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

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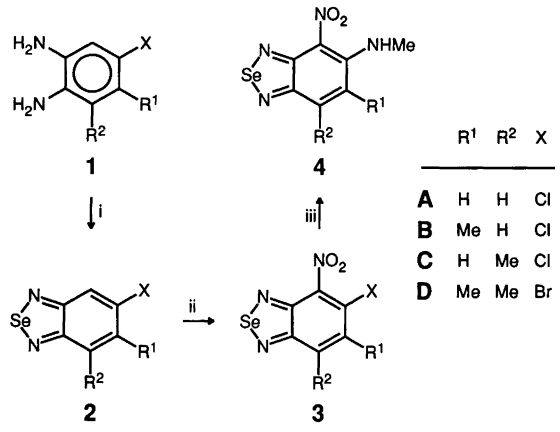
2-Amino-3-methyl-3*H*-imidazo[4,5-*f*]quinoxaline, all its derivatives with 1–4 methyl groups in positions 4, 5, 7 and 8, and 2-amino-3,5-dimethyl-7,8-diphenyl-3*H*-imidazo[4,5-*f*]quinoxaline have been synthesized from the corresponding 6-methylamino-5-nitroquinoxalines through reduction and cyclization 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-3*H*-imidazo-[4,5-*f*]quinoxaline have been synthesized in a slightly different way.

Methyl derivatives of 2-amino-3-methyl-3*H*-imidazo-[4,5-*f*]quinoxaline (**7Aa** in Scheme 2) are found in heated proteinaceous foods and are among the most potent mutagens known.[1] 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 made to predominate 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.

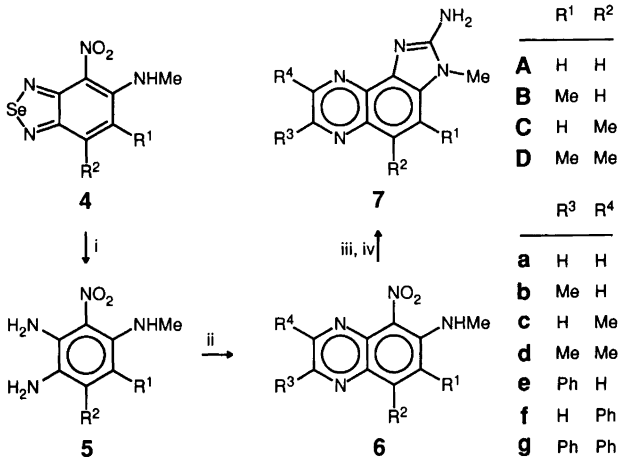
Results and discussion

For one of the desired imidazoquinoxalines (**7Cc**), 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, SeO_2/1 M HCl/80°C; ii, HNO_3/H_2SO_4/0–20°C/1 h; iii, 40% aq. $MeNH_2$/$MeOCH_2CH_2OH$/reflux/15 min.

* To whom correspondence should be adressed.
Dedicated to Professor Salo Gronowitz on the occasion of his 65th birthday.

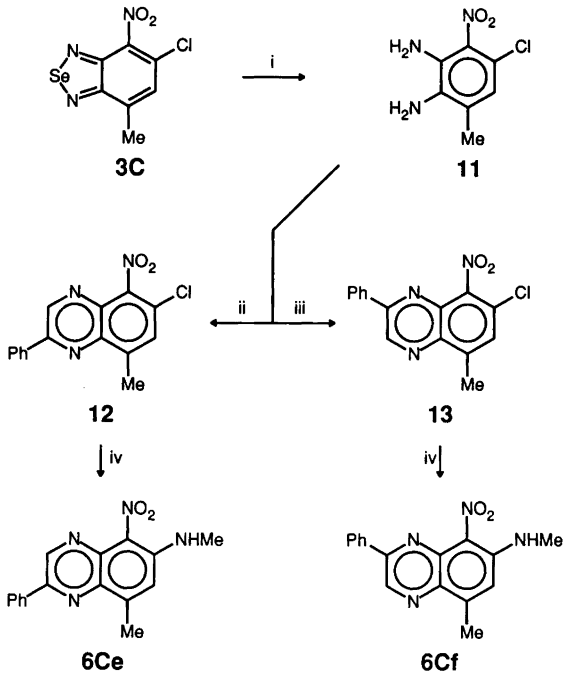


Scheme 2. Synthesis of the 2-aminoimidazo[4,5-*f*]quinoxalines. i, 40% aq. NH_4SH/MeOH/reflux/3 h; ii, R^3COCOR^4/MeOH/reflux/3 h or R^3COCOR^4/2 M KOH/MeOH/reflux/3 h; iii, H_2/Raney-Ni/95% EtOH/r.t./1 h; iv, BrCN/5°C/overnight.

