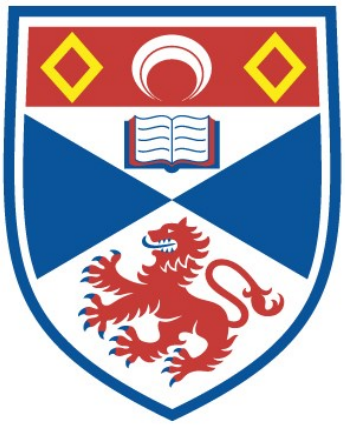
STUDIES OF SOME CONDENSED POLYAZAHETEROAROMATIC COMPOUNDS

Tom Shepherd

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



1984

STUDIES OF SOME CONDENSED POLYAZA-HETEROAROMATIC COMPOUNDS

being a thesis

presented by

TOM SHEPHERD, B.Sc.

to the

UNIVERSITY OF ST. ANDREWS

in application for

THE DEGREE OF DOCTOR OF PHILOSOPHY

St. Andrews November 1983

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DECLARATION

I declare that this thesis is a record of the results of my own experiments, that it is my own composition, and that it has not previously been presented in application for a higher degree.

The work was carried out in the Department of Chemistry of the University of St Andrews, under the supervision of Dr. D.M. Smith.

CERTIFICATE

I hereby certify that Mr. Tom Shepherd, B.Sc., has spent twelve terms at research work under my supervision, has fulfilled the conditions of the resolution of the University Court 1967, No. 1, and is qualified to submit the accompanying thesis in application for the degree of Doctor of Philosophy.

Research Supervisor

UNIVERSITY CAREER

I entered the University of St. Andrews in October 1976, and graduated B.Sc. with First Class Honours in July 1980.

The research described in this thesis was carried out between October 1980 and October 1983, during which time I held a University of St. Andrews Research Scholarship.

ACKNOWLEDGEMENTS

I am most grateful to Dr. D.M. Smith for his continued advice, interest and encouragement during the past three years.

I am also particularly grateful to Dr. C. Glidewell, for carrying out the theoretical investigation mentioned in this work and for permission to use his results in the discussion.

My thanks are also due to the technical staff of the Department, especially Mrs. M. Smith (n.m.r. spectroscopy), Mr. C. Millar (mass spectroscopy) and Mrs. S. Smith (microanalysis).

I am also indebted to Miss C. Finlay for typing a number of the tables contained in this work.

Finally, I would like to thank the University of St. Andrews for the award of a Research Scholarship.

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SUMMARY

The cyanide induced cyclisation of a number of substituted 2-acetamido-*N*-(*o*-nitrobenzylidene)anilines was investigated, resulting in the formation of the appropriate unambiguously substituted quinoxalino[2,3-*c*]cinnolines. During the course of this study, it was found that by-products were formed during the reaction. These were investigated briefly, and found to be the 5-oxide of the parent quinoxalino[2,3-*c*]cinnoline, and a 2-amino-3-(*o*-nitrophenyl)-quinoxaline, thought to be formed by aerial oxidation of intermediates in the cyclisation process.

The reaction of a number of substituted quinoxalinocinnolines with gaseous hydrogen halides was investigated. It was found that those quinoxalinocinnolines with no substituent at position 10 underwent chlorination at this site, by apparent replacement of a hydrogen atom with a chlorine atom. When compounds with substituents at position 10 were reacted, chlorination occurred at position 9 in a few cases, failed in a few others, and often gave product mixtures. With the aid of theoretical studies carried out on the chlorination process by Dr. C. Glidewell, a mechanism for chlorination is proposed, that attempts to explain the distribution of products.

An investigation was carried out on quinoxalinocinnolines with halogeno-substituents, in order to determine whether the substituents are labile to methoxide ion. It was found that chlorine at position 10 was easily replaced in mono and dichloro-derivatives, while chlorine at position 9 was either resistant to replacement by methoxide, or was much less reactive than the chlorine at position 10. Bromine at position 10 was found to be relatively unreactive,

while bromine at position 9 appeared totally inert.

The ^{1}H n.m.r. and mass spectra of the quinoxalino-[2,3-*a*]cinnolines are discussed in detail.

INTRODUCTION

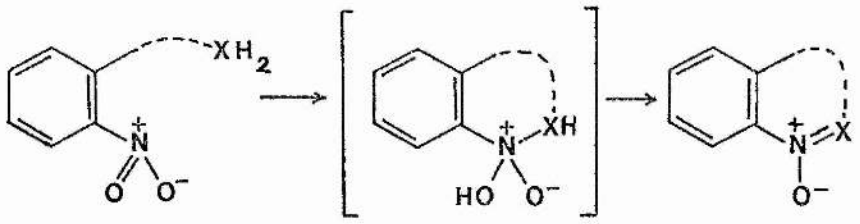
An area of growing synthetic importance is the utilisation of reactions involving chemical interaction between aromatic nitro groups and ortho side chains. There is a wide range of such reactions,[1a,b] involving, for example, cyclisations achieved via intramolecular condensations similar to the aldol type[1,2] where the nitro group provides the electrophilic centre; intramolecular displacement of nitro groups; and photochemical,[1,3] thermal and redox processes.

