Polyaza Heterocycles. Part 1. Halogenation of Quinoxalino[2,3-*c*]cinnolines by Hydrogen Halides†

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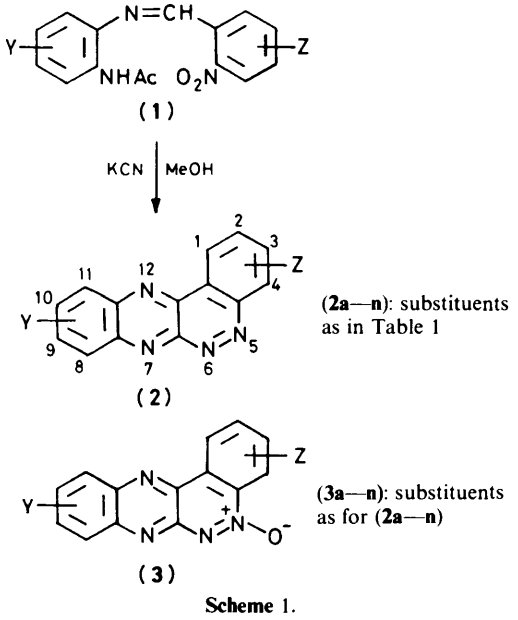
Quinoxalino[2,3-*c*]cinnoline (**2a**) reacts in chloroform solution with hydrogen chloride (or phosphorus trichloride) to give a highly insoluble, deep blue adduct, which on treatment with aqueous sodium hydroxide gives 10-chloroquinoxalino[2,3-*c*]cinnoline (**2b**) in high overall yield. Other quinoxalinocinnolines lacking a substituent at C-10 are also chlorinated at this position by the above procedure, and the corresponding reactions with hydrogen bromide yield 10-bromo analogues.

If the 10-position in the starting compound is already substituted, a blue adduct is still formed, but this is found to give different types of final product according to the nature of the original substituent. In some cases, 9-halogenoquinoxalinocinnolines are obtained; in others, the starting compound is regenerated; and in others, mixtures are produced.

Possible mechanisms for these novel halogenations are discussed: these are supported by MNDO calculations.

In the preceding paper[2] we described the synthesis of variously substituted quinoxalino[2,3-*c*]cinnolines (**2**) by the reaction of *o*-acetamido-*N*-(*o*-nitrobenzylidene)anilines (**1**) with potassium cyanide in methanol (Scheme 1). One such reaction, leading to 10-methoxyquinoxalinocinnoline (**2e**), is rather slow, 2 h being required for a satisfactory yield. If the reaction is stopped after only 45 min, the product isolated is (by ^{1}H n.m.r.) an approximately 1:1 mixture of the quinoxalinocinnoline and its 5-oxide (**3e**) [δ_H(OMe) 4.14 and 4.10 respectively].



Scheme 1.

When this mixture is treated with phosphorus trichloride in chloroform, in an attempt to remove the *N*-oxide (**3e**), it is, surprisingly, the quinoxalinocinnoline itself and not the *N*-oxide which undergoes reaction. The mixture now shows *three* methoxy proton resonances, the new signal appearing at δ 4.27, and the mass spectrum indicates the presence of a monochloro compound, possibly a chloromethoxyquinoxalinocinnoline.

† Preliminary Communication, see reference 1.

Repetition of the reaction with a pure sample of 10-methoxyquinoxalinocinnoline confirms this indication: the product, formed in high yield (79%), is 9-chloro-10-methoxyquinoxalino[2,3-*c*]cinnoline (**2l**). The position of the chlorine is indicated by the ^{1}H n.m.r. spectrum, in which the singlets for 8-H and 11-H are prominent, and is confirmed by independent synthesis from 9,10-dichloroquinoxalinocinnoline (**2j**)[3] and sodium methoxide.

Application of this chlorination procedure to other quinoxalino[2,3-*c*]cinnolines produces further surprises. Quinoxalino[2,3-*c*]cinnoline itself (**2a**) is chlorinated, exclusively and almost quantitatively (92%), at C-10 (*not* C-9), and 9-chloroquinoxalinocinnoline (**2c**) similarly gives the 9,10-dichloro compound (**2j**) (83%). 10-Chloroquinoxalinocinnoline (**2b**), on the other hand, although it reacts initially, is eventually recovered unchanged (93% isolated). Moreover, when freshly redistilled phosphorus trichloride and dried chloroform are used, chlorination of (**2a**) does not occur at all; only on addition of a little water to the mixture does the reaction proceed normally.

In every case where chlorination takes place, the primary reaction product is a dark blue crystalline solid which is insoluble in chloroform and has a molecular ion in its mass spectrum corresponding to a 1:1 adduct of the quinoxalinocinnoline and hydrogen chloride. Even in the case of 10-chloroquinoxalinocinnoline (**2b**), the blue adduct is formed, although it is converted back into starting material in the work-up (with aqueous sodium hydroxide).

The foregoing suggests that the active chlorinating agent in these reactions is not phosphorus trichloride, but hydrogen chloride. This was confirmed by passing hydrogen chloride into a chloroform solution of quinoxalino[2,3-*c*]cinnoline (**2a**), whereupon a deep blue precipitate was immediately formed; this solid has a mass spectrum identical with that of the adduct produced in the reaction with phosphorus trichloride, and on treatment with aqueous base it is converted into 10-chloroquinoxalinocinnoline (**2b**) in high yield.