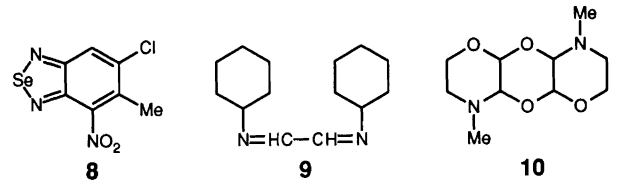
Scheme 2 shows the deselenation of **4** and the condensation of the resulting triamines **5** with the appropriate α-dicarbonyl compounds to give quinoxalines **6**. These were converted into the final products **7** by hydrogenation in the presence of Raney nickel and subsequent cyclization with cyanogen bromide as described previously.[2,8] In the deselenation of **4**, the previously[2,8] used mixture of ammonia and hydrogen sulfide was replaced by a commercial aqueous solution of ammonium sulfide, which was easier to handle and measure. Occasionally, the triamine **5** was isolated and purified, but that was not necessary.[2,8] The condensation of **5** with pyruvaldehyde yielded, of course, isomeric mixtures. In a neutral or acidic medium, the **c** isomer ($R^3 = H$, $R^4 = Me$) was obtained almost exclusively, apparently because of the favoured reaction between the more reactive groups, i.e., the aldehyde group and the unconjugated amino group.[2] However, in the presence of potassium hydroxide, the amount of the **b** isomer ($R^3 = Me$, $R^4 = H$) approached or surpassed that of the **c** isomer. This was probably because **5** now reacted through its conjugate base, formed by deprotonation of the more acidic, i.e., the conjugated amino group.[7,13] Thus, by performing the condensation in the presence or absence of alkali, the desired quinoxaline isomer was generally so predominant that it was isolated readily.

In order to improve the moderate yields (40–50%) of quinoxalines obtained from the triamines **5** and aqueous glyoxal, this was replaced by the glyoxal derivative **9**[14] or **10**.[15] The Schiff base **9** proved to be the more efficient reagent. At room temperature, it converted triamines **5A** and **5C** into the respective quinoxalines **6Aa** and **6Ca** in ⩾85% yield.

At this stage, the previously unknown 6-halo-5-nitroquinoxalines had been synthesized by performing the condensation with the α-dicarbonyl compound before the halogen displacement,[16] i.e., by deselenation of **3** rather than **4**. This was achieved with hydriodic acid.[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-haloquinoxalines[7] more than that of the 6-methylaminoquinoxalines. This new approach was therefore used in the condensations of phenylglyoxal with **11** to give the quinoxalines **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 quinoxalines **6Ce** and **6Cf**. Such displacement of the halogen in 6-halo-5-nitroquinoxalines[7,16] through reaction with isotopically labelled methylamine provides an efficient route to specifically labelled imidazoquinoxalines (**7**).



Scheme 3. Synthesis of the quinoxaline precursors of the monophenyl-substituted 2-aminoimidazo[4,5-*f*]quinoxalines. i, HI/HCl/r.t./2 h; ii, PhCOCHO/KOH/EtOH/reflux/10 min; iii, PhCOCHO/EtOH/reflux/10 min; iv, 40% aq. $MeNH_2$/95% EtOH/reflux/≈4 h.