Reactions of these types often (but not always) lead to benzaza heterocycles, and in many cases afford products that are otherwise inaccessible (e.g. heterocyclic N-oxides of unequivocal structure, and nitrosoarenes).

Condensation reactions generally occur where the electrophilic centre is a carbonyl, nitro or nitroso group, and where the nucleophilic centre is a primary amine or a carbanion derived from a reactive methylene group. Compared to nitroso groups, nitro groups appear to be less reactive towards nucleophiles. It is difficult to find a case showing an unequivocal intermolecular condensation reaction between a nitro group and a nucleophile. However, the steric factors prevalent in intramolecular interactions permit such condensations.

Depending on the nature of the side chain ortho to the nitro group and the position of the nucleophilic centre contained therein, rings of various sizes can be formed containing up to three

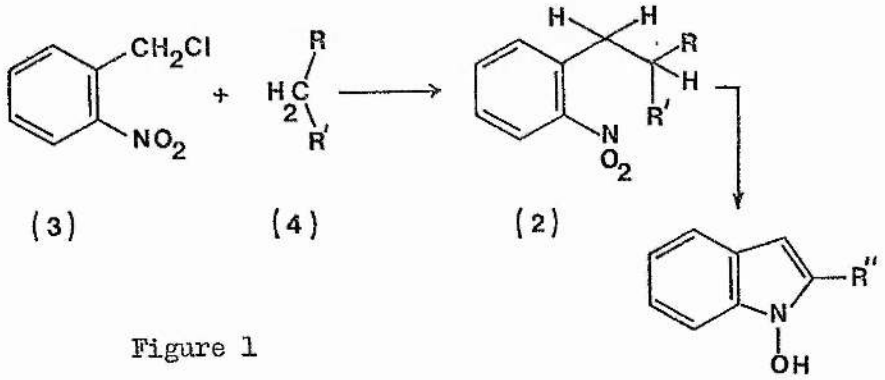
heteroatoms,[1] reaction proceeding by a mechanism of the general type:-



Most such cyclisations are acid or base catalysed, base catalysis predominating. Consequently, alteration of the reaction conditions employed can result in modification of the nature of the reaction and its products (for example, use of strong aqueous bases can result in hydrolysis of esters to acids, cyano groups to amides, and can bring about intramolecular reduction of the nitro group to a nitroso or hydroxylamine function).

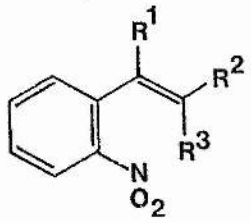
An example of the formation of a heterocyclic compound from an o-nitrobenzene derivative, illustrating some of the points made above, is the formation of 1-hydroxyindole derivatives (1) from o-nitrobenzyl compounds. When the o-nitrobenzyl derivative has at least one reactive centre in the ortho side chain, 1-hydroxyindoles are formed in good yields. If there are two reactive centres, then quinoline-N-oxide formation becomes a complicating factor. Substrates for this cyclisation (2) can be obtained by the reaction of o-nitrobenzyl chloride (3) with reactive methylene compounds (4) in the presence of base (figure 1).[4,5] Alternatively, 1-hydroxyindoles can be formed from the requisite o-nitrobenzylidene derivatives (5) by warming with aqueous ethanolic potassium cyanide (presumably by formation and cyclisation of the corresponding HCN adducts,[6,7,8] such

adducts not normally being isolated). For example the cyclisation of o-nitrophenylcinnamonitriles (6) to 3-cyano-1-hydroxy-2-phenylindole (7)[9] and the quinoline-N-oxide (8)[10] as shown in figure 2.