The hydrogen chloride method has been applied to a number of quinoxalino[2,3-*c*]cinnoline derivatives, with the results shown in Table 1(a). If the starting compound is not already substituted at C-10, chlorination takes place at this position, and the yields are regularly higher than 70%. If the 10-position is already substituted, there are evidently three possible outcomes:

Table 1. Reactions of quinoxalino[2,3-*c*]cinnolines (**2**) with hydrogen halides

(a) With hydrogen chloride

Starting compound			Product				Analysis (found, %)[c]		
No.	Substituent(s)	Adduct m.p. (°C)	No.	Substituent(s)	Overall yield (%)	Product m.p. (°C) [recryst. solvent]	C	H	N
(**2a**)[4]		280	(**2b**)	10-Cl	75	250—252 [DMF]	62.85	2.6	20.8
(**2b**)	10-Cl	274—276	(**2b**)	10-Cl	(90 recovered)				
(**2c**)[4]	9-Cl*	283—286	(**2j**)	9,10-Cl_2	72	257—258 [$CHCl_3$]	55.8	2.0	18.6
(**2d**)[4]	2-Cl	290	(**2k**)	2,10-Cl_2	70	288—290 [DMF]	55.8	1.7	18.8
(**2e**)[2]	10-OMe	275—277	(**2l**)	9-Cl,10-OMe	76	242—243 [$CHCl_3$]	60.6	2.8	19.0
(**2f**)[2]	8-Cl†	270	(**2g**)	8,10-Cl_2	73	250—252 [$CHCl_3$]	55.75	2.0	18.6
(**2g**)[1]	8,10-Cl_2	315—317 (decomp.)	(**2g**)	8,10-Cl_2	(89 recovered)				
(**2h**)[2]	9-Br	300—302 (decomp.)	(**2m**)	9-Br, 10-Cl	70	274—276 [$CHCl_3$]	49.0	1.9	15.8
(**2i**)[2]	10-Br	278—281	(**2n**)	10-Br, 9-Cl	*ca.* 40[a]				
			(**2i**)	10-Br	*ca.* 20[a]				
			(**2j**)	9,10-Cl_2	Trace[b]				

(b) With hydrogen bromide

(**2a**)[4]		283—286	(**2i**)	10-Br	70	261—263 [DMF]	54.2	2.25	18.1
(**2b**)	10-Cl	*ca.* 360	(**2b**)	10-Cl	(90 recovered)	As above			
			(**2m**)	9-Br,10-Cl	Trace[b]				
(**2c**)[4]	9-Cl*	279—281	(**2n**)	10-Br,9-Cl	*ca.* 45[a]				
			(**2c**)	9-Cl	*ca.* 25[a]				

* Referred to in ref. 4 as '9-(or 10-)' chloro-compound † Crude product (*cf.* ref. 2).

[a] Estimated from ^1H n.m.r. integrals. [b] Detected in mass spectrum. [c] For (**2b**), $C_{14}H_7ClN_4$ requires C, 63.05; H, 2.6; N, 21.0%; for (**2g**), (**2j**), and (**2k**), $C_{14}H_6Cl_2N_4$ requires C, 55.8; H, 2.0; N, 18.6%; for (**2i**), $C_{14}H_7BrN_4$ requires C, 54.0; H, 2.3; N, 18.0%; for (**2l**), $C_{15}H_9ClN_4O$ requires C, 60.7; H, 3.05; N, 18.9%; for (**2m**), $C_{14}H_6BrClN_4$ requires C, 48.7; H, 1.75; N, 16.1%.

the starting material is recovered unchanged, as in (**2b**) and (**2g**); or chlorination occurs at C-9, as in (**2e**); or a mixture of products results, as in (**2i**). Reactions of quinoxalinocinnolines with hydrogen bromide appear to follow a similar pattern, Table 1(b).

If the starting compound is contaminated by its 5-oxide (**3**), the latter remains inert during the halogenation procedure, and may be recovered from the chloroform mother-liquor after the blue adduct has been filtered off. Three such oxides, (**3d**), (**3e**), and (**3f**), have been obtained in this way, but the very small quantities isolated, and the residual impurities present, have to date precluded any further study of these compounds.

Halogenation of a benzo-fused heteroaromatic system by hydrogen halides has not, to our knowledge, been previously recorded, and there is certainly no indication in the literature that quinoxaline itself, and its simple analogues, react with hydrogen chloride to give anything other than normal (ionic) hydrochlorides. The structures of the blue intermediates, which are evidently *covalent* adducts of the heterocycle and hydrogen halide, are thus of considerable interest in their own right, as well as holding the obvious key to the overall mechanism of the halogenation process.