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_{254} (Merck). All evaporations were performed under reduced pressure at 40°C. Comparisons with authentic samples were made by means of TLC and ^1H NMR spectroscopy. Melting points (uncorrected) were determined on a Mettler FP5 or FP62 instrument. The ^1H NMR spectra were obtained on a Varian VXR-400 spectrometer at 20°C, and referenced to the solvent ($CHCl_3$ 7.26, MeOD 3.31, Me_2CO 2.04 or Me_2SO 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 ^{79}Br, ^{35}Cl or ^{80}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.[12]

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

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–$CHCl_3$, 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. $C_8H_9BrN_2O_2$: C, H, N. ^1H NMR ($CDCl_3$): 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*, 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 portionwise over 1 h. After 3 h, when the reduction was complete according to TLC ($CHCl_3$–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. $C_8H_{11}BrN_2$: C, H, N. ^1H NMR ($CDCl_3$): δ 2.16 and 2.31 (3- and 4-Me, two s), 3.25 and 3.4 (1- and 2-NH_2, two br s), 6.86 (6-H, s). MS, *m/z* (% rel. int.): 214 (*M*, 74), 135 (100), 108 (27).

4-Chloro-6-methyl-3-nitro-1,2-benzenediamine (**11**) was prepared by reduction of benzoselenadiazole **3C** with hydriodic acid.[16]

Syntheses of halobenzoselenadiazoles **2** *(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–$CHCl_3$, 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-benzoselenadiazole (**2A**), yield 19.6 g (90%), has been obtained previously[18] in essentially the same way. ^1H NMR ($CDCl_3$): 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*, 100), 191 (12), 183 (18), 103 (67), 76 (70).

5-Chloro-6-methyl-2,1,3-benzoselenadiazole (**2B**). Yield 20.4 g (88%), m.p. 154–156°C. Anal. $C_7H_5ClN_2Se$: C, H, N. ^1H NMR ($CDCl_3$): 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*, 100), 205 (19), 197 (28), 117 (43), 90 (53).

6-Chloro-4-methyl-2,1,3-benzoselenadiazole (**2C**), yield 20.8 g (90%), has been obtained previously[8] in essentially the same way.

6-Bromo-4,5-dimethyl-2,1,3-benzoselenadiazole (**2D**). Yield 24.9 g (86%), m.p. 182.5–183.5°C. Anal. $C_8H_7BrN_2Se$: C, H, N. ^1H NMR (DMSO-d_6): δ 2.45 and 2.68 (4- and 5-Me, two s), 8.09 (7-H, s). MS, *m/z* (% rel. int.): 290 (*M*, 50), 211 (11), 184 (14), 131 (21), 77 (100).

Nitration of halobenzoselenadiazoles **2** *(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-benzoselenadiazole (**3A**), yield 21.5 g (82%), has been obtained previously[17] in essen-

tially the same way. ^{1}H NMR ($CDCl_3$): 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-benzoselenadiazole (**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 g (80%) and used for the synthesis of the nitroamine **4B**. For separation of the isomers, the crystallization was replaced by FC (CCl_4–EtOAc, 15:1). The following data were obtained for the pure components, where R_f refers to TLC with the solvent system used for FC.

Isomer **3B**: yield 15.5 g (56%), R_f 0.30, m.p. 218–219°C. Anal. $C_7H_4ClN_3O_2Se$: C, H, N. ^{1}H NMR ($CDCl_3$): δ 2.60 (Me, d, *J* 1.2), 7.88 (7-H, q, *J* 1.2). MS, *m/z* (% rel. int.): 277 (*M*, 81), 247 (60), 219 (73), 196 (18), 115 (100).

Isomer **8**: yield 5.5 g (20%), R_f 0.45, m.p. 230–231°C. Anal. $C_7H_4ClN_3O_2Se$: C, H, N. ^{1}H NMR ($CDCl_3$): δ 2.53 (Me, s), 8.09 (7-H, s). MS, *m/z* (% rel. int.): 277 (*M*, 42), 260 (26), 180 (42), 151 (23), 115 (100).

5-Chloro-7-methyl-4-nitro-2,1,3-benzoselenadiazole (**3C**), yield 27.1 g (98%), has been obtained previously[8] in essentially the same way.