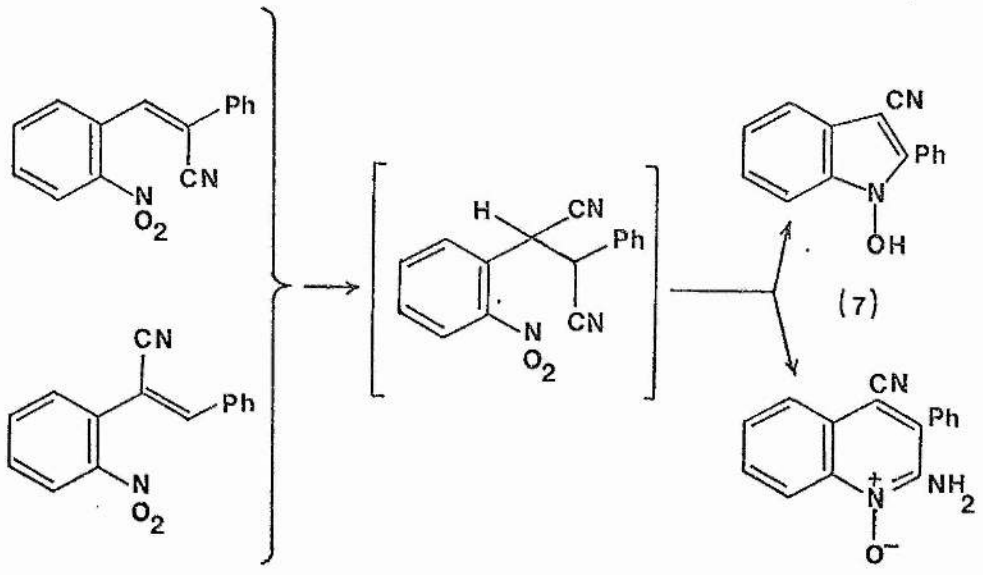


(3) (4) (2) (1)

Figure 1



(5)



(6) (7) (8)

Figure 2

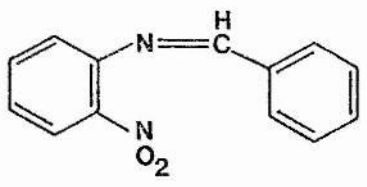
The distribution of products is dependent on the nature of the reaction conditions used, strongly basic media and the presence of electron withdrawing substituents in (5) favouring formation of quinoline-N-oxides, probably via an intramolecular redox process.

Reactions involving addition of cyanide ion to o-nitrobenzylidene compounds are of particular utility, with respect to the wide variety of cyclisation products obtained.

The above mentioned reactions result in the formation of heterocyclic products containing one heteroatom. The introduction of other heteroatoms into the side chain permits formation of rings with more than one heteroatom. Among the substrates for such reactions are the nitro-substituted benzylideneanilines, Schiff bases derived from the condensation of the appropriate primary aromatic amine and aromatic aldehyde.

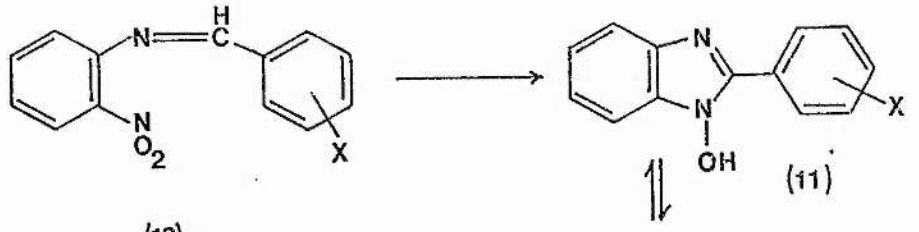
$$ArCHO + NH_2Ar' \longrightarrow ArCH{=}NAr'$$

N-benzylidene-o-nitroaniline (9) is formed by the condensation of o-nitroaniline with benzaldehyde.[11] Schiff bases of this type are very reactive towards nucleophiles, and the reaction of (9) with a number of nucleophiles has been reported.[12]



(9)

Of particular interest is the reaction of (9) with potassium cyanide. In dry methanol, (9) is cyclised to 1-hydroxy-2-phenylbenzimidazole[12] (11:X=H, tautomeric with 2-phenylbenzimidazole-N-oxide). Cyclisation of substituted anils (12) results in formation of 1-hydroxy-2-phenylbenzimidazoles in good yield.[13] In general, benzimidazoles are the only products isolated from such reactions. However when X= p-NO_2 a second product is produced, N-p-nitrobenzoyl-o-nitroaniline (13: Ar= o-$O_2N.C_6H_4$), probably formed by oxidation of the anil.