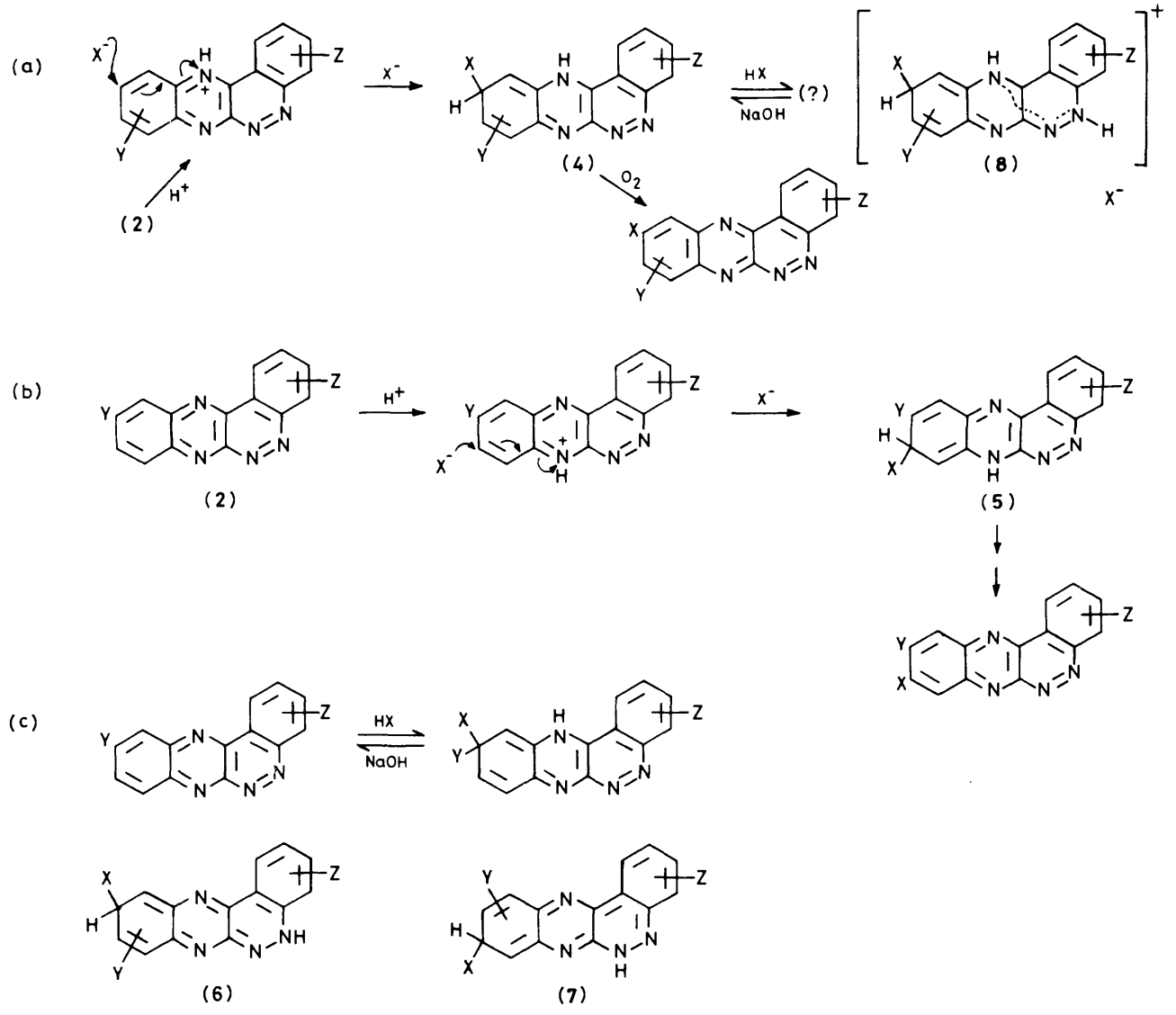
Whether the blue compounds are simple 1:1 adducts of quinoxalinocinnoline and hydrogen halide, or something more complex, must remain, for the present, an open question. None of the adducts are sufficiently soluble in any of the common solvents to permit easy recrystallisation, or even an n.m.r. study; but the quantity of adduct isolated in each experiment is indicative of a formula [(**2**) + *n*HX] where *n* may lie between 1 and 4, and elemental analysis of the adduct from (**2a**) and hydrogen chloride indicates an average value of *n* of *ca.* 2.8.

Our tentative formulation of these reactions is set out in Scheme 2. It is assumed that protonation of one of the basic nitrogens is followed by nucleophilic addition of halide ion at C-9 or C-10, giving a 1:1 covalent adduct which is responsible for the observed mass spectrum. Protonation at N-12 invites nucleophilic attack at C-10 (pathway a) whereas protonation at N-7 leads to the introduction of halogen at C-9 (pathway b). The other possible sites of protonation, *viz.* N-5 and N-6, are considered less likely, since the addition of the nucleophile to these cations would give adducts, (**6**) and (**7**), in which the aromatic nature of the system has undergone greater disruption than in the alternative structures (**4**) and (**5**). We formulate the blue compounds as hydrohalide salts of these primary adducts (**4**) and (**5**), and since each of the adducts contains four potentially basic nitrogen atoms, the extent of protonation may vary considerably from one molecule to another. The preferred site(s) of protonation cannot yet be experimentally determined with certainty: the provisonal structure (**8**), for example, is based only on analogy with the protonation of 4-aminocinnoline [5] and on the expectation that such a structure, with an extended *p*-quinonoid chromophore, would be consistent with the observed blue colour.

MNDO Calculations

The Structure of Quinoxalino[2,3-c]*cinnoline.*—The calculated bond lengths and bond orders for (**2a**) are given in Table 2, together with calculated bond orders for the formal bicyclic constituents of (**2a**), *viz.* quinoxaline (**9**) and cinnoline (**10**). Each of the bicyclic structures shows evidence of considerable bond fixation, with several bonds [*b* and *h* in (**9**); *i*, *o*, *r*, and *t* in (**10**)] of much higher order than the remainder. In this respect, (**9**) and (**10**) have electronic structures very similar to that of naphthalene, where the calculated bond orders [with labelling corresponding to (**11a**)] are *a*, 1.227; *b*, 1.608; *c*, 1.199; *d*, 1.343. The principal influence of the hetero-atoms thus appears to be merely in lowering the symmetry [from D_{2h} in naphthalene to C_{2v} in (**9**) or C_s in (**10**)], rather than in causing a fundamental perturbation of the electronic structure.

