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HALOGENATION OF QUINOXALINO[2,3-*c*]CINNOLINES BY HYDROGEN HALIDES

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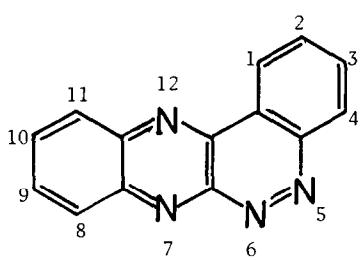
The title compounds are halogenated at C-10 (or, occasionally, at C-9) by reaction with hydrogen chloride or hydrogen bromide in chloroform, and treatment of the resulting blue intermediate with aqueous base.

As part of our study of the new ring system, quinoxalino[2,3-*c*]cinnoline (1)[1], we have investigated its reaction with hydrogen chloride and hydrogen bromide.

When gaseous hydrogen chloride is passed into a dilute solution of the parent compound (1a) in chloroform, the orange colour ($\lambda_{max.}$ 389 nm) rapidly changes to deep blue, and a blue solid is precipitated [$\lambda_{max.}$(acetone) 385, 395, and 569 nm]. When the solid is filtered off and shaken with a mixture of 4 M sodium hydroxide solution and chloroform, the orange colour is restored to the organic layer; evaporation of the chloroform, however, gives not the starting material but its 10-chloro-derivative (1e), in a yield of 75%. Reaction of (1a) with hydrogen bromide similarly gives the 10-bromo-compound (1f: 70%), and the monohalogeno-compounds (1b) - (1d) are converted into the dihalogeno-derivatives (1g) - (1i) (see Table).

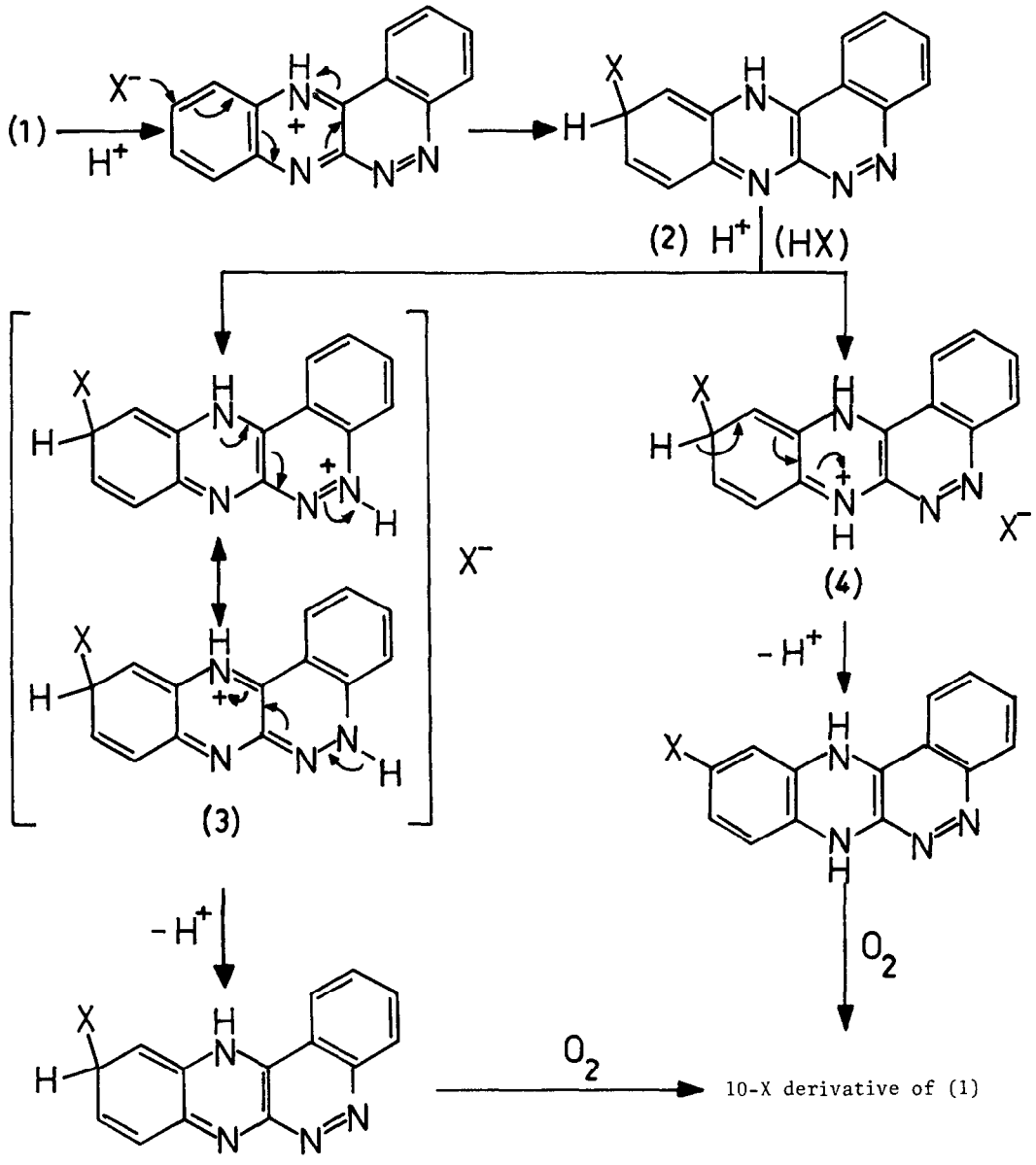
If the 10-position in the starting quinoxalinocinnoline is already substituted, the outcome of the reaction is less predictable, although a blue solid is formed in each case. The starting material may be recovered unchanged, as in the reactions of (1e) with HCl or HBr; or halogenation may occur at C-9, as with (1j) + HCl; or a mixture of products may result, as with (1f) + HCl.