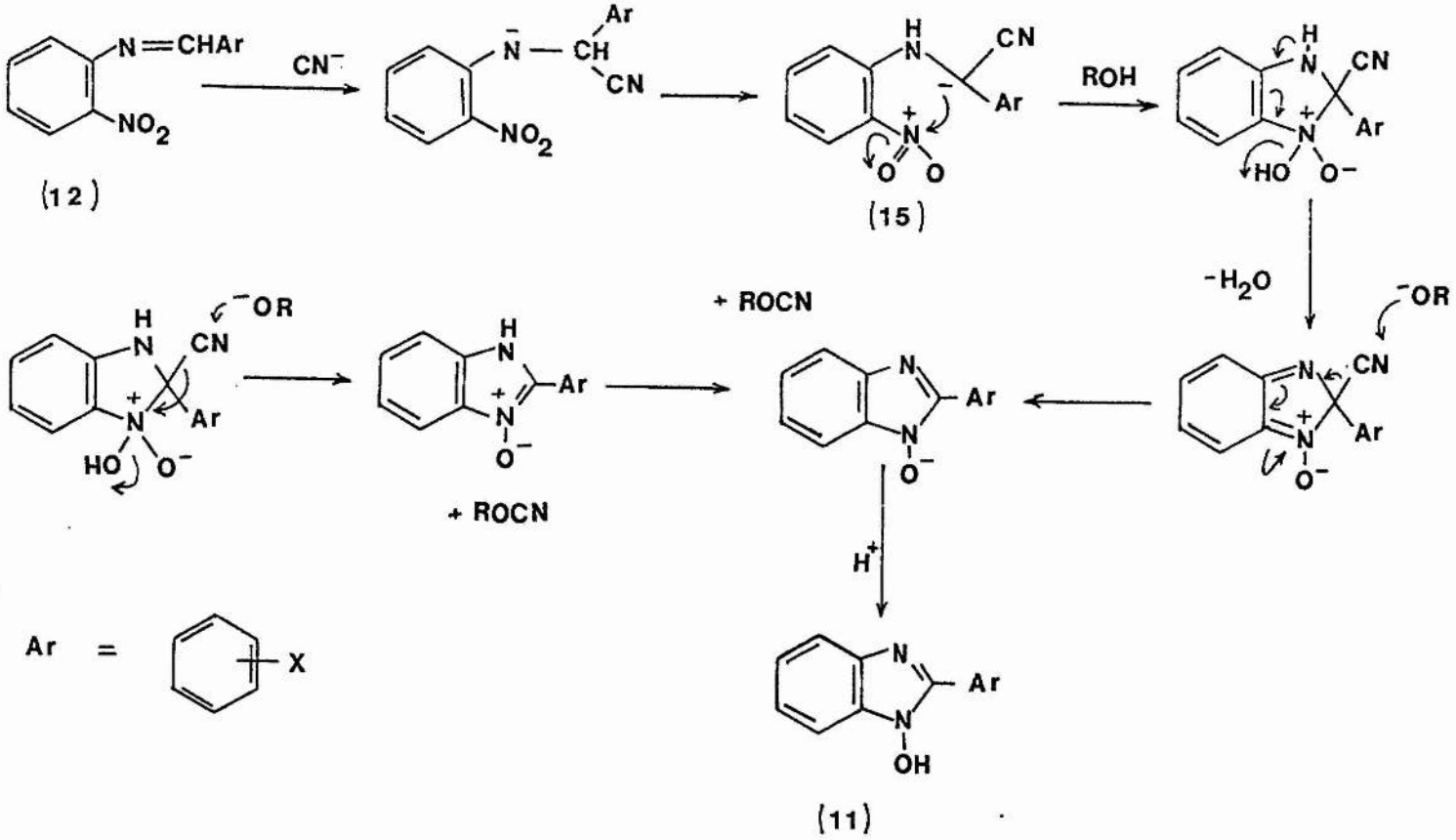
(12)

(11)

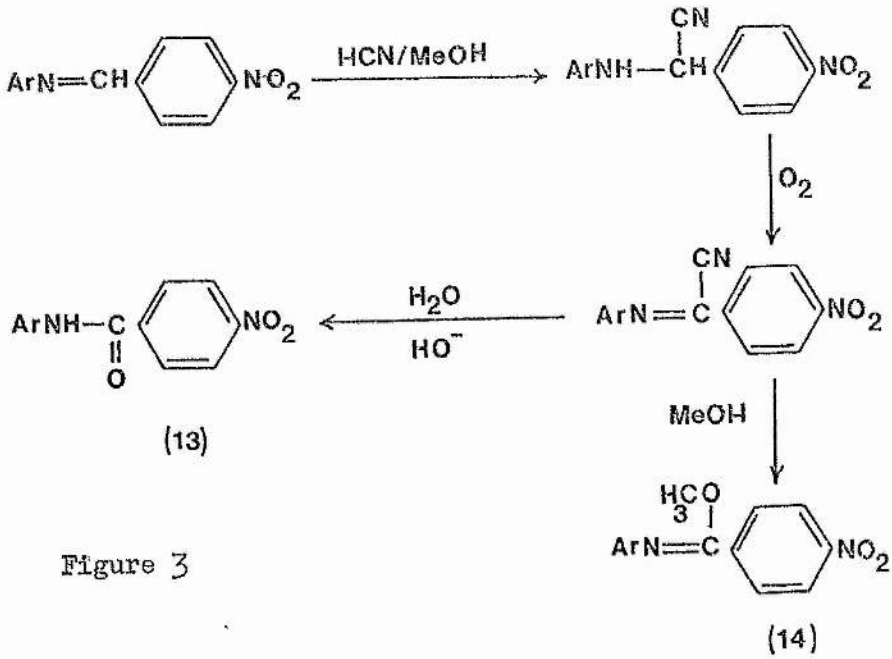
(10)

X = o-Br; o-Cl; o-CH_3
p-Cl; p-OCH_3; p-CH_3; p-NO_2

Benzanilides (13) can be formed by the reaction of N-benzylideneanilines with cyanide ion in an oxidising solvent such as dimethyl sulphoxide,[12,14] and can also be formed indirectly from N-p-nitrobenzylideneanilines in methanolic solution, as illustrated in the sequence in figure 3.[15,16] In absolute methanol, α-methoxyanils (imidate esters) (14) are formed. Thus the formation of (13) in the reaction of N-p-nitrobenzylidene-o-nitroaniline can also be rationalised by means of figure 3, if it is assumed that the α-cyano anil is formed and hydrolysed on isolation.



