Synthesis of Mutagenic Methyl- and Phenyl-substituted 2-Amino-3H-imidazo[4,5-f]quinoxalines via 2,1,3-Benzoselenadiazoles

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2-Amino-3-methyl-3H-imidazo[4,5-f]quinoxaline, all its derivatives with 1-4 methyl groups in positions 4, 5, 7 and 8, and 2-amino-3,5-dimethyl-7,8-diphenyl-3H-imidazo[4,5-f]quinoxaline have been synthesized from the corresponding 6-methylaminoo-5-nitroquinoxalines through reduction and cyclization with cyanogen bromide. The quinoxalines were obtained from the appropriate α-dicarbonyl compounds and 4-methylamino-3-nitro-1,2-benzenediamines. The latter were prepared from 4-halo-1,2-benzenediamines via 2,1,3-benzoselenadiazoles. The 7- and 8-phenyl derivatives of 2-amino-3,5-dimethyl-3H-imidazo[4,5-f]quinoxaline have been synthesized in a slightly different way.

Methyl derivatives of 2-amino-3-methyl-3H-imidazo[4,5-f]quinoxaline (7A in Scheme 2) are found in heated proteinaceous foods and are among the most potent mutagens known. An improved method for their synthesis was developed in our laboratory and briefly communicated by a letter in 1986, 2 see Schemes 1 and 2. By the use of 2,1,3-benzoselenadiazoles 2-4 as intermediates, this method circumvents the generally sluggish and wasteful nitration of quinoxalines, performed in most of the older methods. 3-6 Another merit of the new method concerns the isomeric mixtures obtained from asymmetric α-dicarbonyl compounds, such as pyruvaldehyde: one or other of the isomers can be predominated by appropriate choice of the acidity 7 or the solvent. 8 The method has later been used to solve various synthetic problems. 8-10

The aim of the present paper is to describe the precursors and products in more detail than was done in the letter 2 and to explore the scope of the method. We have prepared the methyl derivatives (7Ab-7Dd) and three methyl phenyl derivatives (7Ce-7Cg). Being closely related to known food mutagens, these derivatives were intended for use in investigations 11 of the relationship between mutagenic activity and substitution pattern.

Results and discussion

For one of the desired imidazooquinazolines (7Ce), detailed synthetic procedures have been published. 8 In general, these procedures could be adopted without change or after only slight modification. The preparation of 2,1,3-benzoselenadiazoles 2-4 is shown in Scheme 1. Among the 4-halo-1,2-benzenediamines 1, used as starting materials, 1A was commercially available. Diamine 1C 8 and the hydrochloride of 1B 12 were prepared essentially according to the literature. Diamine 1D was prepared from commercial 2,3-dimethyl-6-nitroaniline by bromination with pyridinium bromide perbromide, followed by reduction with dithionite. Compound 2B gave two nitration products, viz., 3B and 8 (see below) in the ratio 3:1. However, the separation of these isomers was not necessary, since the minor product (8) did not react in the subsequent treatment with aqueous methylamine. The products 4 were obtained in good yields.

Scheme 1. Synthesis and nitration of the 2,1,3-benzoselenadiazole intermediates. i, SeO₂/1 M HCl at 80°C; ii, HNO₃/H₂SO₄/0–20°C/1 h; iii, 40% aq. MeNH₂/MeOCH₂CH₂OH/reflux/15 min.

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Dedicated to Professor Salo Gronowitz on the occasion of his 65th birthday.
and 5C into the respective quinazolines 6Aa and 6Ca in \( \geq 85\% \) yield.

At this stage, the previously unknown 6-halo-5-nitroquinazolines had been synthesized by performing the condensation with the \( \alpha \)-dicarbonyl compound before the halogen displacement,\textsuperscript{16} i.e., by deselenation of 3 rather than 4. This was achieved with hydriodic acid.\textsuperscript{17} In this way, diamine 11 (Scheme 3) was obtained from 3C. In condensations with pyruvaldehyde, the presence of alkali affected the isomeric ratio of the 6-haloquinazolines\textsuperscript{7} more than that of the 6-methylaminoquinazolines. This new approach was therefore used in the condensations of phenylglyoxal with 11 to give the quinazolines 12 and 13, as outlined in Scheme 3. In the presence of potassium hydroxide, isomer 12 was the main product, whereas 13 predominated under neutral or acidic conditions. Finally, the halogen in each isomer was displaced by heating with aqueous methylamine, yielding the desired quinazolines 6Ce and 6Cf. Such displacement of the halogen in 6-halo-5-nitroquinazolines\textsuperscript{7,16} through reaction with isotopically labelled methylamine provides an efficient route to specifically labelled imidazoquinazolines (7).

Scheme 2. Synthesis of the 2-aminoimidazo[4,5-\( f \)]quinazolines. i. 40% aq. \( \text{NH}_2\text{SH}/\text{MeOH} \)/reflux/3 h; ii. \( \text{R}^2\text{COCOR}^1/\text{MeOH} \)/reflux/3 h or \( \text{R}^2\text{COCOR}^2/2 \text{M KOH/MeOH} \)/reflux/3 h; iii. \( \text{H}_2/\text{Pd-C/MeOH} \)/reflux/1 h; iv. \( \text{BrCN/SiO}_2/\text{MeOH} \)/refluex/1 h.

Scheme 3. Synthesis of the quinazoline precursors of the monophenyl-substituted 2-aminoimidazo[4,5-\( f \)]quinazolines.