6-Bromo-4,5-dimethyl-7-nitro-2,1,3-benzoselenadiazole (**3D**). Yield 23.1 g (69%), m.p. 218–219°C. Anal. $C_8H_6BrN_3O_2Se$: C, H, N. ^{1}H NMR ($CDCl_3$): 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)nitrobenzoselenadiazoles **4** *(Scheme 1): general procedure, cf. Ref. 8.* To a refluxing solution of the appropriate nitro-2,1,3-benzoselenadiazole **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-benzoselenadiazole (**4A**) has been reported but not characterized.[2] Yield 4.56 g (93%), m.p. 258–259°C. Anal. $C_7H_6N_4O_2Se$: C, H, N. ^{1}H NMR ($CDCl_3$): 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-benzoselenadiazole (**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. $C_8H_8N_4O_2Se$: C, H, N, ^{1}H NMR ($CDCl_3$): δ 2.48 (6-Me, s), 3.13 (NMe, 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-benzoselenadiazole (**4C**), yield 4.53 g (88%), has been obtained previously[8] in essentially the same way.

4,5-Dimethyl-6-methylamino-7-nitro-2,1,3-benzoselenadiazole (**4D**). Yield 3.79 g (70%), m.p. 209–210°C. Found: C 37.3; H 3.5; N 19.2. Calc. for $C_9H_{10}N_4O_2Se$: C 37.9; H 3.5; N 19.7. ^{1}H NMR ($CDCl_3$): δ 2.39 and 2.69 (4- and 5-Me, two s), 3.13 (NMe, 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-benzoselenadiazole **4** (40 mmol) in methanol (300 ml), was added dropwise commercial 40% aqueous ammonium sulfide (20 ml, 160 mmol). After 3 h, TLC (CH_2Cl_2–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[9] been prepared in solution. It has now also been isolated and characterized. Yield 5.8 g (80%), m.p. 147–150°C. Anal. $C_7H_{10}N_4O_2$: C, H, N. ^{1}H NMR ($CDCl_3$); δ 2.8 (1-NH_2, br s), 2.91 (Me, d, *J* 4.9), 5.83 (5-H, d, *J* 8.7), 6.5 (2-NH_2, 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. $C_8H_{12}N_4O_2$: C, H, N. ^{1}H NMR ($CDCl_3$): δ 2.23 (6-Me, s), 2.6 (1-NH_2, br s), 2.91 (NMe, d, *J* 5.0), 5.74 (5-H, s), 6.6 (2-NH_2, 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** (4.0 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 α-dicarbonyl compound. Unless otherwise stated, 30% aqueous glyoxal (3.9 g, 20 mmol), 40% aqueous pyruvaldehyde (3.6 g, 20 mmol), biacetyl (1.7 g, 20 mmol), phenylglyoxal 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 ($R^3 \neq R^4$), this procedure strongly favoured the isomer with a pyrazine hydrogen remote from the nitro group ($R^3 = H$). The other isomer ($R^4 = H$) 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-nitroquinoxaline (**6Aa**). The yield (480 mg, 59%) was improved by the following modification. The Schiff base **9**[14] (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. $C_9H_8N_4O_2$: C, H, N. ^{1}H NMR ($CDCl_3$): 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-nitroquinoxaline (**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-nitroquinoxaline (**6Ac**). Without alkali, the crude product was a 3:97 mixture of **6Ab** and **6Ac**, according to ^{1}H NMR spectroscopy. Yield 700 mg (80%) of pure **6Ac**, identical with an authentic sample.[3]

2,3-Dimethyl-6-methylamino-5-nitroquinoxaline (**6Ad**). Yield 810 mg (87%), identical with an authentic sample.[5]

7-Methyl-6-methylamino-5-nitroquinoxaline (**6Ba**). Yield 445 mg (51%), m.p. 141–142°C. Anal. $C_{10}H_{10}N_4O_2$: C, H, N. ^{1}H NMR ($CDCl_3$): 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-nitroquinoxaline (**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-nitroquinoxaline (**6Bc**). Without alkali, the crude product was a 5:95 mixture of **6Bb** and **6Bc**, according to ^{1}H NMR spectroscopy. Yield 700 mg (75%) of pure **6Bc**, identical with an authentic sample.[4]