To the best of our knowledge, this type of halogenation in a heteroaromatic system is unprecedented, and it opens up a simple route to a wide range of substituted quinoxalinocinnolines, since we have also shown that 10-halogeno-substituents in these molecules are readily displaced by nucleophiles like methoxide ion and piperidine.



(1)

(1a) : unsubstituted
(1b) : 2-Cl
(1c) : 9-Cl
(1d) : 9-Br
(1e) : 10-Cl
(1f) : 10-Br
(1g) : 2,10-Cl_2
(1h) : 9,10-Cl_2
(1i) : 9-Br,10-Cl
(1j) : 10-OCH_3
(1k) : 9-Cl,10-OCH_3
(1l) : 10-Br,9-Cl



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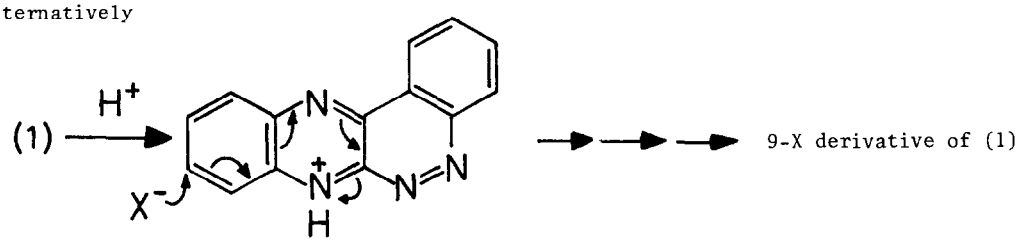


TABLE Products from the reaction (1) + HX

Starting Compounds	Product	M.p. (°C)[a]	Yield (%)
1a + HCl	1e[b]	250–252	75
1a + HBr	1f[b]	261–263	70
1b + HCl	1g[b]	288–290	70
1c[c] + HCl	1h[b]	257–258	72
1c + HBr	1ℓ 1c		*ca.* 45 *ca.* 25 [d]
1d + HCl	1i	274–276	70
1e + HCl	1e recovered	as above	90
1e + HBr	1e recovered 1i		90 trace[e]
1f + HCl	1ℓ 1f		*ca.* 40 *ca.* 20 [d] [f]
1j + HCl	1k[b]	242–243	76

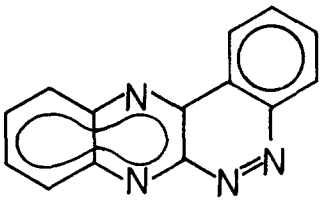
[a]Recrystallised from dimethylformamide. [b]Identical with an authentic sample, independently synthesised. All new compounds gave satisfactory analyses, ^{1}H n.m.r., and mass spectra. [c]This was previously described[1] as 'the 9-(or 10-)chloro-derivative'. [d]Estimated from n.m.r. integrals. [e]<5%: detected in the mass spectrum. [f]Traces of a dichloro-compound (presumably 1h) detected in the mass spectrum.

Although the precise mechanistic details of these reactions remain to be established, a tentative formulation is shown in the Scheme. MNDO calculations[2] indicate that protonation of (1a), (1c), (1e) and (1j) is to be expected either at N-12 (in each case the site of highest electron density) or at N-7 (which always gives the cation of lowest energy), and nucleophilic addition to the protonated species has some analogy in the reactions of 12- and 7-substituted benzo[*a*]phenazinium salts[3]. Although the blue intermediates have mass spectra which correspond to 1:1 adducts of (1) and HX, we formulate them not as simple adducts [*e.g.* (2)] but rather as protonated species, *e.g.* (3) or (4), since the approximate analysis[†] indicates more than one halogen atom per molecule. Protonation of (2) would be expected either at N-7 [which gives the cation of (marginally) lowest energy] or at N-5 (by analogy with the protonation of 4-aminocinnoline[4]). Basification of these adducts would give a dihydroquinoxalinocinnoline, which would be expected to undergo spontaneous dehydrogenation in air[5].

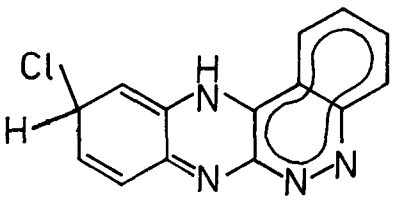
The ease of HX addition to (1), as compared with the unreactive nature of simpler systems such as quinoxalines, may be understood by reference to the total bond orders obtained from the MNDO calculations. In (1a), the bond orders indicate that the structure should best be represented as (5): in particular the bonds 4a-5, 6-6a, and 12a-12b are all of order <1.04, whereas the bond orders in the HCl adduct indicate the structure (6). In (5) and (6), the bond orders in the 10π fragments are remarkably similar to those calculated for isolated molecules

[†]These compounds cannot be purified for analysis, and are insufficiently soluble in the common solvents to permit an n.m.r. study.

of quinoxaline and cinnoline respectively. Despite the disruption of the 10π-system in (5) upon HCl addition, a cyclic 10π-system is still present in the adduct (6), whereas in quinoxaline itself the cyclic π-system is wholly disrupted upon adduct formation.



(5)



(6)

In accordance with this, the calculated $\Delta H^{\ominus}$ value for the addition of HCl to (1a), *i.e.* for (5) ⟶ (6), is +24.6 kJ mol^{-1}, while that for addition of HCl to quinoxaline is +43.8 kJ mol^{-1}. The proton affinities of the two species are almost identical; it is the addition of chloride ion which gives rise to the difference in energy, because of disruption of the π-system in the case of quinoxaline.

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