Experimental

General methods. Flash liquid chromatography (FC) was performed on silica gel (230–400 mesh ASTM, Merck). All reactions and purifications were monitored by TLC with UV detection on aluminium sheets coated with silica
gel 60 F<sub>254</sub> (Merck). All evaporation were performed under reduced pressure at 40°C. Comparisons with authentic samples were made by means of TLC and <sup>1</sup>H NMR spectroscopy. Melting points (uncorrected) were determined on a Mettler FP5 or FP62 instrument. The <sup>1</sup>H NMR spectra were obtained on a Varian VX9-400 spectrometer at 20°C, and referenced to the solvent (CHCl<sub>3</sub>, 7.26, MeOD 3.31, Me<sub>2</sub>CO 2.04 or Me<sub>3</sub>SO 2.49 ppm). Coupling constants J are given in Hz and without sign. The mass spectra were obtained on a Finnigan 4021 instrument, with direct insertion, 70 eV electron impact ionization, and an ion source temperature of 200°C. Ions containing isotopes other than <sup>79</sup>Br, <sup>35</sup>Cl or <sup>80</sup>Se are not listed.

**Materials.** Unless otherwise stated, these were commercial samples. All organic solvents were either freshly distilled or of p.a. quality. Solvent mixtures are defined by volume ratios (v/v). Petroleum refers to petroleum ether, b.p. 60–70°C.

**4-Chloro-5-methyl-1,2-benzenediamine (1B).** The hydrochloride of 1B was prepared from 2-chloro-4-nitrotoluene by nitration, followed by reduction with tin(II) chloride in hydrochloric acid.<sup>12</sup>

**5-Chloro-3-methyl-1,2-benzenediamine (1C) was prepared by hydrogenation of 4-chloro-2-methyl-6-nitroaniline.<sup>8</sup>**

**4-Bromo-2,3-dimethyl-6-nitroaniline.** 2,3-Dimethyl-6-nitroaniline (50 g, 0.30 mol) was added in one portion to a mixture of pyridinium bromide perbromide (116 g, 0.36 mol) in acetic acid (730 ml). After stirring at room temperature for 30 min, TLC (EtOAc–CHCl<sub>3</sub>, 1:1) indicated complete reaction. Water (320 ml) was added, and the product was filtered off. The crude product was crystallized from aqueous ethanol. Evaporation of the mother liquor, followed by a second crystallization, increased the yield from 64.4 g (87%) to 70.5 g (95%), m.p. 150.5–151.5°C. Anal. C<sub>9</sub>H<sub>11</sub>BrN<sub>2</sub>O; C, H, N. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.22 and 2.45 (2- and 3-Me, two s), 6.2 (NH, br s), 8.29 (5-H, s). MS, m/z (% rel. int.): 244 (M<sup>+</sup>, 100), 198 (36), 118 (81).

**5-Bromo-3,4-dimethyl-1,2-benzenediamine (1D).** 4-Bromo-2,3-dimethyl-6-nitroaniline (30 g, 0.12 mol) was dissolved in a mixture of methanol (900 ml) and 25% aqueous ammonia (75 ml). To the refluxing solution, solid sodium dithionite (90 g, 0.5 mol) was added portiionwise over 1 h. After 3 h, when the reduction was complete according to TLC (CHCl<sub>3</sub>–EtOAc, 1:1), the reaction mixture was filtered hot from the white precipitate obtained in the reduction. The precipitate was washed with hot methanol. The combined filtrates were evaporated to half the original volume, and water was added until the product precipitated. Crystallization from benzene–petroleum yielded 1D (22.5 g, 87%), m.p. 85.5–86.5°C. Anal. C<sub>9</sub>H<sub>11</sub>BrN<sub>2</sub>; C, H, N. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.16 and 2.31 (3- and 4-Me, two s), 3.25 and 3.4 (1- and 2-NH<sub>2</sub>, two br s), 6.86 (6-H, s). MS, m/z (% rel. int.): 214 (M<sup>+</sup>, 74), 135 (100), 108 (27).

**4-Chloro-6-methyl-3-nitro-1,2-benzenediamine (1I) was prepared by reduction of benzozelenediazole 3C with hydriodic acid.<sup>16</sup>**

**Syntheses of halobenzozelenediazoles (Scheme 1): general procedure, cf. Ref. 8.** The appropriate diamine 1 (0.100 mol) or its hydrochloride was heated at 80°C in 1 M hydrochloric acid (300 ml). A solution of selenium dioxide (22.2 g, 0.2 mol) in water (150 ml) was added dropwise. The product precipitated immediately. When all the selenium dioxide had been added, TLC (EtOAc–CHCl<sub>3</sub>, 1:1) showed complete reaction. The product 2 was filtered off and washed with plenty of cold water. Further purification was not necessary.

**5-Chloro-2,1,3-benzozelenediazole (2A), yield 19.6 g (90%), has been obtained previously<sup>18</sup> in essentially the same way. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.43 (6-H, dd, J 2.0 and 9.5), 7.77 (7-H, d, J 9.5), 7.86 (4-H, d, J 2.0), MS, m/z (% rel. int.): 218 (M<sup>+</sup>, 100), 191 (12), 183 (18), 103 (67), 76 (70).**

**5-Chloro-6-methyl-2,1,3-benzozelenediazole (2B).** Yield 20.4 g (88%), m.p. 154–156°C. Anal. C<sub>9</sub>H<sub>11</sub>NMR (CDCl<sub>3</sub>): δ 2.51 (Me, d, J 1.2), 7.69 (7-H, q, J 1.2), 7.89 (4-H, s). MS, m/z (% rel. int.): 232 (M<sup>+</sup>, 100), 205 (19), 197 (28), 117 (43), 90 (53).