In contrast, (**2a**) contains three bonds [those marked *l*, *n*, and *p* in structure (**11a**)] of almost unit bond order; in addition, the



Scheme 2.

Table 2. Calculated bond orders in (**2a**), (**9**), and (**10**)

(**2a**)†	*a* 1.175 (1.439)	*h* 1.502 (1.339)	*o* 1.865 (1.225)
	b 1.662 (1.378)	*i* 1.157 (1.448)	*p* 1.007 (1.433)
	c 1.136 (1.448)	*j* 1.498 (1.340)	*q* 1.343 (1.418)
	d 1.242 (1.445)	*k* 1.321 (1.370)	*r* 1.455 (1.402)
	e 1.133 (1.450)	*l* 1.036 (1.469)	*s* 1.359 (1.410)
	f 1.664 (1.377)	*m* 1.328 (1.430)	*t* 1.460 (1.400)
	g 1.314 (1.370)	*n* 1.037 (1.428)	*u* 1.324 (1.421)
(**9**)	*a* 1.222	*g* 1.215	
	b 1.611	*h* 1.650	
	c 1.182	*i* 1.137	
	d 1.302		
(**10**)	*i* 1.590	*p* 1.197	
	l 1.211	*q* 1.202	
	m 1.324	*r* 1.605	
	n 1.174	*s* 1.227	
	o 1.672	*t* 1.605	

† Bond lengths (Å) in parentheses: bonds labelled as in (**11a**)

bonds (*m* and *q*—*u*) in the angularly fused carbocyclic ring are all of approximately equal length (1.40—1.43 Å), and of bond order (1.32—1.46) comparable with that calculated[6] for benzene (1.412). Consequently the best simple representation of (**2a**) is that in structure (**11b**), in which systems containing 2π-, 6π-, and 10π-electrons are separated by bonds of low order. The tendency of $(4n + 2)\pi$-systems ($n = 0$, 1, or 2) to minimise destabilising interaction between themselves appears to be quite general in conjugated carbocyclic systems,[6] and the benzo-1,4-diazepinium cation provides a heterocyclic example in which two 6π-systems are separated by long bonds of low order.[7] In the case of quinoxalino[2,3-*c*]cinnoline (**2a**), there is evidently no tendency whatever for the isolated π-systems to interact giving a delocalised 18π-system around the molecular periphery.

Protonation of (**2a**).—Table 3 shows the calculated net atomic charges on the four nitrogen atoms of (**2a**), together with the ΔH_f° values for the four isomeric cations [denoted $(MH)^+$] obtained on protonation of these nitrogen atoms. Inspection of the molecular orbitals of (**2a**) shows that all the lone pairs on the nitrogen atoms lie in the plane of the molecule, and protonation thus results in the added proton also being in the molecular plane.

Table 3. Protonation of quinoxalino[2,3-*c*]cinnoline (**2a**)

Site	*q*(N)	ΔH_f°/kJ mol^{-1} for $(MH)^+$
N-5	−0.034e	+1 183.6
N-6	−0.004e	+1 160.6
N-7	−0.101e	+1 121.8
N-12	−0.157e	+1 144.1

Table 4. Adducts of (**2a**) and HCl

Sites of addition		ΔH_f°/kJ mol^{-1} for adduct
H	Cl	
N-7	C-9	+398.2
N-7	C-11	+401.5
N-12	C-8	+418.6
N-12	C-10	+414.5

The most electron-rich nitrogen atom is N-12, followed by N-7; however, despite these electron populations, it is protonation at N-7 which yields the cation $(MH)^+$ of lowest ΔH_f°. We can suggest no simple and convincing explanation for this difference: steric crowding, when N-12 is protonated, seems unlikely to be a significant factor, since in the optimised geometry of the (N-12)-protonated cation the hydrogens attached to N-12 and C-1 are separated by 2.26 Å, a distance well outside the sum (2.0 Å) of the van der Waals' radii of two hydrogens attached to aromatic nuclei.[8]

For the substituted quinoxalino[2,3-*c*]cinnolines (**2b**), (**2c**), and (**2e**), having 10-chloro, 9-chloro, and 10-methoxy substituents, the nitrogen of highest electron density is always N-12, but the lowest-energy cation is always formed by protonation at N-7, just as for the parent heterocycle (**2a**).

Addition of Chloride to Protonated (**2a**).—If the parent heterocycle (**2a**) is protonated at N-7, a fully conjugated hydrogen chloride adduct is obtained if addition of chloride occurs at C-9 [*e.g.* structure (**5**)] or at C-11; if the initial protonation occurs at N-12, a fully conjugated adduct results by chloride addition at C-8 or C-10 [as in structure (**4**)]. In the interests of computational economy, we have investigated only these fully conjugated adducts, since in the model quinoxaline system the non-conjugated adducts have ΔH_f° values almost 70 kJ mol^{-1} above those of the fully conjugated adducts, and we believe that a similar situation is likely to exist in adducts of (**2a**).

Table 4 shows the ΔH_f° values of the various conjugated adducts formed from (**2a**). For protonation at N-12, the lower-energy adduct has the chlorine at C-10, *i.e.* at the correct site for the observed product; for protonation at N-7, the lower-energy adduct has the chlorine at C-9, *i.e.* at the other site where chlorination is occasionally observed.

