Polyaza heterocycles. Part 3.[1] Halogenation of 1-substituted quinoxalino[2,3-*c*]cinnolines: mechanistic implications

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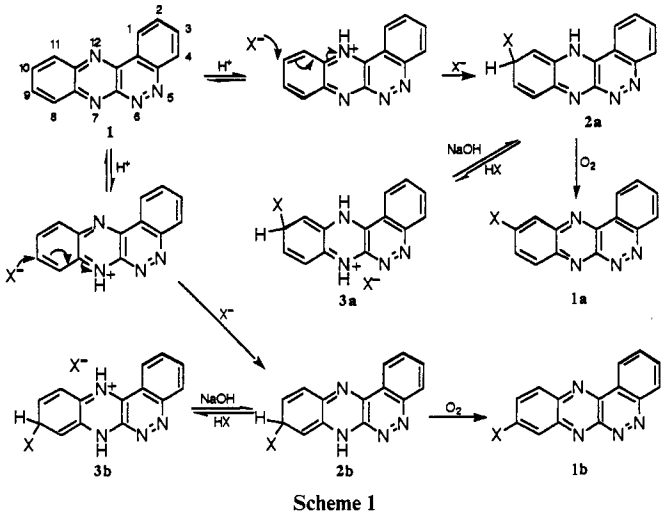
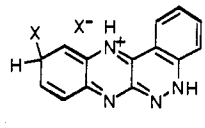
Since it has been proposed that halogenation of quinoxalino[2,3-*c*]cinnolines at C-10, using hydrogen chloride or bromide in chloroform, occurs through initial protonation of the substrate at N-12, attempts have been made to inhibit this protonation by the introduction of an additional substituent at C-1. Where this substituent is chloro, bromo or methyl, chlorination still occurs preferentially at C-10, although the yield and the reaction rate decrease along the series, lending weight to the mechanistic proposal.

One of the most remarkable features of the chemistry of the quinoxalino[2,3-*c*]cinnoline ring system **1** is the ease with which it undergoes substitutive halogenation.[2] The reaction merely involves passing gaseous hydrogen chloride or hydrogen bromide through the (orange) solution of the quinoxalinocinnoline in chloroform, whereupon a deep blue precipitate is formed. This precipitate, when filtered off and shaken with a mixture of aqueous sodium hydroxide and fresh chloroform until the blue colour is discharged and the orange colour restored to the organic layer, is converted into a chloro- or bromo-quinoxalino[2,3-*c*]cinnoline in yields which are almost invariably in excess of 70%. The halogen is almost always introduced at C-10, although when C-10 is already substituted it sometimes happens that the halogen is introduced at C-9. We believe that this type of halogenation may be unique among aza-heterocycles, and as such is worthy of further attention.

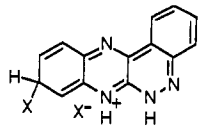
The mechanism proposed for this remarkable reaction is outlined in Scheme 1. Initial protonation of the quinoxalinocinnoline can occur, in principle, at any of the four nitrogen atoms, although MNDO calculations[2] indicate that N-5 and N-6 are essentially non-basic, and that protonation is therefore most likely at N-7 or N-12. Protonation at N-7 may be followed by nucleophilic attack of halide ion at C-9, giving **2b**, whereas attack of halide ion at C-10 (giving **2a**) ought to follow protonation at N-12. The idea that *addition* of hydrogen halide to the quinoxalinocinnolines may have occurred is supported by the mass spectra of the deep blue intermediates, which show in each case a molecular ion corresponding to the quinoxalinocinnoline plus one (*covalently bonded*) molecule of hydrogen halide.[2] The elemental analyses, however, suggest that further protonation of these initial adducts takes place, to form *ionic* hydrohalides: MNDO calculations support the formulation of these compounds as **3a** or **3b**, whereas the deep blue colour is more consistent with structures such as **4a** or **4b**, containing extended *para*-quinonoid systems. It is even possible that the blue compounds contain doubly protonated species.[2] In any event, however, reaction of base with these blue compounds is presumed to regenerate the simple adducts, **2a** or **2b**, and it is then supposed that these undergo atmospheric oxidation to restore the fully conjugated ring system and produce **1a** and **1b**.