**6-Chloro-4-methyl-2,1,3-benzozelenediazole (2C), yield 20.8 g (90%), has been obtained previously<sup>8</sup> in essentially the same way.**

**6-Bromo-4,5-dimethyl-2,1,3-benzozelenediazole (2D).** Yield 24.9 g (86%), m.p. 182.5–183.5°C. Anal. C<sub>9</sub>H<sub>11</sub>BrN<sub>2</sub>; C, H, N. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 2.45 and 2.68 (4- and 5-Me, two s), 8.09 (7-H, s); MS, m/z (% rel. int.): 290 (M<sup>+</sup>, 50), 211 (11), 184 (14), 131 (21), 77 (100).

**Nitration of halobenzozelenediazoles (Scheme 1 and formula 8): general procedure, cf. Ref. 8.** The appropriate intermediate 2 (0.100 mol) was added portionwise with stirring to concentrated sulfuric acid (50 ml), cooled in ice. Next, a cold solution of concentrated nitric acid (10 ml, 0.14 mol) in concentrated sulfuric acid (20 ml) was added dropwise so slowly that the temperature remained below room temperature. After 1 h, TLC (PhMe–MeCN, 3:1) showed complete reaction, and the reaction mixture was poured onto ice (200 g). The precipitated product 3 was filtered off, washed with water (5 × 50 ml) and crystallized from 2-methoxyethanol.

**5-Chloro-4-nitro-2,1,3-benzozelenediazole (3A), yield 21.5 g (82%), has been obtained previously<sup>17</sup> in essen-**

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tially the same way. ^1H NMR (CDCl₃): δ 7.60 (6-H, d, J 9.5), 7.96 (7-H, d, J 9.5). MS, m/z (% rel. int.): 263 (M + 100), 233 (64), 217 (14), 205 (74), 182 (47).

5-Chloro-6-methyl- and 6-chloro-5-methyl-4-nitro-2,1,3-benzoazeniadazole (3B and 8). According to GC, the product was an approximately 4:1 mixture of 3B and 8. It was obtained in a yield of ca. 22 % (80 %) and used for the synthesis of the nitroamine 4B. For separation of the isomers, the crystallization was replaced by FC (CCl₃-EtOAc, 15:1). The following data were obtained for the pure components, where Rₜ refers to TLC with the solvent system used for FC.

Isomer 3B: yield 15.5 g (56 %), Rₜ 0.30, m.p. 218–219°C. Anal. C₉H₈ClN₂O₂S: C, H, N. ^1H NMR (CDCl₃): δ 2.60 (Me, d, J 12), 7.88 (7-H, q, J 12). MS, m/z (% rel. int.): 277 (M + 81), 247 (60), 219 (73), 196 (18), 115 (100).

Isomer 8: yield 5.5 g (20%), Rₜ 0.45, m.p. 230–231°C. Anal. C₉H₈ClN₂O₂S: C, H, N. ^1H NMR (CDCl₃): δ 2.53 (Me, s), 8.09 (7-H, s). MS, m/z (% rel. int.): 277 (M + 2), 260 (26), 180 (42), 151 (24), 115 (100).

5-Chloro-7-methyl-4-nitro-2,1,3-benzoazeniadazole (3C), yield 27.1 g (98 %), has been obtained previously in essentially the same way.

6-Bromo-4,5-dimethyl-7-nitro-2,1,3-benzoazeniadazole (3D). Yield 23.1 g (69 %), m.p. 218–219°C. Anal. C₇H₆BrN₂O₂S: C, H, N. ^1H NMR (CDCl₃): δ 2.60 and 2.81 (4- and 5-Me, two s). MS, m/z (% rel. int.): 335 (M + 31), 305 (38), 209 (22), 129 (24), 76 (100).

Syntheses of (methylamino)nitrobenezenediazoles 4 (Scheme 1): general procedure, cf. Ref. 8. To a refluxing solution of the appropriate nitro-2,1,3-benzoazeniadazole 3 (19 mmol) in 2-methoxyethanol (30 ml), was added 40 % aqueous methylamine (4.6 g, 60 mmol) dropwise over 5 min. After 10 min, TLC (PhMe–MeCN, 2:1) showed complete reaction. The product 4 separated as a yellow precipitate on cooling and dilution with water (100 ml). It was collected and crystallized from aqueous ethanol.

5-Methylamino-4-nitro-2,1,3-benzoazeniadazole (4A) has been reported but not characterized. Yield 4.56 g (93 %), m.p. 258–259°C. Anal. C₇H₆N₂O₂S: C, H, N. ^1H NMR (CDCl₃): δ 3.32 (Me, d, J 5.3), 7.43 (6-H, d, J 10.0), 7.92 (7-H, d, J 10.0), 10.3 (NH, br s). MS, m/z (% rel. int.): 258 (M + 72), 224 (17), 213 (21), 201 (18), 93 (100).