2,3,7-Trimethyl-6-methylamino-5-nitroquinoxaline (**6Bd**). Yield 820 mg (83%), m.p. 181–182°C. Anal. $C_{12}H_{14}N_4O_2$: C, H, N. ^{1}H NMR ($CDCl_3$): 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-nitroquinoxaline (**6Ca**). By the modification described for **6Aa**, the yield was raised from ca. 45% to 95 mg (87%), m.p. 115–118°C. Anal. $C_{10}H_{10}N_4O_2$: C, H, N. ^{1}H NMR ($CDCl_3$): 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-nitroquinoxaline (**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-nitroquinoxaline (**6Cc**). Without alkali, the crude product was a 5:95 mixture of **6Cb** and **6Cc**, according to ^{1}H NMR spectroscopy. Yield 630 mg (68%) of pure **6Cc**, identical with an authentic sample.[8]

2,3,8-Trimethyl-6-methylamino-5-nitroquinoxaline (**6Cd**). Yield 900 g (91%), m.p. 183–185°C. Anal. $C_{12}H_{14}N_4O_2$: C, H, N. ^{1}H NMR ($CDCl_3$): 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-phenylquinoxaline (**6Ce**). With alkali, an 80:20 mixture of **6Ce** and **6Cf** was obtained in 76% yield. FC (CH_2Cl_2) and crystallization yielded pure **6Ce** (670 mg, 57%), m.p. 188–190°C. Anal. $C_{16}H_{14}N_4O_2$: C, H, N. ^{1}H NMR ($CDCl_3$): 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-phenylquinoxaline (**6Cf**). Without alkali, a 5:95 mixture of **6Ce** and **6Cf** was obtained in 68% yield. FC (CH_2Cl_2) and crystallization yielded pure **6Cf** (750 mg, 64%), m.p. 237–240°C. Anal. $C_{16}H_{14}N_4O_2$: C, H, N. ^{1}H NMR ($CDCl_3$): 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).

8-Methyl-6-methylamino-5-nitro-2,3-diphenylquinoxaline (**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. Crystallization from aqueous ethanol yielded **6Cg** (1.30 g, 88%), m.p. 265–267°C. Anal. $C_{22}H_{18}N_4O_2$: C, H, N. ^{1}H NMR ($CDCl_3$): δ 2.81 (8-Me, s), 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-nitroquinoxaline (**6Da**). Yield 420 mg (45%; the modification described for **6Aa** was not tried), m.p. 161–162°C. Anal. $C_{11}H_{12}N_4O_2$: C, H, N. ^{1}H NMR ($CDCl_3$): 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-nitroquinoxaline (**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. $C_{12}H_{14}N_4O_2$: C, H, N. ^{1}H NMR ($CDCl_3$): 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), 8.61 (3-H, s). MS, *m/z* (% rel. int.): 246 (*M*, 100), 227 (30), 213 (36), 201 (55), 185 (44).

2,5,6-Trimethyl-7-methylamino-8-nitroquinoxaline (**6Dc**). 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. $C_{12}H_{14}N_4O_2$: C, H, N. ^{1}H NMR ($CDCl_3$): 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-nitroquinoxaline (**6Dd**). Yield 650 mg (62%), m.p. 173–174°C. Anal. $C_{13}H_{16}N_4O_2$: C, H, N. ^{1}H NMR (DMSO-d_6): 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 aminoimidazoquinoxalines **7** *from quinoxalines* **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–$CHCl_3$, 1:8). The purified product was crystallized from 95% ethanol.

7Aa,[10] **7Ab**,[3] **7Ac**[3] and **7Ad**[5] 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-f]quinoxaline* (**7Ba**). Yield 250 mg (51%), m.p. >300°C. Anal. $C_{11}H_{11}N_5$: C, H, N. ^{1}H NMR (DMSO-d_6): δ 2.82 (4-Me, s), 3.84 (3-Me, s), 6.5 (NH_2, 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[4] 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-f]quinoxaline* (**7Bd**). Yield 265 mg (48%), m.p. >300°C. Anal. $C_{13}H_{15}N_5$: C, H, N. ^{1}H NMR (DMSO-d_6): δ 2.59 and 2.62 (7- and 8-Me, s), 2.76 (4-Me, s), 3.80 (3-Me, s), 6.35 (NH_2, 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-f]quinoxaline* (**7Ca**). Yield 147 mg (30%), m.p. >300°C. Anal. $C_{11}H_{11}N_5$: C, H, N. ^{1}H NMR ($CDCl_3$): δ 2.86 (5-Me, s), 3.70 (3-Me, s), 4.8 (NH_2, 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-f]quinoxaline* (**7Cb**). Yield 315 mg (60%), m.p. >300°C. Anal. $C_{12}H_{13}N_5$: C, H, N. ^{1}H NMR ($CDCl_3$): δ 2.78 and 2.84 (5- and 7-Me, two s), 3.69 (3-Me, s), 4.65 (NH_2, 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-f]quinoxaline* (**7Cc**), yield 365 mg (70%), has been obtained previously[8] in essentially the same way.