Scheme 1



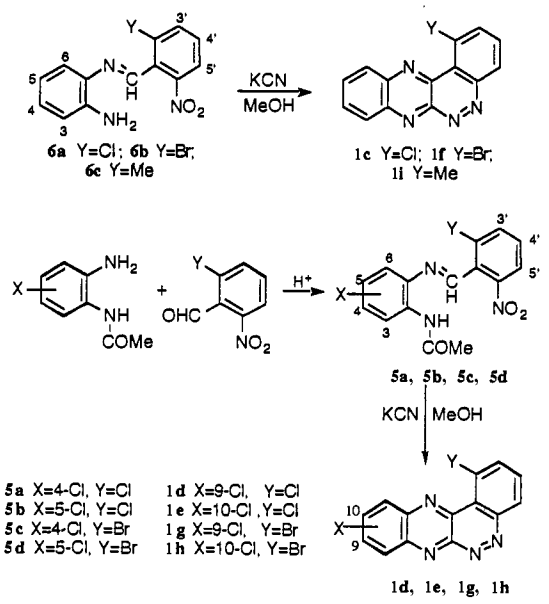
4a



4b

The MNDO calculations indicate little difference, in terms of energy, between protonation at N-12, leading ultimately to the 10-halogeno compound, and protonation at N-7, which should lead to the introduction of the halogen at C-9. The most electron-rich (and therefore, presumably, the most basic) nitrogen is N-12, but it is protonation at N-7 which yields the cation of lowest $\Delta H_f^{\ominus}$. The study which we now report represents an attempt to hinder protonation at N-12, in the hope either of inhibiting the halogenation altogether, or of diverting the site of protonation to N-7 (or elsewhere) and hence the position at which halogenation might occur. Protonation at N-12 ought to be hindered by the presence of a large substituent at C-1, and 1-choloroquinoxalino[2,3-*c*]cinnoline, **1c**, was already available in connection with a previous study;[1] accordingly we have studied the reaction of this compound with hydrogen chloride in chloroform.

This reaction follows the expected pattern, and gives (*via* a deep blue intermediate) a single product (66%), clearly (by ^{1}H NMR) either 1,9- **1d** or 1,10-dichloroquinoxalinocinnoline **1e**. 9- and 10-Chloro isomers in this series have very similar ^{1}H NMR spectra,[2] and a positive identification requires independent syntheses of both isomers. The syntheses use the standard method described in previous papers,[1,2] *viz.* the formation of the Schiff bases **5a** and **5b** from 2-chloro-6-nitrobenzaldehyde and 2-amino-4- or -5-chloroacetanilide, and cyclisation of the Schiff bases with potassium cyanide in methanol (Scheme 2). The product from the reaction of



Scheme 2

1-chloroquinoxalinocinnoline and hydrogen chloride is, undoubtedly, the 1,10-dichloro compound **1e**, and any steric or other effect due to the 1-chloro substituent is evidently insufficient to divert the 'normal' halogenation pathway.

An approximate scale drawing† of the chloroquinoxalino-[2,3-*c*]cinnoline molecule **1c**, using the bond lengths obtained from MNDO calculations on the parent ring system, taking the covalent radius of chlorine at 1.04 Å,[3] and the C–Cl bond length as 1.74 Å (as in chlorobenzene derivatives),[3] indicates that the approach of a proton to N-12, at least in the plane of the ring, certainly ought to be impeded by the chlorine, and that, unless the N-12 to C-12a bond is somewhat longer in the cation than in the parent quinoxalinocinnoline, the distance between N-12 and C-1 is scarcely sufficient to allow both an N-12 proton and the chlorine to lie in the plane of the ring without either N–H · · · Cl hydrogen bonding or distortion of normal inter-bond angles. The steric crowding ought to be greater still in the case of 1-bromoquinoxalinocinnoline, **1f** (covalent radius of Br = 1.20 Å; C–Br bond length in bromobenzene derivatives = 1.90 Å),[3] and the reaction of this compound with hydrogen chloride has therefore been investigated.

Compound **1f** is obtained by the standard reaction sequence. 2-Bromo-6-nitrobenzaldehyde, obtained, like its 2-chloro analogue,[1] from the corresponding toluene derivative using the Kröhnke oxidation, is condensed with 1 molar equiv. of *o*-phenylenediamine, and the resulting anil **6b** is cyclised by potassium cyanide in methanol. 1-Bromoquinoxalinocinnoline reacts with hydrogen chloride to give, *via* the usual type of blue intermediate, a single mono-chlorinated product, although the yield is, by a substantial margin, lower than usual in these reactions. Independent syntheses have again shown that the product is the 1-bromo-10-chloro compound **1h** rather than the 1-bromo-9-chloro isomer **1g**. Attempts to synthesize 1-iodoquinoxalino[2,3-*c*]cinnoline, so as to increase further the steric effect of the 1-substituent, have so far proved unsuccessful: several attempts to brominate the methyl group of 2-iodo-6-nitrotoluene[4] (the first step in the Kröhnke oxidation) have failed.

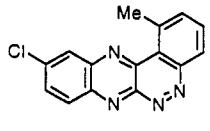
Of course, the possibility that halogeno substituents attached to C-1 may actually *promote* protonation at N-12 (by hydrogen bonding to the incoming proton) rather than inhibit it (through steric hindrance) cannot be ruled out, especially since intramolecular hydrogen bonding in the protonated species forms an additional six-membered ring. Hydrogen bonding of this type cannot play a part, however, in the reaction of 1-methylquinoxalino[2,3-*c*]cinnoline **1i** with hydrogen chloride: here the effect of the substituent is expected to be only steric.