6-Methyl-5-methylamino-4-nitro-2,1,3-benzoazeniadazole (4B). After correction for the amount of 8 present in the starting material, the yield was 4.22 g (82 %), m.p. 207–208°C. Anal. C₇H₈N₂O₂S: C, H, N. ^1H NMR (CDCl₃): δ 2.48 (6-Me, s), 3.13 (4Me, d, J 5.5), 6.7 (NH, br s), 7.62 (7-H, s). MS, m/z (% rel. int.): 272 (M + 41), 238 (22), 227 (29), 211 (14), 93 (100).

7-Methyl-5-methylamino-4-nitro-2,1,3-benzoazeniadazole (4C), yield 4.53 g (88 %), has been obtained previously in essentially the same way.

4,5-Dimethyl-6-methylamino-7-nitro-2,1,3-benzoazeniadazole (4D). Yield 3.79 g (70 %), m.p. 209–210°C. Found: C 37.3; H 3.5; N 19.2. Calc. for C₉H₁₀N₂O₃S: C 37.9; H 3.5; N 19.7. ^1H NMR (CDCl₃): δ 2.39 and 2.69 (4- and 5-Me, two s), 3.13 (4Me, d, J 5.6), 7.3 (NH, br s). MS, m/z (% rel. int.): 286 (M + 27), 241 (17), 160 (23), 107 (30), 53 (100).

Syntheses of triamines 5 (Scheme 2): general procedure, cf. Ref. 8. To a refluxing suspension of the appropriate 5-methylamino-4-nitro-2,1,3-benzoazeniadazole 4 (40 mmol) in methanol (300 ml), was added dropwise commercial 40 % aqueous ammonium sulfide (20 ml, 160 mmol). After 3 h, TLC (CH₃Cl–EtOAc, 2:1) showed complete reaction. The reaction mixture was filtered hot, and the precipitate washed with hot methanol (3 × 50 ml). The combined filtrates were used as a stock solution of crude 5 in the syntheses of quinoxalines 6 according to Scheme 2 and for the isolation of pure 5A and 5C. For the latter purpose, the solution was concentrated to 20 ml. The crude product 5 precipitated, when cold water (20 ml) was added. It was recrystallized from aqueous ethanol.

4-Methylamino-3-nitro-1,2-benzenediamine (5A) has previously been prepared in solution. It has now also been isolated and characterized. Yield 5.8 g (80 %), m.p. 147–150°C. Anal. C₆H₅N₂O₂S: C, H, N. ^1H NMR (CDCl₃): δ 2.8 (1-NH₂, br s), 2.91 (Me, d, J 4.9), 5.83 (5-H, d, J 8.7), 6.5 (2-NH₂, br s), 6.92 (6-H, d, J 8.7), 8.0 (4-NH, br s). MS, m/z (% rel. int.): 182 (M + 91), 165 (49), 147 (100), 135 (42), 120 (32).

6-Methyl-4-methylamino-3-nitro-1,2-benzenediamine (5C). Yield 5.57 g (71 %), m.p. 148–151°C. Anal. C₆H₁₂N₂O₂S: C, H, N. ^1H NMR (CDCl₃): δ 2.23 (6-Me, s), 2.6 (1-NH₂, br s), 2.91 (4Me, d, J 5.0), 5.74 (2-NH₂, br s), 8.1 (4-NH, br s). MS, m/z (% rel. int.): 196 (M + 32), 179 (21), 161 (40), 149 (27), 57 (100).

Syntheses of quinoxalines 6 via triamines 5 (Scheme 2): general procedure, cf. Ref. 8. The solution of crude 5, obtained from 4 (40 mmol) was used, except for the solutions of 5C, which were prepared by dissolving pure 5C (785 mg, 4.0 mmol) in 95 % ethanol (45 mol). However, the purification of 5C is not necessary and hardly worthwhile. To the refluxing solution of 5, was added dropwise the appropriate a-dicarboxyl compound. Unless otherwise stated, 30 % aqueous glyoxal (3.9 g, 20 mmol), 40 % aqueous pyruvaldehyde (3.6 g, 20 mmol), butyacetyl (1.7 g, 20 mmol), phenyglyoxal monohydrate (0.62 g, 4.1 mmol) or benzil (1.7 g, 8 mmol) was employed. After 1–3 h, all 5 had been consumed according to TLC (EtOAc–PhMe, 1:1). The reaction mixture was diluted.
with cold water (75 ml), concentrated to 75 ml and extracted with chloroform (5 × 20 ml). The extract was evaporated onto silica gel and purified by FC (EtOAc-petroleum, 1:2). The purified product was crystallized from methanol or aqueous ethanol.

When two isomeric products were possible (R° ≠ R'), this procedure strongly favoured the isomer with a pyrazine hydrogen remote from the nitro group (R° = H). The other isomer (R° = H) was obtained by repeating the experiment with alkali, i.e., the methanolic solution of 5 was made alkaline with 2 M potassium hydroxide (7 ml) before the addition of the α-dicarbonyl compound. In general, this resulted in the formation of both isomers in considerable amounts, but repeated FC and crystallization always yielded the desired isomer in a pure state.