Scheme 1 Formation of 2-aryl-1-hydroxybenzimidazoles (11) from N-benzylidene-o-nitroanilines (12)

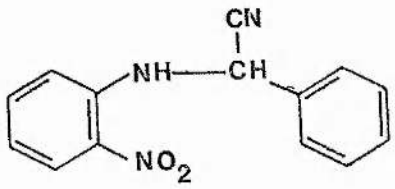


(13)

(14)

Figure 3

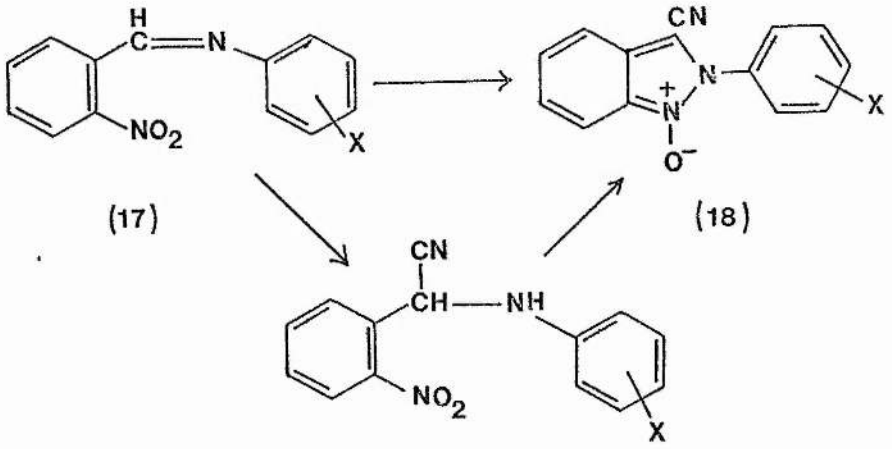
A possible mechanism for the cyclisation of (12) to (11) is shown in scheme 1, and is similar to that proposed for the formation of 1-hydroxyindoles from o-nitrobenzylidene derivatives.[6,8] The intermediacy of the adduct (15) is suggested by the conversion of the anilinonitrile (16) to (11) by mild base.[17]



(16)

This conversion of benzylidene-o-nitroanilines to 2-aryl-1-hydroxybenzimidazoles (2-arylbenzimidazole-3-oxides)[18] is of synthetic importance since the reaction conditions employed are less severe than base-catalysed processes used on other o-nitroaniline derivatives[19] to produce similar compounds.

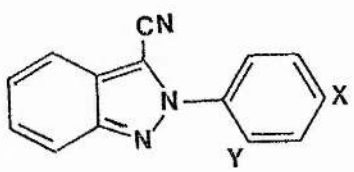
The structurally related Schiff bases, the N-o-nitrobenzylideneanilines (17), react with potassium cyanide in glacial acetic acid or under aqueous conditions to form 2-aryl-3-cyanoindazole-1-oxides (18).[20,21,22] These reactions presumably involve addition of hydrogen cyanide across the double bond in (17), and cyclisation of the resultant adducts (19), since some of the adducts, made by alternative methods, yield the same indazole oxides on treatment with mild base.[21]



(17) (18) (19)

When N-o-nitrobenzylideneaniline derivatives (17) are heated with cyanide ion in methanol, the products are different, the major products generally being 2-aryl-3-cyanoindazoles (20),[23] and 4-arylamino-3-methoxycinnoline-1-oxides (21:R=H=Y) being the minor products.

(21)



(20)

When X is a methoxy substituent, the indazole oxide is also a major product. When the anilines from which the anils are derived are ortho substituted (Y=Br;CO_2CH_3;p-Me.C_6H_4-), the only isolable products are cinnoline-1-oxides (21:X=H).

A general route for the formation of the observed products is shown in figure 4, the HCN adduct of the anil being an intermediate in the formation of the cinnoline-1-oxide and the indazole. This is reasonable since it has been shown[22] that the HCN adducts of N-o-nitrobenzylideneanilines are intermediate in the formation of indazole-1-oxides. There is also precedent for the deoxygenation of heterocyclic-N-oxides in basic media,[24,25,26] thus the indazole may be derived from the indazole oxide via deoxygenation. The lack of formation of indazoles or indazole oxides when anils derived from ortho-substituted anilines are cyclised, may be attributed to steric hindrance. It has not been found possible to form indazole oxides from ortho- substituted anils, except where the ortho- substituent is methyl or fluoro. No stable HCN adducts have been isolated from such reactions, except in the two cases mentioned; if the conditions do not permit cyclisation to the cinnoline oxide, the anil is generally recovered unchanged.[27]

