from $CHCl_3$–n-C_6H_{14} gave **4b** (0.14 g, 80%, mp 218—220°C, PMR ($CDCl_3$); δ, 2.44 (s), 2.56 (s), 7.19 (dd, J=6 Hz, 8 Hz), 7.36 (s), 8.05 (dd, J=2 Hz, 8 Hz), 8.66 (dd, J=2 Hz, 6 Hz)). **4b** (0.14 g) was dissolved in EtOH (10 ml), and BrCN (0.12 g) was added. Stirring was continued for 2 h. The mixture was basified with NaOH and extracted with CH_2Cl_2. The extract was subjected to silica gel column chromatography. Recrystallization of the product from CH_3OH gave brown crystals, **1b**, mp 294—296°C. Spectral data of **1b** were consistent with those described for Me-IQ isolated from broiled sardines. Recrystallization from MeOH–AcOEt containing dilute HBr gave **1b**·HBr salt, mp >300°C in 70% yield (*Anal.* Calcd for $C_{12}H_{12}N_4$·HBr: C, 49.16; H, 4.82; N, 19.11; Found: C, 49.29; H, 4.52; N, 18.60).

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