6-Methylamino-5-nitroquinoline (6AA). The yield (480 mg, 59%) was improved by the following modification. The Schiff base 9° (220 mg, 1.0 mmol) was dissolved in 5 M hydrochloric acid (1.0 ml) and added to a solution of pure 5A (91 mg, 0.50 mmol) in 95% ethanol (10 ml). The mixture was stirred for ca. 30 min to ensure complete reaction (TLC: petroleum–EtOAc, 5:1), concentrated to ca. 2 ml and diluted with water (2 ml). On cooling, 6AA separated as yellow needles. Recrystallization from 95% ethanol yielded 87 mg (85%), m.p. 195–196°C. Anal. C16H13N2O2: C, H, N. 'H NMR (CDCl3): δ 3.19 (Me, d, J 5.1), 7.42 and 8.08 (7- and 8-H, two d, J 9.7), 7.7 (NH, br s), 8.62 and 8.86 (2- and 3-H, two d, J 1.9). MS, m/z (% rel. int.): 204 (M, 100), 170 (21), 157 (26), 143 (58), 129 (51).

2-Methyl-6-methylamino-5-nitroquinoline (6AB). With alkali, a 44:56 mixture of 6AB and 6AC was obtained in 65% yield. The pure 6AB was identical with an authentic sample.3

2-Methyl-7-methylamino-8-nitroquinoline (6AC). Without alkali, the crude product was a 3:97 mixture of 6AB and 6AC, according to ²H NMR spectroscopy. Yield 700 mg (80%) of pure 6AC, identical with an authentic sample.3

2,3-Dimethyl-6-methylamino-5-nitroquinoline (6AD). Yield 810 mg (87%), identical with an authentic sample.5

7-Methyl-6-methylamino-5-nitroquinoline (6BA). Yield 445 mg (51%), m.p. 141–142°C. Anal. C16H15N2O2: C, H, N. 'H NMR (CDCl3): δ 2.44 (7-Me, s), 3.10 (NMe, d, J 5.5), 4.6 (NH, br s), 7.82 (8-H, s), 8.61 and 8.71 (2- and 3-H, two d, J 2.0). MS, m/z (% rel. int.): 218 (M, 100), 184 (30), 171 (41), 157 (49), 143 (54).

2,7-Dimethyl-6-methylamino-5-nitroquinoline (6BB). With alkali, a 45:55 mixture of 6BB and 6BC was obtained in 65% yield. The pure 6BB was identical with an authentic sample.4

2,6-Dimethyl-7-methylamino-8-nitroquinoline (6BC). Without alkali, the crude product was a 5:95 mixture of 6BB and 6BC, according to ²H NMR spectroscopy. Yield 700 mg (75%) of pure 6BC, identical with an authentic sample.4

2,3,7-Trimethyl-6-methylamino-5-nitroquinoline (6BD). Yield 820 mg (83%), m.p. 181–182°C. Anal. C16H14N2O2: C, H, N. ¹H NMR (CDCl3): δ 2.39 (7-Me, s), 2.64 and 2.66 (2- and 3-Me, two s), 3.06 (NMe, d, J 5.7), 4.4 (NH, br s), 7.70 (8-H, s). MS, m/z (% rel. int.): 246 (M, 100), 212 (20), 199 (36), 185 (33), 171 (39).

8-Methyl-6-methylamino-5-nitroquinoline (6CA). By the modification described for 6AA, the yield was raised from ca. 45% to 95 mg (87%), m.p. 115–118°C. Anal. C16H16N2O2: C, H, N. ¹H NMR (CDCl3): δ 2.76 (8-Me, s), 3.18 (NMe, d, J 5.1), 7.25 (7-H, s), 8.0 (NH, br s), 8.62 and 8.86 (2- and 3-H, two d, J 2.0). MS, m/z (% rel. int.): 218 (M, 100), 199 (17), 184 (15), 173 (21), 156 (44).

2,8-Dimethyl-6-methylamino-5-nitroquinoline (6CB). With alkali, a 66:34 mixture of 6CB and 6CC was obtained in 62% yield. The pure 6CB was identical with an authentic sample.8

2,5-Dimethyl-7-methylamino-8-nitroquinoline (6CC). Without alkali, the crude product was a 5:95 mixture of 6CB and 6CC, according to ²H NMR spectroscopy. Yield 630 mg (68%) of pure 6CC, identical with an authentic sample.8

2,3,8-Trimethyl-6-methylamino-5-nitroquinoline (6CD). Yield 900 g (91%), m.p. 183–185°C. Anal. C16H14N2O2: C, H, N. ¹H NMR (CDCl3): δ 2.65 and 2.70 (2- and 3-Me, two s), 2.71 (8-Me, d, J 1.0), 3.12 (NMe, d, J 5.1), 7.07 (7-H, q, J 1.0), 7.7 (NH, br s). MS, m/z (% rel. int.): 246 (M, 100), 227 (18), 212 (15), 201 (22), 185 (31).

8-Methyl-6-methylamino-5-nitro-2-phenylquinoline (6CE). With alkali, an 80:20 mixture of 6CE and 6CF was obtained in 76% yield. FC (CH₂Cl₂) and crystallization yielded pure 6CE (670 mg, 57%), m.p. 188–190°C. Anal. C20H16N2O2: C, H, N. ¹H NMR (CDCl3): δ 2.85 (8-Me, d, J 1.0), 3.20 (NMe, d, J 5.0), 7.25 (7-H, q, J 1.0), 7.50–7.58 and 8.17–8.20 (Ph, two m), 8.15 (NH, br s), 9.34 (3-H, s). MS, m/z (% rel. int.): 294 (M, 100), 275 (16), 260 (28), 249 (33), 232 (30).