2-Methyl-6-nitrobenzaldehyde was synthesized from the corresponding carboxylic acid by a modification of the published method:[5] conversion of the acid into the acid chloride, reduction of the latter using sodium borohydride and re-oxidation of the resulting benzyl alcohol with pyridinium chlorochromate. The aldehyde was then converted into the Schiff base **6c**, and thence into 1-methylquinoxalino[2,3-*c*]-cinnoline **1i**, by the standard procedure.

Reaction of compound **1i** with hydrogen chloride is both very slow and (surprisingly) incomplete. Whereas saturation of the chloroform solution of a quinoxalinocinnoline once with hydrogen chloride is generally sufficient to produce a high yield of the insoluble blue intermediate, in this case a substantial proportion of **1i** remains unchanged in the mother liquor, and even after two further treatments with hydrogen chloride approximately 15–20% of **1i** remains in the filtrate. Standard work-up of this blue intermediate in aqueous sodium hydroxide reveals a further anomaly: the final product is indeed a chloromethylquinoxalinocinnoline, but ^{1}H NMR and mass spectrometry show that it is contaminated by a substantial amount of unchanged starting compound **1i**.

Attempts to synthesize the authentic 9- and 10-chloro-1-methylquinoxalinocinnolines, by the general method of Scheme 2, have to date been unsuccessful. 2-Methyl-6-nitrobenzaldehyde fails to undergo condensation with the appropriately substituted aminochloroacetanilides under a variety of conditions; it is unclear if this failure is due to steric or electronic factors. The identity of the product from the chlorination of **1i** has therefore been determined from the ^{1}H NMR spectrum of the mixture in relation to the spectra of other 9- and 10-chloro-quinoxalino[2,3-*c*]cinnolines.

In the ^{1}H NMR spectrum of quinoxalino[2,3-*c*]cinnoline itself and those of its simple analogues, the order of deshielding is 1-H > 4-H > 8-H > 11-H > 2-, 3-, 9- and 10-H; in medium- or high-field spectra the difference in chemical shift between the 8-H and 11-H resonances is obvious (see, for example, Fig. 1). The presence of a chloro substituent at C-9 or C-10 appears not to affect the relative positions of the 8-H and 11-H resonances.[1,2] In the present case, the 300 MHz spectrum of the product mixture (Fig. 2) shows the 8-H resonance of the chloromethylquinoxalinocinnoline as an *ortho*-coupled doublet and the 11-H resonance, overlapping the corresponding resonance of **1i**, as a *meta*-coupled doublet; this coupling leaves little doubt that the chlorination product is, once again, the 10-chloro isomer (in this case, **1j**).



1j

Steric hindrance to protonation at N-12, therefore, although not apparently able to divert the course of the halogenation reaction, may at least diminish the efficiency of the process. This offers support for the proposed mechanism,[1] although admittedly it is not conclusive. The failure of the 1-methyl compound **1i** to undergo complete conversion into the blue intermediate, and the partial recovery of compound **1i** (unchlorinated) by basification of the intermediate, still require explanations. It is conceivable that an alternative (less basic) protonation site may come into play when N-12 is hindered, and that protonation at this alternative site is not followed by

† Compound **1c**, like all other quinoxalino[2,3-*c*]cinnolines isolated to date, crystallises in the form of fine needles which are not amenable to X-ray crystallographic examination.

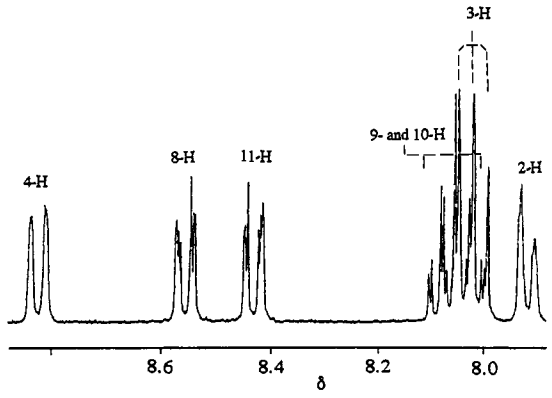


Fig. 1 The aromatic region of the ^{1}H NMR spectrum of 1-methylquinoxalino[2,3-*c*]cinnoline **1i**

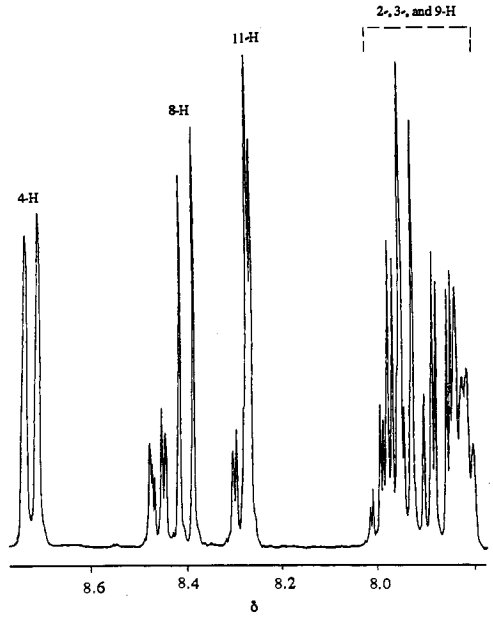


Fig. 2 Partial ^{1}H NMR spectrum of the product mixture from the reaction of **1i** with HCl: the resonances attributed to **1j** are indicated

addition of chloride ion but leads merely to a simple salt which is precipitated along with the blue adduct. It is also possible that the halogenation may occur through protonation at another site (*e.g.* N-5), or indeed that protonation is not the necessary first step in the halogenation sequence at all. These are questions to which answers are still being sought.