At N-12, the proton affinity of (**2a**) is calculated as +835.8, virtually identical with that calculated for quinoxaline itself (+838.6). However, the calculated ΔH° value for the addition of HCl to (**2a**), across N-12 and C-10, is +24.6 kJ mol^{-1}, significantly lower than for the corresponding addition to quinoxaline, +43.8 kJ mol^{-1}. A possible reason for this difference may be found by inspection of the bond orders for the two adducts, (**12**) and (**13**) (Table 5). In (**12**) the aromatic delocalisation of quinoxaline has been completely destroyed, whereas (**13**) still retains a 10π cinnoline system, as shown in (**13a**). A similar bond structure is found in the adduct (**14**) (Scheme 3).

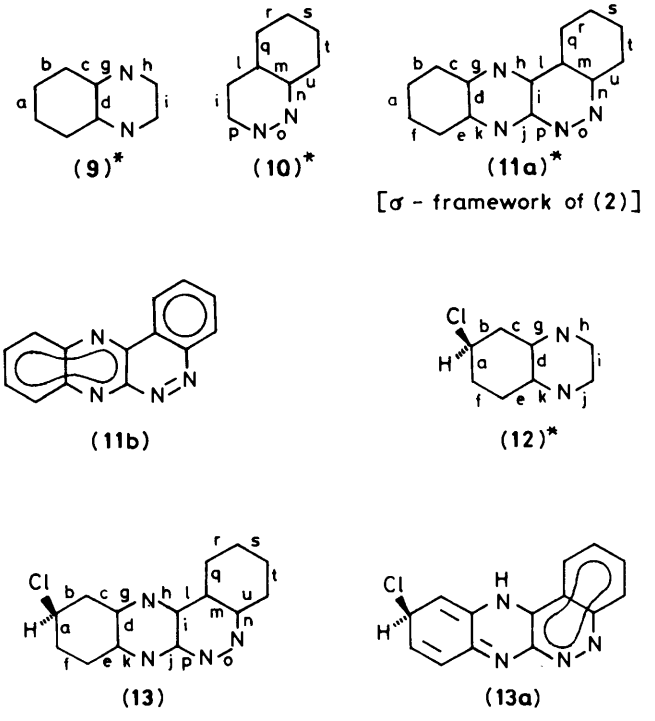
Protonation of Quinoxalinocinnoline–HCl *Adducts.*—Since the experimental evidence indicates that the blue intermediates have the formula [(**2**) + *n*HX] where *n* is usually >1, it is pertinent to consider the further protonation of the primary adducts (**13a**) and (**14**). Each of these may, in principle, undergo protonation at four possible sites, and the ΔH_f° value for each of the possible cations is shown in Table 6. In both cases, the lowest-energy cation is that having one hydrogen bonded to

Table 5. Calculated bond orders in (**12**) and (**13**)

(**12**)	*a* 0.987	*e* 1.002	*i* 1.661
	b 1.000	*f* 1.880	*j* 1.142
	c 1.728	*g* 1.035	*k* 1.722
	d 0.990	*h* 1.090	
(**13**)	*a* 0.985	*h* 1.100	*o* 1.717
	b 0.994	*i* 1.394	*p* 1.148
	c 1.758	*j* 1.097	*q* 1.224
	d 0.981	*k* 1.758	*r* 1.577
	e 0.998	*l* 1.147	*s* 1.252
	f 1.883	*m* 1.330	*t* 1.573
	g 1.019	*n* 1.130	*u* 1.219

Table 6. Protonation of HCl adducts of (**2a**)

HCl Sites		Site of protonation	ΔH_f°/ kJ mol^{-1}
H	Cl		
N-7	C-9	N-5	+1 097.2
		N-6	+1 115.3
		N-7	+1 150.9
		N-12	+1 088.0
N-12	C-10	N-5	+1 097.7
		N-6	+1 104.8
		N-7	+1 083.7
		N-12	+1 193.9



* In all structures indicating the labelling of bonds, only the σ-framework is drawn.

each of N-7 and N-12, and the highest-energy cation has both hydrogens bonded to the same nitrogen (either N-7 or N-12). Inspection of bond orders and residual charges shows that these two stable cations, with chlorine at C-9 and C-10, should be represented as (**15**) and (**16**) respectively, in which a delocalised 10π cinnoline system is present. This pattern of protonation is such that subsequent loss of a proton from C-9 in (**15**) or C-10 in (**16**) can yield 9- or 10-chloro-7,12-dihydroquinoxalinocinnoline, and thus, by aerial oxidation, the observed final products.