5-Methyl-7-methylamino-8-nitro-2-phenylquinoline (6CF). Without alkali, a 5:95 mixture of 6CE and 6CF was obtained in 68% yield. FC (CH₂Cl₂) and crystallization yielded pure 6CF (750 mg, 64%), m.p. 237–240°C. Anal. C20H14N2O2: C, H, N. ¹H NMR (CDCl3): δ 2.78 (5-Me, d, J 1.0), 3.18 (NMe, d, J 5.1), 7.17 (6-H, q, J 1.0), 7.51–7.57 and 8.26–8.29 (Ph, two m), 7.95 (NH, br s), 9.10 (3-H, s). MS, m/z (% rel. int.): 294 (M, 100), 275 (22), 260 (15), 249 (31), 232 (26).

SYNTHESIS OF IMIDAZOQUINOXALINES
8-Methyl-6-methylamino-5-nitro-2,3-diphenylquinazoline (6Cg). Acetic acid was used as the solvent rather than ethanol. After 30 min at 100°C, TLC (PhMe–MeCN, 2:1) showed complete reaction. The product precipitated, when water (4 ml) was added. Crystalization from aqueous ethanol yielded 6Cg (1.30 g, 88%), m.p. 265–267°C. Anal. C_{32}H_{19}N_{3}O_{2}: C, H, N. 'H NMR (CDCl₃): δ 2.81 (8-Me), 3.19 (NMe, d, J 4.9), 7.19 (7-H, s), 7.31–7.37 and 7.61–7.70 (2- and 3-Ph, two m), 8.3 (NH, br s). MS, m/z (% rel. int.): 370 (M⁺, 55), 351 (5), 340 (6), 335 (14), 325 (11), 105 (100).

5,6-Dimethyl-7-methylamino-8-nitroquinazoline (6Da). Yield 420 mg (45%); the modification described for 6AA was not tried, m.p. 161–162°C. Anal. C₇H₁₂N₂O₃: C, H, N. 'H NMR (CDCl₃): δ 2.37 and 2.76 (5- and 6-Me, two s), 3.08 (NMe, d, J 5.5), 4.65 (NH, br s), 8.63 and 8.71 (2- and 3-H, two d, J 2.0). MS, m/z (% rel. int.): 232 (M⁺, 100), 213 (26), 199 (29), 187 (47), 170 (42).

2,7,8-Trimethyl-6-methylamino-5-nitroquinazoline (6Db). With alkali, an 86:14 mixture of 6Db and 6Dc was obtained in 80% yield. Yield 680 mg (69%) of pure 6Db, m.p. 184–185°C. Anal. C_{14}H_{16}N₂O₃: C, H, N. 'H NMR (CDCl₃): δ 2.37, 2.71 and 2.76 (2-, 7- and 8-Me, three s), 3.05 (NMe, d, J 5.1), 4.55 (NH, br s), 8.71 (3-H, s), MS, m/z (% rel. int.): 246 (M⁺, 100), 227 (30), 213 (36), 201 (55), 185 (44).

2,6-Trimethyl-7-methylamino-8-nitroquinazoline (6Db). Without alkali, the crude product was a 10:90 mixture of 6Db and 6Dc. Yield 650 mg (66%) of pure 6Dc, m.p. 178–179°C. Anal. C_{14}H_{16}N₂O₃: C, H, N. 'H NMR (CDCl₃): δ 2.34, 2.68 and 2.73 (2-, 5- and 6-Me, three s), 3.06 (NMe, d, J 5.6), 4.55 (NH, br s), 8.50 (3-H, s), MS, m/z (% rel. int.): 246 (M⁺, 100), 227 (29), 213 (36), 201 (52), 185 (41).

2,3,5,6-Tetramethyl-7-methylamino-8-nitroquinazoline (6Dd). Yield 650 mg (62%), m.p. 173–174°C. Anal. C_{15}H_{18}N₂O₃: C, H, N. 'H NMR (DMSO-d₆): δ 2.26, 2.54, 2.59 and 2.63 (2-, 3-, 5- and 6-Me, four s), 2.82 (NMe, d, J 5.2), 6.2 (NH, br s). MS, m/z (% rel. int.): 260 (M⁺, 100), 241 (28), 227 (34), 215 (54), 199 (42).

Syntheses of aminoimidazoquinazolines 7 from quinazolines 6 (Scheme 2): general procedure, cf. Refs. 3 and 8. Raney nickel (one teaspoonful) was added to a solution of 6 (2.3 mmol) in 95% ethanol (15 ml). The mixture was hydrogenated under ambient conditions and with vigorous stirring. After 1 h, TLC (PhMe–EtOAc, 1:1) indicated complete reaction. The catalyst was filtered off quickly by suction through Celite. Cyanogen bromide (0.3 g, 3.2 mmol) was added immediately to the filtrate. The reaction mixture was put in the refrigerator overnight, which caused the hydrobromide of 7 to precipitate. The salt was filtered off, washed with cold ethanol (3 × 1 ml) and dissolved in the minimum of water. To the clear solution was added 25% aqueous ammonia (1 ml, 15 mmol). The precipitate of the free amine 7 was collected, washed with cold water (3 × 1 ml) and crystallized from PhMe–PrOH.

Occasionally, the hydrobromides of 7Da–d did not precipitate. In this case, the reaction mixture was evaporated, and the residue dissolved in water (25 ml). The solution was made basic with 25% aqueous ammonia (1 ml, 15 mmol) and extracted with 1-butanol (3 × 10 ml). The extract was dried, evaporated onto silica gel and purified by FC (MeOH–CHCl₃, 1:8). The purified product was crystallized from 95% ethanol.