Experimental

The recorded IR spectra were those of Nujol mulls. ^{1}H NMR spectra were recorded at 200, 300 or 360 MHz, and ^{13}C NMR spectra at 50.3 MHz, in $CDCl_3$ solution with tetramethylsilane ($\delta_H = \delta_C = 0$) as reference, unless otherwise indicated. Coupling constants are expressed in Hz. Ether refers to diethyl ether.

2-Amino-4-chloroacetanilide, mp 144 °C (lit.,[6] 144 °C), and 2-amino-5-chloroacetanilide, mp 143 °C (lit.,[2] 144–145 °C; [7] 130–132 °C), were prepared (yields, 53 and 55%, respectively) by reduction of the corresponding nitro compounds using iron and acetic acid.[6] 2-Chloro-6-nitrobenzaldehyde, mp 69–71 °C, was prepared from 2-chloro-6-nitrotoluene by Kröhnke oxidation, and 1-chloroquinoxalino[2,3-*c*]cinnoline **1c**, mp 255–259 °C, was prepared by reaction of the anil **6a** with potassium cyanide in methanol, both as described in Part 2.[1]

2-Acetamido-4-chloro-*N*-(2-chloro-6-nitrobenzylidene)aniline 5a
A mixture of 2-amino-5-chloroacetanilide (0.42 g, 2.3 mmol), 2-chloro-6-nitrobenzaldehyde (0.40 g, 2.15 mmol), ethanol (15 cm^3) and a few crystals of toluene-*p*-sulfonic acid was heated under reflux for 10 min and then cooled. The *anil* **5a** (0.61 g, 80%) was filtered off; it had mp 221–223 °C (from ethanol) (Found: C, 51.0; H, 3.1; N, 11.8. $C_{15}H_{11}Cl_2N_3O_3$ requires C, 51.2; H, 3.15; N, 11.9%); ν_{max}/cm^{-1} 3370 (NH), 1695 (CO), 1500 and 1365 (NO_2); δ_H 2.32 (3 H, s, Me), 7.05 (1 H, dd, H-5), 7.19 (1 H, d, H-6), 7.53–7.59 (2 H, m, H-3′ and -4′), 7.69 (1 H, dd, H-5′), 8.25 (1 H, br s, NH), 8.62 (1 H, d, H-3) and 8.92 (1 H, s, CH=N); $J_{3',4'}$ 6.2, $J_{3,5}$ 2.4 and $J_{5,6}$ 8.6.

2-Acetamido-5-chloro-*N*-(2-chloro-6-nitrobenzylidene)aniline 5b
This anil was prepared similarly from 2-amino-4-chloroacetanilide (1.49 g, 8.1 mmol) and 2-chloro-6-nitrobenzaldehyde (1.5 g, 8.1 mmol); yield 2.19 g (77%); mp 201–203 °C (from ethanol) (Found: C, 51.0; H, 3.05; N, 11.9. $C_{15}H_{11}Cl_2N_3O_3$ requires C, 51.2; H, 3.15; N, 11.9%); ν_{max}/cm^{-1} 3350 (NH), 1700 (CO), 1510 and 1350 (NO_2); δ_H 2.32 (3 H, s, Me), 7.24 (1 H, d, H-6), 7.31 (1 H, dd, H-4), 7.55–7.65 (2 H, m, H-3′ and 4′), 7.66–7.75 (1 H, m, H-5′), 8.17 (1 H, br s, NH), 8.50 (1 H, d, H-3) and 8.95 (1 H, s, CH=N); $J_{3,4}$ 8.5 and $J_{4,6}$ 2.3.

1,9-Dichloroquinoxalino[2,3-*c*]cinnoline 1d
The anil **5a** (0.61 g, 1.73 mmol), potassium cyanide (0.30 g, 4.6 mmol) and methanol (45 cm^3) were heated together under reflux, in a nitrogen atmosphere, for 3 h; the mixture was then cooled in ice and the precipitate filtered off. The quinoxalinocinnoline **1d** (0.30 g, 58%) had mp 270–272 °C (from dimethylformamide) (Found: C, 55.6; H, 2.0; N, 18.6. $C_{14}H_6Cl_2N_4$ requires C, 55.8; H, 2.0; N, 18.6%); δ_H 8.00 (1 H, dd, H-10), 8.03 (1 H, t, H-3), 8.13 (1 H, dd, H-2), 8.40 (1 H, dd, H-11), 8.50 (1 H, dd, H-8) and 8.89 (1 H, dd, H-4); $J_{2,3}$ 7.8, $J_{3,4}$ 8.0, $J_{2,4}$ 1.3, $J_{8,10}$ 2.3, $J_{10,11}$ 9.1 and $J_{8,11}$ 0.5.