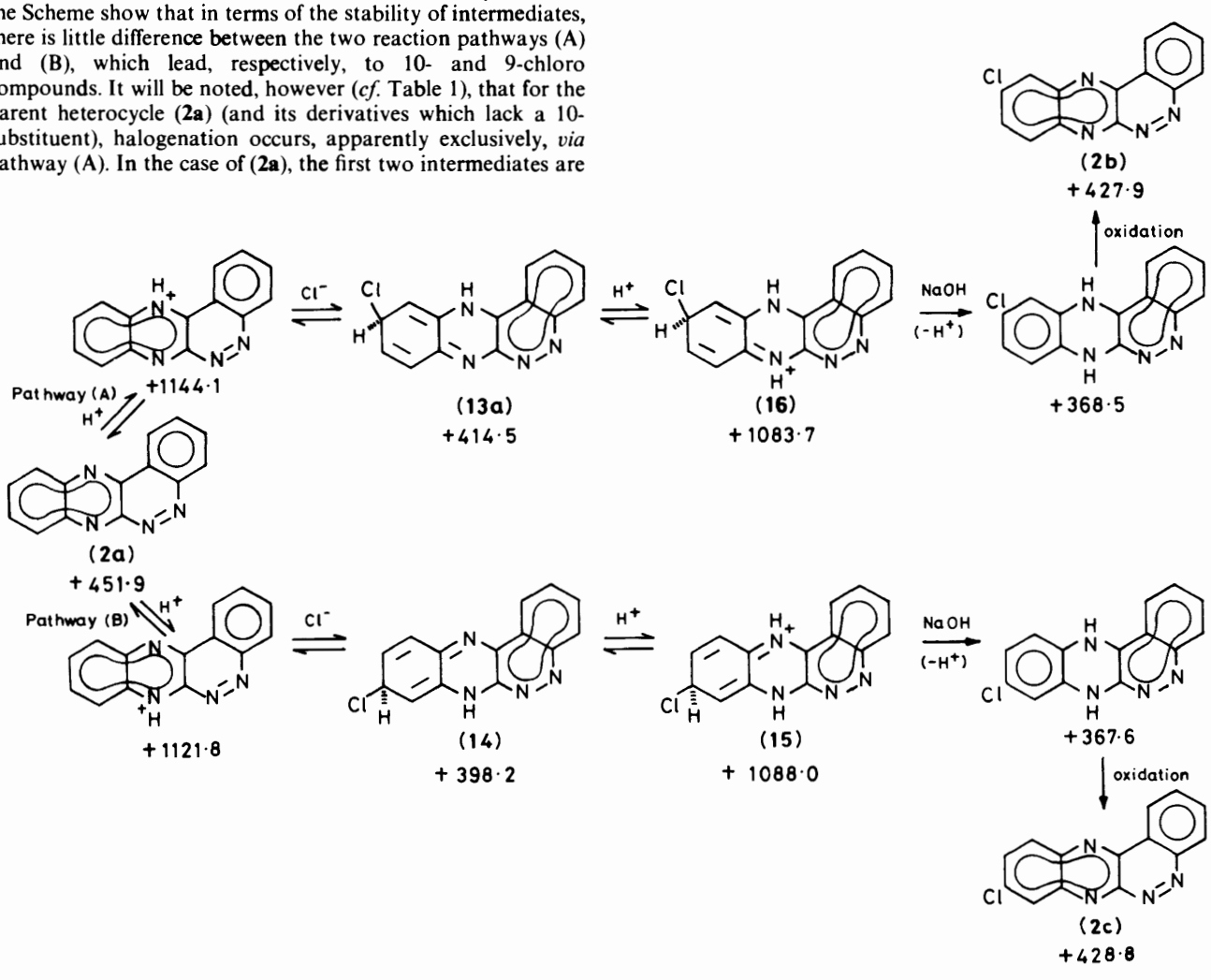
It must be recalled, however, that the value of n in the formula [(**2**) + nHX] may be greater than 2, and it is not possible to say at this stage whether, for example, the product with $n = 3$ is best represented as a doubly protonated heterocyclic cation with $2X^-$, or a singly protonated cation with the counter ion HX_2^-.

Reaction Mechanism in Relation to Calculations.—The MNDO calculations described above lend support to the empirical mechanistic proposals set out in Schemes 2a and b, except that they indicate the preferred site of second protonation to be at a quinoxaline nitrogen [giving (**15**) or (**16**)] rather than in the cinnoline moiety [giving structures such as (**8**)]. This does not mean, of course, that (**8**) is necessarily excluded from the reaction pathway, especially if it is kinetic rather than thermodynamic factors which control the final outcome (see below).