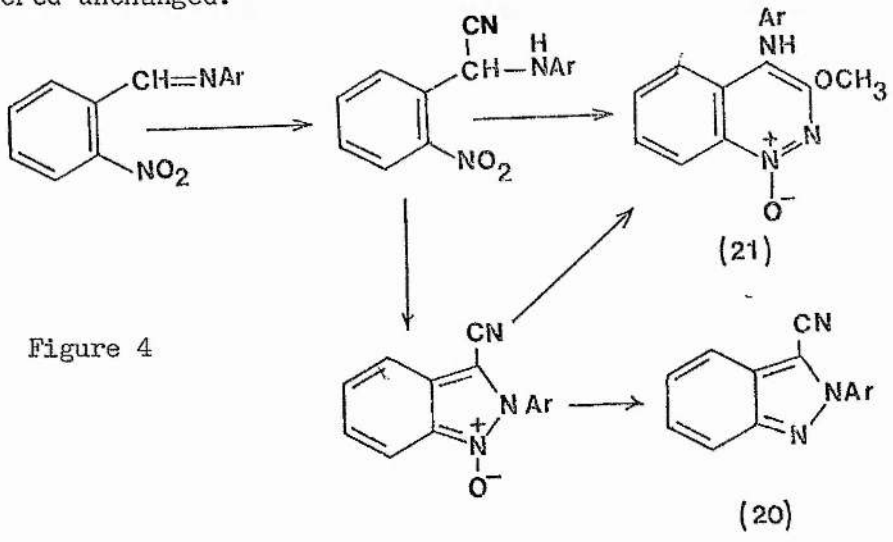
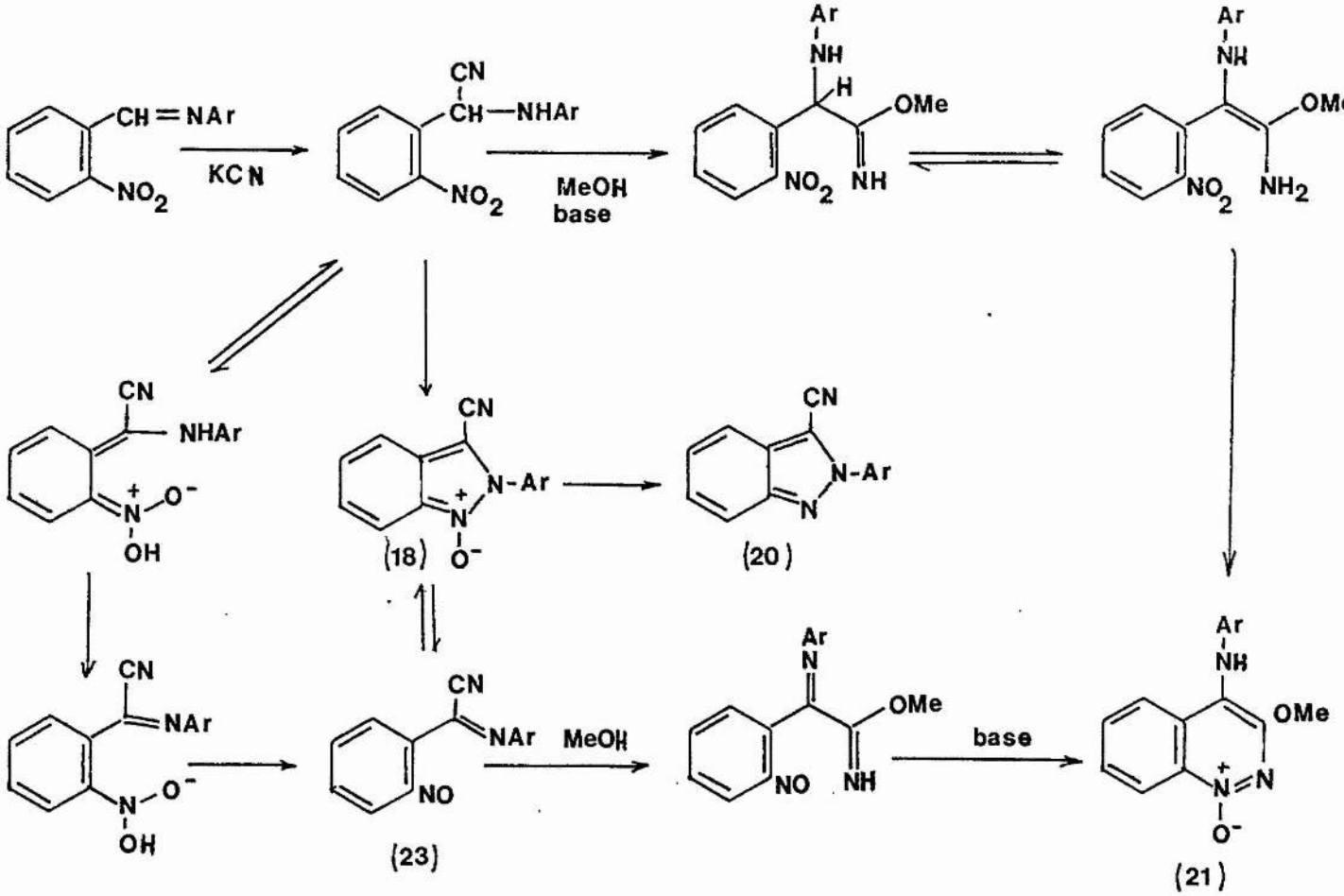