7AA, 7Ab, 7Ac and 7Ad have been obtained previously in essentially the same way. The respective yields were 197 mg (43%), 350 mg (71%), 378 mg (77%) and 375 mg (72%).

2-Amino-3,4-dimethyl-3-H-imidazo[4,5-1]quinazoline (7Ba). Yield 250 mg (51%), m.p. > 300°C. Anal. C₇H₁₁N₂: C, H, N. 'H NMR (DMSO-d₆): δ 2.82 (4-Me, s), 3.84 (3-Me, s), 6.5 (NH₂, br s), 7.31 (5-H, s), 8.67 and 8.70 (7- and 8-H, two d, J 1.8). MS, m/z (% rel. int.): 213 (M⁺, 100), 212 (65), 198 (16), 185 (24), 171 (8).

7BB and 7BC have been obtained previously in essentially the same way. The respective yields were 365 mg (70%) and 390 mg (75%).

2-Amino-3,4,7,8-tetramethyl-3-H-imidazo[4,5-1]quinazoline (7Bd). Yield 265 mg (48%), m.p. > 300°C. Anal. C₁₉H₁₃N₅: C, H, N. 'H NMR (DMSO-d₆): δ 2.59 and 2.62 (7- and 8-Me, s), 2.76 (4-Me, s), 3.80 (3-Me, s), 6.35 (NH₂, br s), 7.17 (5-H, s). MS, m/z (% rel. int.): 241 (M⁺, 100), 240 (70), 226 (10), 213 (15), 159 (28).

2-Amino-3,5-dimethyl-3-H-imidazo[4,5-1]quinazoline (7Ca). Yield 147 mg (30%), m.p. > 300°C. Anal. C₇H₁₁N₂: C, H, N. 'H NMR (CDCl₃): δ 2.86 (5-Me, s), 3.70 (3-Me, s), 4.8 (NH₂, br s), 7.49 (4-H, s), 8.80 and 8.85 (7- and 8-H, two d, J 1.8). MS, m/z (% rel. int.): 213 (M⁺, 100), 212 (72), 197 (24), 185 (10), 171 (6).

2-Amino-3,5,7-trimethyl-3-H-imidazo[4,5-1]quinazoline (7Cb). Yield 315 mg (60%), m.p. > 300°C. Anal. C₁₉H₁₃N₅: C, H, N. 'H NMR (CDCl₃): δ 2.78 and 2.84 (5- and 7-Me, two s), 3.69 (3-Me, s), 4.65 (NH₂, br s), 7.44 (4-H, s), 8.75 (8-H, s). MS, m/z (% rel. int.): 227 (M⁺, 100), 226 (72), 212 (7), 199 (12), 185 (4).

2-Amino-3,5,8-trimethyl-3-H-imidazo[4,5-1]quinazoline (7Cc). Yield 365 mg (70%), has been obtained previously in essentially the same way.

2-Amino-3,5,7,8-tetramethyl-3-H-imidazo[4,5-1]quinazoline (7Cd). Yield 450 mg (81%), m.p. > 300°C. Anal. C₂₁H₁₅N₅: C, H, N. 'H NMR (CDCl₃): δ 2.74 and 2.78 (7- and 8-Me, two s), 2.82 (5-Me, s), 3.67 (3-Me, s), 4.5 (NH₂, br s), 7.35 (4-H, s). MS, m/z (% rel. int.): 241 (M⁺, 100), 240 (59), 226 (3), 213 (8), 159 (24).
SYNTHESIS OF IMIDAZOQUINOXALINES

2-Amino-3,5-dimethyl-7-phenyl-3H-imidazo[4,5-f]quinoxaline (7Ce). Yield 485 mg (73%), m.p. >300°C. Anal. C_{17}H_{14}N_{2}: C, H, N. ^1H NMR (DMSO-d_6): δ 2.85 (5-Me, s), 3.68 (3-Me, s), 7.3 (NH, br s), 7.5-7.62 and 8.38-8.38 (Ph, two m), 7.87 (4-H, s), 9.53 (8-H, s). MS, m/z (% rel. int.): 289 (M, 100), 288 (52), 274 (10), 261 (9), 159 (12).

2-Amino-3,5-dimethyl-8-phenyl-3H-imidazo[4,5-f]quinoxaline (7CT). Yield 500 mg (75%), m.p. >300°C. Anal. C_{17}H_{14}N_{2}: C, H, N. ^1H NMR (DMSO-d_6): δ 2.77 (5-Me, s), 3.65 (3-Me, s), 6.55 (NH, br s), 7.5-7.60 and 8.33-8.36 (Ph, two m), 7.70 (4-H, s), 9.40 (7-H, s). MS, m/z (% rel. int.): 289 (M, 100), 288 (46), 274 (5), 261 (8), 159 (10).

2-Amino-3,5-dimethyl-7,8-diphenyl-3H-imidazo[4,5-f]quinoxaline (7CG). Yield 690 mg (82%), m.p. >300°C. Anal. C_{17}H_{14}N_{2}: C, H, N. ^1H NMR (DMSO-d_6): δ 2.79 (5-Me, s), 3.66 (3-Me, s), 6.55 (NH, br s), 7.33-7.37 and 7.49-7.52 (7- and 8-Ph, two m), 7.75 (4-H, s). MS, m/z (% rel. int.): 365 (M, 100), 364 (49), 350 (30), 159 (35), 158 (15).