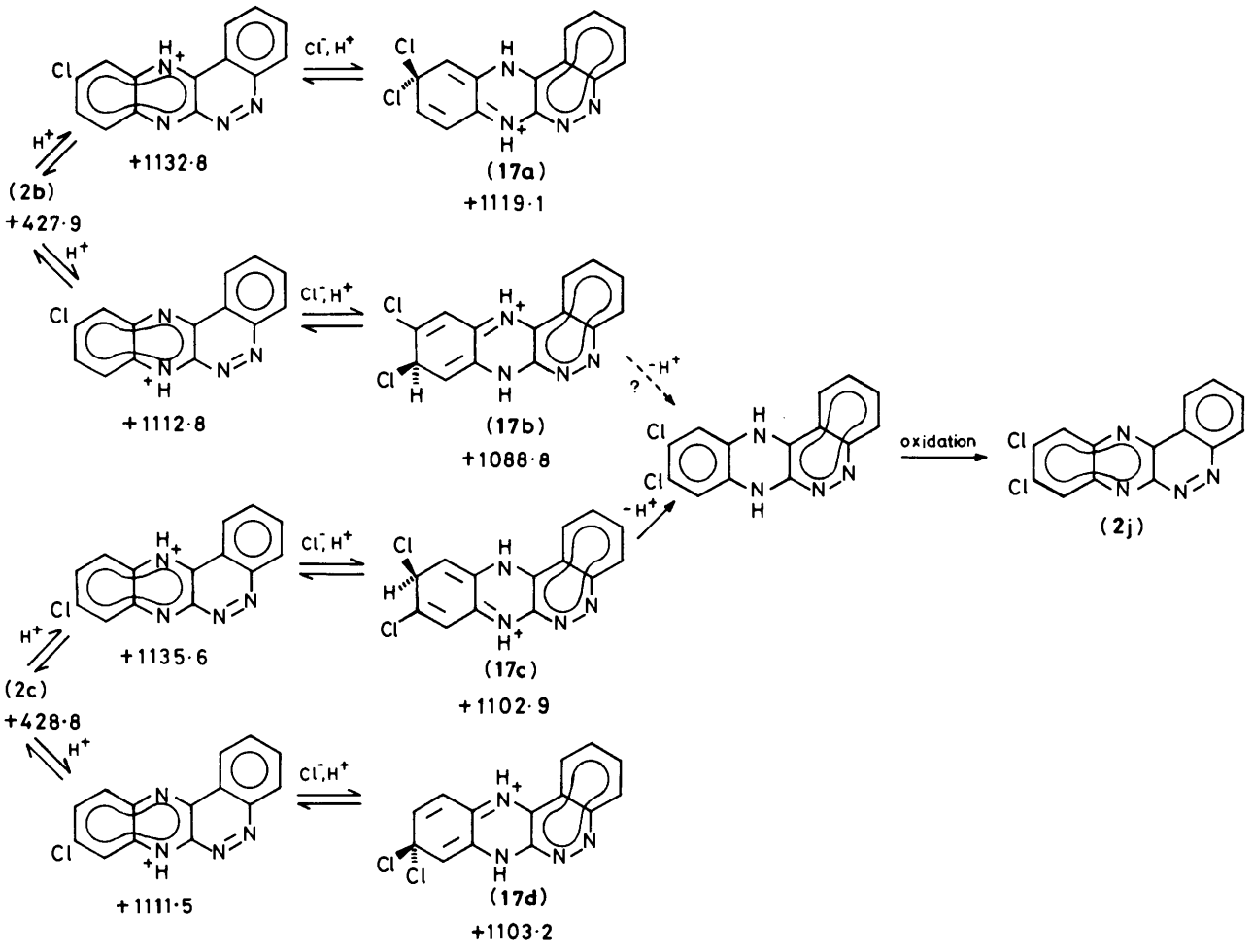
A modified mechanistic scheme, which provides the best fit with the calculations, is set out as Scheme 3. The ΔH_f° values in the Scheme show that in terms of the stability of intermediates, there is little difference between the two reaction pathways (A) and (B), which lead, respectively, to 10- and 9-chloro compounds. It will be noted, however (*cf.* Table 1), that for the parent heterocycle (**2a**) (and its derivatives which lack a 10-substituent), halogenation occurs, apparently exclusively, *via* pathway (A). In the case of (**2a**), the first two intermediates are of higher energy than their counterparts on pathway (**B**), and it is only after the second protonation that pathway (A) gives the lower-energy species.

The foregoing argument is, of course, based on the assumptions: (i) that the solvent (chloroform) does not significantly affect the stability of these intermediates, and (ii) that the first three steps along both reaction pathways are reversible. The precipitation of the blue intermediate, however, is effectively irreversible, and it is as yet impossible to tell whether this particular intermediate in any given reaction (which determines the orientation of halogen in the final product) is the one which is *kinetically favoured*, or the one which happens to be *the least soluble in chloroform*.

The reactions of 9- and 10-halogenoquinoxalinocinnolines with hydrogen halides provide a good illustration of the fine balance which exists between the different reaction pathways. The various possibilities for the reactions of the chloro derivatives (**2b**) and (**2c**) with HCl are illustrated in Scheme 4. In the case of (**2b**) we regard the blue intermediate as a derivative of (**17a**), since basification leads only to recovery of (**2b**) and not to (**2j**). By a similar argument we regard the adduct from (**2c**) as a derivative of (**17c**); however, in the corresponding reactions of (**2b**) and (**2c**) with HBr, and of the 10-bromo compound (**2i**) with HCl, bromo analogues of all four adducts (**17a—d**) may be involved.



Scheme 3. Addition of HCl to (**2a**). [Calculated ΔH_f° (kJ mol^{-1}) are shown for each structure.]



Scheme 4. Addition of HCl to (**2b**) and (**2c**). [Calculated ΔH_f° values (kJ mol^{-1}) are shown for each structure.]

Experimental

^{1}H N.m.r. spectra were recorded at 80 MHz in $CDCl_3$ solution.

Reactions of Quinoxalino[2,3-c]*cinnolines with Phosphorus Trichloride.*—The quinoxalino[2,3-*c*]cinnoline (0.15 g), phosphorus trichloride (0.3 ml), and chloroform (5 ml) were heated together under reflux for 1 h. The mixture was then neutralised (4M-NaOH) and the organic products extracted with more chloroform. The extract was dried (Na_2SO_4), evaporated, and the residue recrystallised from the appropriate solvent (see Table 1).

The following conversions were carried out by this method: (**2a**)→(**2b**), yield 92%; (**2c**)→(**2j**), yield 83%; (**2e**)→(**2l**), yield 79%.

Reactions of Quinoxalino[2,3-c]*cinnolines with Hydrogen Halides.*—The following procedure is typical. (The quantity of chloroform required to dissolve the quinoxalinocinnoline varies between different members of the series.)

Dry hydrogen chloride was passed into a solution of quinoxalino[2,3-*c*]cinnoline (**2a**) (2.0 g) in chloroform (200 ml) for *ca.* 1 min. The deep blue precipitate thus formed was filtered off, washed thoroughly with chloroform, and dried in air (3.02 g). It was then shaken with chloroform (500 ml) and 4M-sodium hydroxide solution (500 ml); when all the blue solid had reacted, the (orange) chloroform layer was separated, dried (Na_2SO_4), and evaporated, giving 10-chloroquinoxalino[2,3-*c*]cinnoline (**2b**) (1.75 g, 75%), m.p. 250—252 °C (from dimethylformamide).