1,10-Dichloroquinoxalino[2,3-*c*]cinnoline 1e
(a) Compound **1e** was similarly obtained from the anil **5b** (1.50 g, 4 mmol), potassium cyanide (0.52 g, 8 mmol) and methanol (90 cm^3); yield 0.80 g (63%), mp 274–276 °C (from dimethylformamide).

(b) Hydrogen chloride gas was passed through a solution of 1-chloroquinoxalino[2,3-*c*]cinnoline **1c** (0.26 g, 0.98 mmol) in chloroform (50 cm^3) for *ca.* 15 min. The deep blue crystalline precipitate was filtered off, washed with chloroform, and allowed to dry. It was then shaken with aqueous sodium hydroxide (6 M; 40 cm^3) and chloroform (40 cm^3) until dissolution was complete and the blue colour was discharged. The orange chloroform layer was then washed with water, dried (Na_2SO_4) and evaporated to give the dichloroquinoxalinocinnoline **1e** (0.20 g, 68%), mp 271–274 °C (from dimethylformamide) (Found: C, 55.8; H, 1.9; N, 18.7. $C_{14}H_6Cl_2N_4$ requires C, 55.8; H, 2.0; N, 18.6%); δ_H 7.97 (1 H, dd, H-9), 8.04 (1 H, t, H-3), 8.14 (1 H, dd, H-2), 8.48 (1 H, dd, H-8),‡ 8.49 (1 H, dd, H-11)‡ and 8.90 (1 H, dd, H-4); $J_{2,4}$ 1.4, $J_{3,4}$ 7.9, $J_{8,9}$ 9.2 and $J_{9,11}$ 2.4; *m*/*z* 300/302/304 ($M^{+\bullet}$).

2-Bromo-6-nitrobenzaldehyde
The method of Clarke[8] was modified as follows. 2-Methyl-3-nitroaniline (5.0 g, 33 mmol) was heated briefly under reflux with hydrobromic acid (48%; 16 cm^3) and water (40 cm^3), and the solution then cooled to 0 °C and stirred while a solution of sodium nitrite (2.3 g, 33 mmol) in water (12 cm^3) was added dropwise. The temperature throughout the addition was maintained at 3–5 °C. When the addition was complete, the solution was allowed to warm to room temperature, when a solution of copper(I) bromide (5.1 g, 33 mmol) in hydrobromic acid (11 cm^3) and water (26 cm^3) was cautiously added. The mixture was then heated to 100 °C and steam distilled. The distillate was extracted with ether and the extract was dried

‡ Overlapping signals.

(Na_2SO_4) and concentrated to give 2-bromo-6-nitrotoluene (5.31 g, 75%), mp 35–37 °C (lit.,[9] 42 °C). This was then heated with *N*-bromosuccinimide (4.39 g, 25 mmol), benzoyl peroxide (1.24 g, 5 mmol) and carbon tetrachloride (400 cm^3) under reflux for 4 h; the mixture was then cooled and filtered, and the filtrate concentrated to give 6-bromo-2-nitrobenzyl bromide as an orange oil. The latter was treated at 0 °C with a mixture of dry pyridine (3 cm^3) and dry ethanol (4 cm^3) and the mixture was set aside overnight at room temperature. *N*-(2-Bromo-6-nitrobenzyl)pyridinium bromide was then filtered off and washed with a little ether; it had mp 204–206 °C (lit.,[8] 210 °C). The yield was 6.30 g (69%).

A solution of the foregoing pyridinium salt (3.0 g, 8 mmol) and *N*,*N*-dimethyl-*p*-nitrosoaniline (1.5 g, 8 mmol) in ethanol (37 cm^3) was cooled to 0 °C. Sodium hydroxide solution (1 M; 23 cm^3) was added dropwise, with stirring, to the mixture so that the temperature was maintained below 2 °C. When the addition was complete, the mixture was stirred at room temperature for 3 h and then diluted with water (50 cm^3) and cooled in ice. The nitrone was filtered off, washed with water and recrystallised from ethyl acetate; it had mp 160–162 °C (lit.,[8] 162 °C). The yield was 2.24 g (76%).

The nitrone (22.1 g, 0.06 mol) was added in small portions, with stirring, to sulfuric acid (3 M; 335 cm^3) at room temperature. Stirring was continued for a further 30 min after which the mixture was cooled in ice and the solid product filtered off and recrystallised from ethanol to give 2-bromo-6-nitrobenzaldehyde (12.5 g, 89%), mp 81–82 °C (lit.,[8] 82 °C).