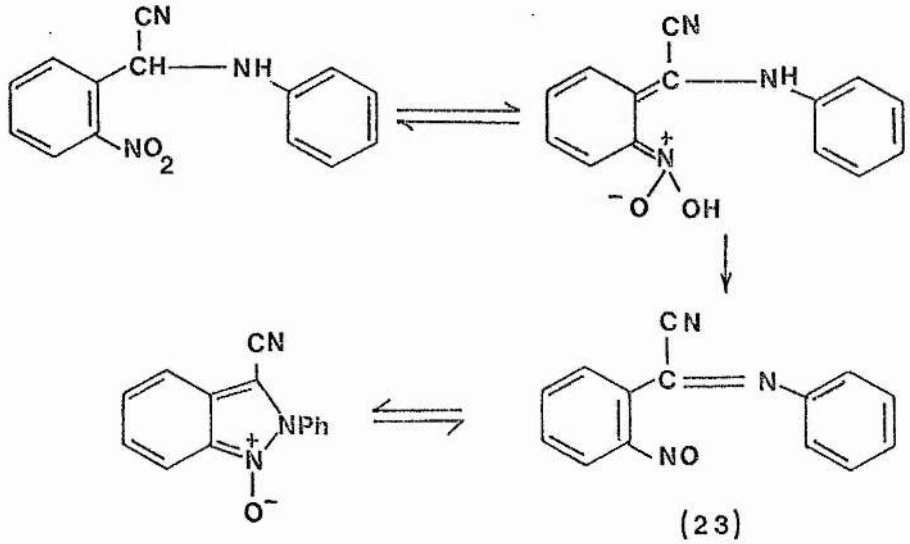
Figure 4



Scheme 2 Formation of 4-arylamino-3-methoxycinnoline-1-oxides (21), 2-aryl-3-cyanoindazoles (20) and 2-aryl-3-cyanoindazole-1-oxides (18) from N-o-nitrobenzylideneaniline derivatives

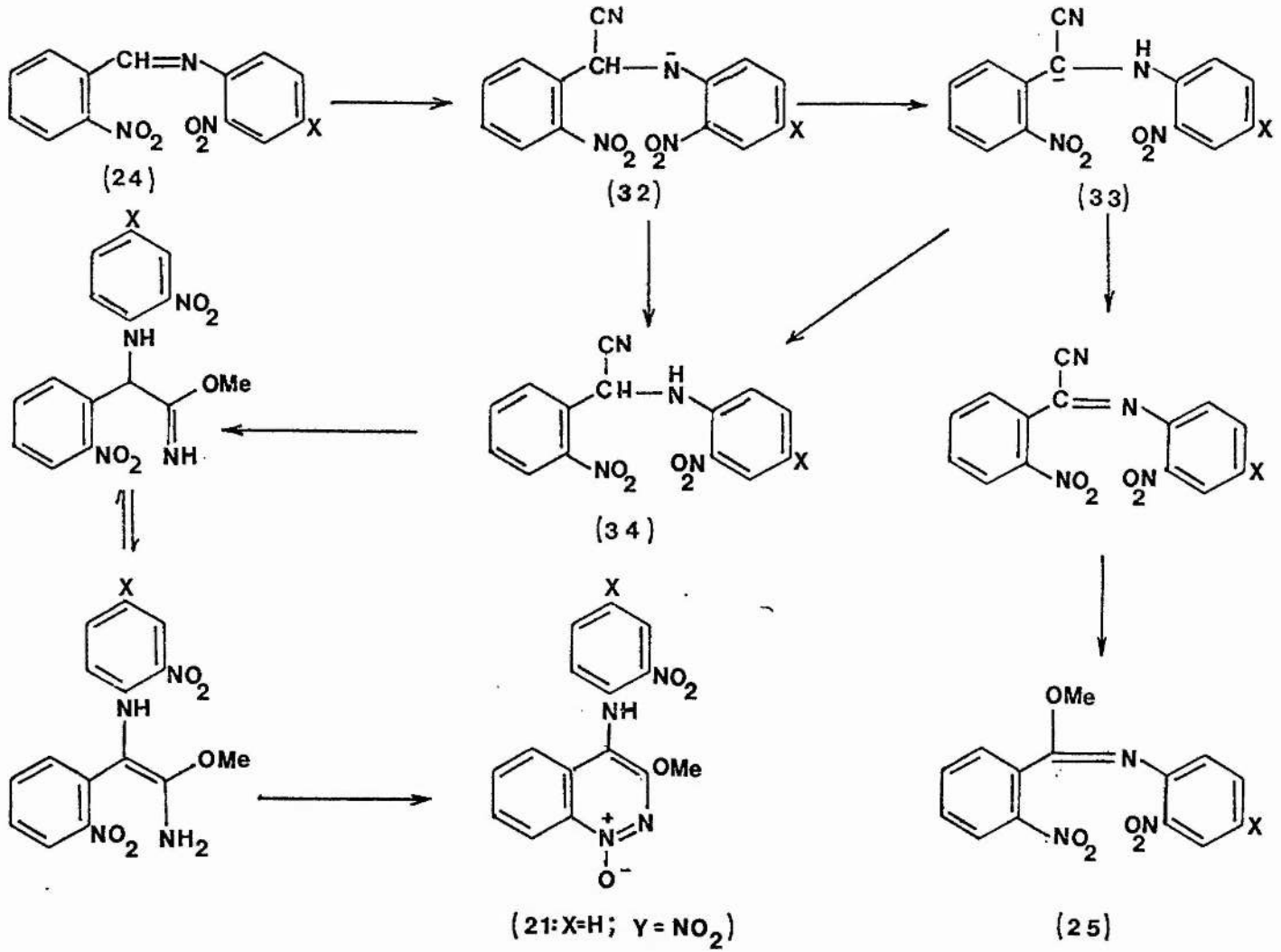
The HCN adducts of N-o-nitrobenzylideneanilines on treatment with mild base (e.g. 0.5M sodium carbonate), or in some cases on recrystallisation from ethanol, cyclise to give the corresponding 2-aryl-3-cyanoindazole-1-oxides.[27] This implies that if the HCN adducts of the anils are intermediates in the formation of cinnoline oxides and indazoles, so might the indazole oxides. Indeed, 2-(p-bromophenyl)-3-cyanoindazole-1-oxide and 2-(p-tolyl)-3-cyanoindazole-1-oxide on treatment with methanolic potassium hydroxide are converted into indazole and cinnoline-1-oxide products in the same proportions as obtained by cyclisation of the corresponding anils.[23]