Reactions carried out by this general method are listed in Table 1. The ^{1}H n.m.r. spectra of the products are collected in Table 7 of this paper, and Table 5 of the preceding paper.[2]

Quinoxalino[2,3-c]*cinnoline 5-Oxides* (**3**).—A mixture of the quinoxalino[2,3-*c*]cinnoline (**2**) and the 5-oxide (**3**) was obtained by cyclisation of the appropriate *o*-acetamido-*N*-(*o*-nitrobenzylidene)aniline (**1**) with potassium cyanide in methanol, as previously described.[2] The mixture, dissolved in chloroform, was then treated with hydrogen chloride (see above), and the blue quinoxalinocinnoline–HCl adduct filtered off. The chloroform filtrate was then evaporated to give the quinoxalinocinnoline oxide (**3**). The following were obtained in this way, although none were entirely free from residual impurities, even after recrystallisation: 2-chloro- (**3d**), orange-yellow, m.p. 304—306 °C; 10-methoxy- (**3e**), orange-yellow needles, m.p. 274—276 °C; 8-chloro- (**3f**), bright yellow needles, m.p. 319—321 °C (from ethanol).

9,10-*Dichloroquinoxalino*[2,3-c]*cinnoline* (**2j**) (*with Arshad Ahmad*).—A solution of 3,4-dibromocinnoline[9] (0.29 g) and 4,5-dichloro-*o*-phenylenediamine (0.18 g) in *N*-methyl-2-pyrrolidone (4 ml) was stirred at 115—120 °C in an oil-bath for 17 h and then allowed to cool. The dark blue precipitate was filtered off and dissolved in water (20 ml), aqueous ammonia (*d* 0.88; 20

Table 7. ^{1}H N.m.r. spectra of 8,10- and 9,10-disubstituted quinoxalino[2,3-*c*]cinnolines (very dilute solutions in $CDCl_3$)

Compd. no.	Substituents	1-H	2-H and 3-H	4-H	8-H	9-H	11-H	Others	Coupling constants (*J*/Hz)
(**2g**)	8,10-Cl_2	9.35—9.50m	8.22—8.40m	9.05—9.22m		8.26d	8.53d		2.6 (9,11)
(**2j**)	9,10-Cl_2	9.32—9.41m	8.18—8.31m	8.96—9.11m	8.80d		8.67d		0.6 (8,11)
(**2l**)	9-Cl,10-OMe	9.15—9.30m	8.06—8.21m	8.87—9.00m	8.57s		7.67s	4.27 (OMe)	
(**2m**)	9-Br, 10-Cl	9.19—9.35m	8.08—8.23m	8.90—9.07m	8.92d		8.60d		0.6 (8,11)
(**2n**)	10-Br,9-Cl	(Not obtained pure)			8.77s*		8.90s*		

* Provisional assignments, by analogy with ref. 2.

ml) was added to the solution, and the mixture stirred at room temperature until the blue colour disappeared (3—4 h). The product was extracted with chloroform and the extract dried (Na_2SO_4) and evaporated; compound (**2j**) (59%) had m.p. 256—258 °C, and was identical in all respects with the product obtained from 9-chloroquinoxalinocinnoline (**2c**) and hydrogen chloride.

9-Chloro-10-methoxyquinoxalino[2,3-c]*cinnoline* (**2l**) (*with Arshad Ahmad*).—9,10-Dichloroquinoxalino[2,3-*c*]cinnoline (0.15 g, 5 mmol) and sodium methoxide (from sodium, 0.023 g) in methanol (15 ml) were heated under reflux for 3 h. The mixture was cooled and filtered, giving 9-chloro-10-methoxyquinoxalinocinnoline (**2l**) (0.09 g, 61%), m.p. 232—235 °C, spectroscopically identical with the product obtained from 10-methoxyquinoxalinocinnoline (**2e**) and hydrogen chloride.

Calculations.—All calculations were made using the MNDO method[10,11] implemented on a VAX 11/780 computer, and using the published[12,13] atomic parameterisation for H, C, N, O, and Cl. Complete optimisation of molecular geometries, without the imposition of any constraints, was undertaken throughout this work.

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References

1 C. Glidewell, T. Shepherd, and D. M. Smith, *Tetrahedron Lett.*, 1983, **24**, 3151.
2 T. Shepherd and D. M. Smith, *J. Chem. Soc., Perkin Trans. 1*, preceding paper.
3 Arshad Ahmad, M.Sc. Thesis, University of St. Andrews, 1978.
4 Arshad Ahmad, F. A. Brand, D. Johnston, and D. M. Smith, *J. Chem. Res.*, 1980, (*S*) 208.
5 D. E. Ames, G. V. Boyd, R. F. Chapman, A. W. Ellis, A. C. Lovesey, and D. Waite, *J. Chem. Soc. B*, 1967, 748.
6 C. Glidewell and D. Lloyd, *Tetrahedron*, 1984, **40**, 4455.
7 C. Glidewell and D. Lloyd, *Tetrahedron Lett.*, 1982, **23**, 4379.
8 A. Bondi, *J. Phys. Chem.*, 1964, **68**, 441.
9 S. Kanoktanaporn and J. A. H. MacBride, *J. Chem. Res.*, 1980, (*S*), 206; (*M*) 2941.
10 M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, 1977, **99**, 4899.
11 W. Thiel, P. Wiener, J. Stewart, and M. J. S. Dewar, Quantum Chemistry Program Exchange, Indiana University, Program No. 428 (1981).
12 M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, 1977, **99**, 4907.
13 M. J. S. Dewar, M. L. McKee, and H. S. Rzepa, *J. Am. Chem. Soc.*, 1978, **100**, 3607.

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