N-(2-Bromo-6-nitrobenzylidene)-*o*-phenylenediamine 6b

2-Bromo-6-nitrobenzaldehyde (0.50 g, 2.17 mmol), *o*-phenylenediamine (0.24 g, 2.22 mmol), a few crystals of toluene-*p*-sulfonic acid and ethanol (8 cm^3) were heated together, under reflux, for 10 min. The solution was cooled and concentrated *in vacuo* to give the *anil* **6b** (0.42 g, 60%), mp 101–103 °C (from ethanol) (Found: C, 48.5; H, 3.1; N, 12.9. $C_{13}H_{10}BrN_3O_2$ requires C, 48.8; H, 3.15; N, 13.1%); ν_{max}/cm^{-1} 3460 and 3380 (NH_2) and 1510 and 1330 (NO_2); δ_H(80 MHz) 3.85 (2 H, br s, NH_2), 6.57–6.80 (2 H, m) and 6.97–7.17 (2 H, m) (both ArH), 7.40 (1 H, t, H-4′), 7.60 (1 H, dd, H-5′), 7.80 (1 H, dd, H-3′) and 8.75 (1 H, s, CH=N); $J_{3',4'}$ 8.0, $J_{4',5'}$ 8.2 and $J_{3',5'}$ 2.0.

1-Bromoquinoxalino[2,3-*c*]cinnoline 1f

N-(2-Bromo-6-nitrobenzylidene)-*o*-phenylenediamine **6b** (1.60 g, 5 mmol), potassium cyanide (0.65 g, 10 mmol) and methanol (100 cm^3) were heated together, under reflux, for 4 h. The mixture was then cooled in ice and the orange product filtered off and washed with water, to give the *title compound* **1f** (1.0 g, 64%), mp 237–238 °C (from dimethylformamide) (Found: C, 54.1; H, 2.2; N, 18.1. $C_{14}H_7BrN_4$ requires C, 54.0; H, 2.3; N, 18.0%); δ_H 7.88 (1 H, t, H-3),§ 7.98–8.07 (2 H, m, H-9 and 10), 8.29 (1 H, dt, H-2),§ 8.38–8.42 (1 H, m, H-11), 8.47–8.51 (1 H, m, H-8) and 8.89 (1 H, dd, H-4);§ $J_{2,3} = J_{3,4} = 7.9$ and $J_{2,4}$ 1.3.

Reaction of compound 1f with hydrogen chloride

Hydrogen chloride gas was passed for 15 min through a chloroform solution of the quinoxalinocinnoline (0.30 g, 0.96 mmol). The resulting blue solid was filtered off and shaken with a mixture of aqueous sodium hydroxide (5 M) and fresh chloroform until the blue colour was discharged. The orange chloroform layer was washed with water, dried (Na_2SO_4) and concentrated *in vacuo* to give 1-bromo-10-chloroquinoxalino-[2,3-*c*]cinnoline **1h** (0.10 g, 30%), identical with an authentic sample.

2-Acetamido-4-chloro-*N*-(2-bromo-6-nitrobenzylidene)aniline 5c

2-Amino-5-chloroacetanilide (1.32 g, 7.2 mmol) and 2-bromo-6-nitrobenzaldehyde (1.64 g, 7.1 mmol) were added to ethanol (25 cm^3) containing a few crystals of toluene-*p*-sulfonic acid, and the mixture was heated under reflux for 15 min. It was then cooled and the orange product filtered off and recrystallised from butanone to give the *anil* **5c** (2.14 g, 75%), mp 219–220 °C (Found: C, 45.4; H, 2.7; N, 10.4. $C_{15}H_{11}BrClN_3O_3$ requires C, 45.4; H, 2.8; N, 10.6%); ν_{max}/cm^{-1} 3380 (NH), 1700 (CO), 1520 and 1360 (NO_2); δ_H([$^2H_6$]-DMSO) 2.14 (3 H, s, Me), 7.23 (1 H, dd, H-5), 7.39 (1 H, d, H-6), 7.70 (1 H, t, H-4′),§ 8.06 (1 H, d, H-5′),§ 8.13 (1 H, dd, H-3′),§ 8.29 (1 H, d, H-3), 8.73 (1 H, br s, NH) and 8.91 (1 H, s, CH=N); $J_{4,5} = J_{3,4} = 8.1$, $J_{5,6}$ 8.5 and $J_{3,5}$ 2.4.

2-Acetamido-5-chloro-*N*-(2-bromo-6-nitrobenzylidene)aniline 5d

This compound was prepared from 2-amino-4-chloroacetanilide (1.32 g) and 2-bromo-6-nitrobenzaldehyde (1.64 g) by the same method as used for the preparation of the isomer **5c**, above. The bright yellow *anil* **5d** (2.21 g, 77%) had mp 214 °C (from ethanol) (Found: C, 45.4; H, 2.7; N, 10.6. $C_{15}H_{11}BrClN_3O_3$ requires C, 45.4; H, 2.8; N, 10.6%); ν_{max}/cm^{-1} 3300 (NH), 1690 (CO), 1510 and 1300 (NO_2); δ_H([$^2H_6$]-DMSO) 2.11 (3 H, s, Me), 7.37 (1 H, dd, H-4), 7.40 (1 H, d, H-6), 7.71 (1 H, t, H-4′), 8.07 (1 H, d, H-3), 8.12–8.20 (2 H, m, H-3′ and 5′), 8.71 (1 H, br s, NH) and 8.95 (1 H, s, CH=N); $J_{3,4}$ 8.2, $J_{4,6}$ 2.3 and $J_{3',4'} = J_{4',5'} = 8.7$.