*2-Amino-3,5,7,8-tetramethyl-3*H*-imidazo[4,5-f]quinoxaline* (**7Cd**). Yield 450 mg (81%), m.p. >300°C. Anal. $C_{13}H_{15}N_5$: C, H, N. ^{1}H NMR ($CDCl_3$): δ 2.74 and 2.78 (7- and 8-Me, two s), 2.82 (5-Me, s), 3.67 (3-Me, s), 4.5 (NH_2, br s), 7.35 (4-H, s). MS, *m/z* (% rel. int.): 241 (*M*, 100), 240 (59), 226 (3), 213 (8), 159 (24).

*2-Amino-3,5-dimethyl-7-phenyl-3*H-*imidazo[4,5-f]quinoxaline* (**7Ce**). Yield 485 mg (73%), m.p. >300°C, Anal. $C_{17}H_{15}N_5$: C, H, N. ^{1}H NMR (DMSO-d_6): δ 2.85 (5-Me, s), 3.68 (3-Me, s), 7.3 (NH_2, br s), 7.53–7.62 and 8.35–8.38 (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-3*H-*imidazo[4,5-f]quinoxaline* (**7Cf**). Yield 500 mg (75%), m.p. >300°C. Anal. $C_{17}H_{15}N_5$: C, H, N. ^{1}H NMR (DMSO-d_6): δ 2.77 (5-Me, s), 3.65 (3-Me, s), 6.55 (NH_2, br s), 7.50–7.60 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-3*H-*imidazo[4,5-f]-quinoxaline* (**7Cg**). Yield 690 mg (82%), m.p. >300°C. Anal. $C_{23}H_{19}N_5$: C, H, N. ^{1}H NMR (DMSO-d_6): δ 2.79 (5-Me, s), 3.66 (3-Me, s), 6.55 (NH_2, 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 (3), 159 (35), 158 (15).

*2-Amino-3,4,5-trimethyl-3*H-*imidazo[4,5-f]quinoxaline* (**7Da**). Yield 355 mg (68%), m.p. >300°C. Anal. $C_{12}H_{13}N_5$: C, H, N. ^{1}H NMR ($CDCl_3$): δ 2.81 (4- and 5-Me, s), 3.94 (3-Me, s), 4.55 (NH_2, 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-3*H-*imidazo[4,5-f]quinoxaline* (**7Db**). Yield 320 mg (58%), m.p. >300°C. Anal. $C_{13}H_{15}N_5$: C, H, N. ^{1}H NMR ($CDCl_3$): δ 2.76, 2.78 and 2.79 (4-, 5- and 7-Me, three s), 3.92 (3-Me, s), 4.5 (NH_2, 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-3*H-*imidazo[4,5-f]quinoxaline* (**7Dc**). Yield 305 mg (55%), m.p. >300°C. Anal. $C_{13}H_{15}N_5$: C, H, N. ^{1}H NMR ($CDCl_3$): δ 2.78 (4-, 5- and 8-Me, s), 3.94 (3-Me, s), 4.75 (NH_2, 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-3*H-*imidazo[4,5-f]quinoxaline* (**7Dd**). Yield 364 mg (62%), m.p. >300°C. Anal. $C_{14}H_{17}N_5$: C, H, N. ^{1}H 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_2, 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 (10 ml). A solution of phenylglyoxal monohydrate (80 mg, 0.52 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. $C_{15}H_{10}ClN_3O_2$: C, H, N. ^{1}H 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 (100).

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. $C_{15}H_{10}ClN_3O_2$: C, H, N. ^{1}H 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 (**6Cf**). 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, **6Cf** 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.[19]

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