2-Amino-3,4,5,6-tetramethyl-3H-imidazo[4,5-f]quinoxaline (7Da). Yield 355 mg (68%), m.p. >300°C. Anal. C_{17}H_{14}N_{2}: C, H, N. ^1H NMR (CDCl_3): δ 2.81 (4- and 5-Me, s), 3.94 (3-Me, s), 4.55 (NH, br s), 8.77 (7- and 8-H, s). MS, m/z (% rel. int.): 227 (M, 100), 226 (62), 212 (22), 199 (14), 185 (5).

2-Amino-3,4,5,7-tetramethyl-3H-imidazo[4,5-f]quinoxaline (7Db). Yield 320 mg (58%), m.p. >300°C. Anal. C_{17}H_{14}N_{2}: C, H, N. ^1H NMR (CDCl_3): δ 2.76, 2.78 and 2.79 (4-, 5- and 7-Me, three s), 3.92 (3-Me, s), 4.55 (NH, br s), 8.66 (8-H, s). MS, m/z (% rel. int.): 241 (M, 100), 240 (76), 226 (27), 213 (15), 198 (7).

2-Amino-3,4,5,8-tetramethyl-3H-imidazo[4,5-f]quinoxaline (7Dc). Yield 305 mg (55%), m.p. >300°C. Anal. C_{17}H_{14}N_{2}: C, H, N. ^1H NMR (CDCl_3): δ 2.78 (4- and 5-Me, s), 3.94 (3-Me, s), 4.75 (NH, br s), 8.66 (7-H, s). MS, m/z (% rel. int.): 241 (M, 100), 226 (73), 226 (27), 212 (17), 198 (27).

2-Amino-3,4,5,7,8-pentamethyl-3H-imidazo[4,5-f]quinoxaline (7Dd). Yield 364 mg (62%), m.p. >300°C. Anal. C_{17}H_{14}N_{2}: C, H, N. ^1H NMR (CDCl_3): δ 2.73, 2.77, 2.77 and 2.79 (4-, 5-, 7- and 8-Me, three s), 3.92 (3-Me, s), 4.4 (NH, br s). MS, m/z (% rel. int.): 255 (M, 100), 254 (84), 240 (28), 227 (15), 173 (10).

Alternative syntheses of quinoxalines 6 (Scheme 3): 6-chloro-8-methyl-5-nitro-2-phenylquinoxaline (12). Potassium hydroxide (30 mg, 0.5 mmol) was dissolved in hot ethanol (3 ml) and added to a solution of the diamine 11 (98 mg, 0.5 mmol) in ethanol (2 ml) was added to the hot mixture, which was refluxed for 10 min. On cooling, a 80:20 mixture of 12 and 13 was obtained in 68% yield. Pure 12 was separated from 13 by FC (CCl_4–EtOAc, 20:1), R_f 0.41, m.p. 248–250°C. Anal. C_{17}H_{10}ClN_2O_2: C, H, N. `^1H NMR (CDCl_3): δ 2.85 (8-Me, d, J 1.0), 7.56–7.58 and 8.21–8.23 (Ph, two m), 7.63 (7-H, q, J 1.0), 9.44 (3-H, s). MS, m/z (% rel. int.): 299 (M, 69), 269 (34), 253 (10), 217 (10), 105 (10).

7-Chloro-5-methyl-8-nitro-2-phenylquinoxaline (13). Phenylglyoxal monohydrate (80 mg, 0.52 mmol) was dissolved in ethanol (2 ml) and added to a solution of the diamine 11 (98 mg, 0.5 mmol) in ethanol (10 ml). The mixture was refluxed for 10 min. On cooling, a 40:60 mixture of 12 and 13 was obtained in 80% yield. Pure 13 was separated from 12 by FC (CCl_4–EtOAc, 20:1), R_f 0.50, m.p. 249–251°C. Anal. C_{17}H_{10}ClN_2O_2: C, H, N. `^1H NMR (CDCl_3): δ 2.91 (5-Me, d, J 1.0), 7.58–7.62 and 8.23–8.26 (Ph, two m), 7.68 (6-H, q, J 1.0), 9.42 (3-H, s). MS, m/z (% rel. int.): 299 (M, 100), 269 (47), 253 (25), 218 (19), 205 (12).

8-Methyl-6-methylamino-5-nitro-2-phenylquinoxaline (6Ce). A mixture of the chloroquinoxaline 12 (150 mg, 0.5 mmol), 40% aqueous methylamine (3 ml, 40 mmol) and 95% ethanol (15 ml) was refluxed, until TLC (CCl_4–EtOAc, 20:1) indicated that 12 had disappeared (ca. 4 h). On cooling, 6Ce precipitated (137 mg, 93%), identical with a sample prepared from 5C (see above).

5-Methyl-7-methylamino-8-nitro-2-phenylquinoxaline (6 Cf). A mixture of the chloroquinoxaline 13 (150 mg, 0.5 mmol), 40% aqueous methylamine (3 ml, 40 mmol) and 95% ethanol (15 ml) was refluxed, until TLC (CCl_4–EtOAc, 20:1) indicated that 13 had disappeared (ca. 4 h). On cooling, 6 Cf precipitated (139 mg, 95%), identical with a sample prepared from 5C (see above).

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Note added in proof: Six of the methyl-substituted imidazoquinoxalines were recently synthesised via an entirely different route.\textsuperscript{19}

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