1-Bromo-9-chloroquinoxalino[2,3-*c*]cinnoline 1g

The foregoing anil **5c** (2.21 g, 5.6 mmol), potassium cyanide (0.78 g, 12 mmol) and methanol (100 cm^3) were heated together under reflux for 5 h. The mixture was then cooled in ice and the orange product filtered off and washed with water to give the *title compound* **1g** (0.70 g, 37%), mp 277 °C (from dimethylformamide) (Found: C, 48.9; H, 1.7; N, 16.0. $C_{14}H_6BrClN_4$ requires C, 48.7; H, 1.75; N, 16.2%); δ_H 7.94 (1 H, t, H-3), 7.99 (1 H, dd, H-10), 8.38 (1 H, dd, H-2), 8.42 (1 H, dd, H-11), 8.51 (1 H, dd, H-8) and 8.95 (1 H, d, H-4); $J_{3,4}$ 7.9, $J_{10,11}$ 9.2, $J_{8,10}$ 2.3 and $J_{8,11}$ 0.3.

1-Bromo-10-chloroquinoxalino[2,3-*c*]cinnoline 1h

A similar procedure to the above was followed. The anil **5d** (2.14 g) and potassium cyanide (0.78 g) in methanol (80 cm^3) gave after 5 h the *title compound* **1h** (0.94 g, 50%), mp 288–289 °C (from dimethylformamide) (Found: C, 48.2; H, 1.6; N, 16.1. $C_{14}H_6BrClN_4$ requires C, 48.7; H, 1.75; N, 16.2%); δ_H 7.94 (1 H, t, H-3), 7.97 (1 H, dd, H-9), 8.37 (1 H, dd, H-2), 8.47 (1 H, dd, H-8),‡ 8.47 (1 H, dd, H-11)‡ and 8.93 (1 H, dd, H-4); $J_{2,3} = J_{3,4} = 8.0$, $J_{2,4}$ 1.2, $J_{8,9}$ 9.2, $J_{9,11}$ 2.2 and $J_{8,11}$ 0.5.

2-Methyl-6-nitrobenzaldehyde

A suspension of 2-methyl-6-nitrobenzoic acid (8.0 g, 44.2 mmol) in thionyl chloride (15.8 g, 132.5 mmol) containing dimethylformamide (1.0 g) was heated under reflux for 5 h and then cooled. The excess of thionyl chloride was evaporated off under reduced pressure and the crude acid chloride, dissolved in dry tetrahydrofuran (30 cm^3), was added during 30 min under nitrogen to a stirred slurry of sodium borohydride (6.35 g, 172.8 mmol) in the same solvent (30 cm^3), so that the temperature remained below 5 °C. The mixture was stirred for 20 min and then treated with water (200 cm^3) followed by hydrochloric acid (4 M; 45 cm^3). The mixture was then extracted with ether (5 × 50 cm^3) and the combined extracts were dried (Na_2SO_4) and concentrated to give a brown oil which was chromatographed (silica gel; eluent, dichloromethane) to afford 2-methyl-6-nitrobenzyl alcohol (4.63 g, 63%), mp 62–64.5 °C (lit.,[5] 58–62 °C); ν_{max}/cm^{-1} 3390 (OH) and 1510 and 1350 (NO_2); δ_H 2.52 (3 H, s, CH_3), 2.81 (1 H, br s, OH), 4.70 (2 H, s, CH_2), 7.32 (1 H, t, 4-H), 7.45 (1 H, d, 3-H), 7.65 (1 H, d, 5-H); $J_{3,4} = J_{4,5} =$ *ca.* 8; δ_C 19.8 (CH_3), 58.3 (CH_2), 122.5 (C-3), 129.0 (C-2), 133.0 (C-5), 135.8 (C-1), 141.0 (C-6) and 151.3 (C-4).

§ Non first-order spectrum.

A solution of pyridinium chlorochromate (1.77 g, 8.17 mmol) was added to a stirred solution of the foregoing alcohol (0.91 g, 5.45 mmol) in dichloromethane (10 cm^3), and the mixture then stirred for 48 h. It was then diluted with ether and filtered through Celite. The residue was extracted with ether (5 × 50 cm^3) and refiltered through Celite. The combined organic solutions were concentrated under reduced pressure, and the resulting dark waxy solid (0.90 g), mp 41.5–43 °C, was purified by chromatography (silica gel; eluent, ether) to give 2-methyl-6-nitrobenzaldehyde, mp 46–47 °C (lit.,[5] 47.5–48.5 °C); ν_{max}/cm^{-1} 1690 (C=O) and 1510 and 1350 (NO_2); δ_H 2.52 (3 H, s, CH_3), 7.50–7.71 (2 H, m, 3- and 4-H), 7.98 (1 H, d, 5-H) and 10.39 (1 H, s, CHO); δ_C 19.9 (CH_3), 122.2 (C-1), 131.6 (C-5),¶ 132.3 (C-2), 132.4 (C-3),¶ 137.2 (C-4), 139.4 (C-6) and 190.6 (CHO). Scaling-up was not attempted; larger quantities were obtained if necessary by multiple small-scale experiments.

N-(2-Methyl-6-nitrobenzylidene)-*o*-phenylenediamine 6c

2-Methyl-6-nitrobenzaldehyde (0.10 g, 0.61 mmol) and *o*-phenylenediamine (0.065 g, 0.61 mmol) were dissolved in the minimum volume of hot ethanol (*ca.* 1 cm^3). After 2 min the solution was cooled in ice and the *anil* **6c** (0.14 g, 91%) filtered off. It had mp 69–70 °C (from propan-2-ol).

On a larger scale (8 times the above) attempted recrystallisation from propan-2-ol gave first a small quantity of a high-melting solid (mp 260 °C), probably 2-(2-methyl-6-nitrophenyl)benzimidazole, and then the more soluble anil **6c** (0.37 g, 30%), mp 75–76 °C. The analytical sample had mp 77–78 °C (from ethyl acetate–petroleum) (Found: C, 65.8; H, 4.7; N, 16.2. $C_{14}H_{13}N_3O_2$ requires C, 65.9; H, 5.1; N, 16.5%); ν_{max}/cm^{-1} 3490br (NH), 1610 (CH=N) and 1510 and 1350 (NO_2); δ_H 2.62 (3 H, s, CH_3), 4.10 (2 H, br s, NH_2), 6.65–6.85 (2 H, m, 3- and 6-H), 7.05–7.20 (2 H, m, 4- and 5-H), 7.38–7.52 (2 H, m, 3′- and 4′-H), 7.75 (1 H, d, 5′-H) and 8.81 (1 H, s, CH=N); $J_{4',5'}$ 7.4.

1-Methylquinoxalino[2,3-*c*]cinnoline 1i

Compound **6c** (2.70 g, 10.6 mmol), potassium cyanide (1.42 g, 21.2 mmol) and methanol (250 cm^3) were heated together under reflux for 5.5 h. The solution was then cooled and filtered, and the resulting orange precipitate recrystallised from toluene, to give the title compound **1i**, mp 236–237 °C (Found: C, 73.2; H, 3.7; N, 22.6. $C_{15}H_{10}N_4$ requires C, 73.2; H, 4.1; N, 22.8%); δ_H 3.45 (3 H, s, CH_3), 7.91 (1 H, dd, 2-H), 7.98–8.10 (3 H, m, 3-, 9- and 10-H), 8.40–8.46 (1 H, m, 11-H), 8.52–8.58 (1 H, m, 8-H), 8.82 (1 H, dd, 4-H); $J_{2,3}$ 7.5, $J_{3,4}$ 8.0, $J_{2,4}$ < 1; *m/z* 246 ($M^{+\bullet}$, 100%), 218 (86), 190 (22), 149 (10), 115 (13), 109 (10), 89 (11) and 77 (39), *etc.*

¶ Provisional assignments.

Reaction of 1-methylquinoxalino[2,3-*c*]cinnoline 1i with hydrogen chloride

Hydrogen chloride gas was bubbled for 15 min into a stirred solution of compound **1i** (0.10 g, 0.407 mmol) in chloroform (10 cm^3). The mixture (containing a blue–black precipitate) was set aside for a further 15 min after which it was filtered, and the orange filtrate re-saturated with hydrogen chloride. The procedure was repeated for a third time, and the combined precipitates were then worked up in the standard manner with aqueous sodium hydroxide. The orange product (0.092 g), mp 252–253 °C, was a mixture of 10-chloro-1-methylquinoxalino-[2,3-*c*]cinnoline **1j** and unchanged starting material **1i**, in a ratio of approximately 3:5 (by NMR). For compound **1j**, δ_H 3.30 (3 H, s, CH_3), 7.80–8.02 (3 H, m, 2-, 3- and 9-H), 8.28 (1 H, d, 11-H), 8.40 (1 H, d, 8-H) and 8.72 (1 H, d, 4-H); $J_{8,9}$ 9.0, $J_{9,11}$ 2.2; *m/z* 282 ($M^{+\bullet}$, 35%), 280 ($M^{+\bullet}$, 100), 254 (31), 252 (92), 217 (45), 190 and 141, *etc.*

The original reaction mother-liquor, on evaporation of the chloroform, gave unchanged 1-methylquinoxalinocinnoline **1i** (0.017 g, 17% recovery).

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