Indazole-1-oxides may be tautomeric with the open chain α-cyano-o-nitrosobenzylideneanilines (23), which in turn may be derived from the HCN adducts of the corresponding anils by an intramolecular redox process. Reaction of (23) with methoxide and base could be an alternative route to the cinnoline-1-oxides.

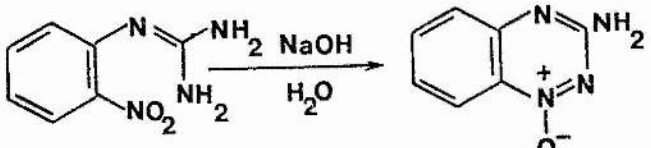


(23)

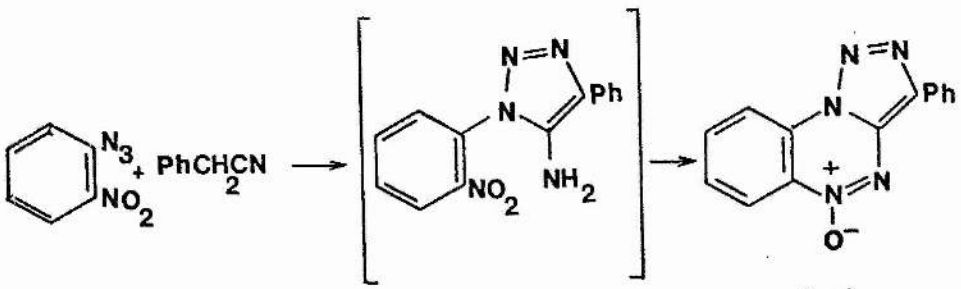
Scheme 2 represents the various routes by which the products



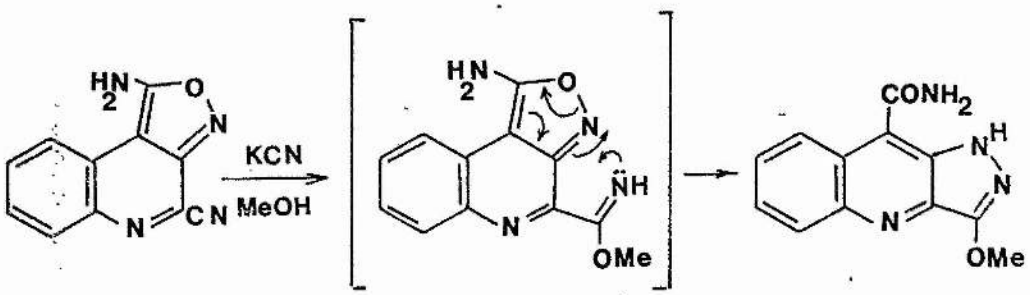
Scheme 3 Formation of 3-methoxy-4-(o-nitroanilino)cinnoline-1-oxides (21) and N-(o-nitrophenyl)-o-nitrobenzimidates (25) from N-o-nitrobenzylidene-o-nitroaniline (24)



(26) (27)



(28) (29)



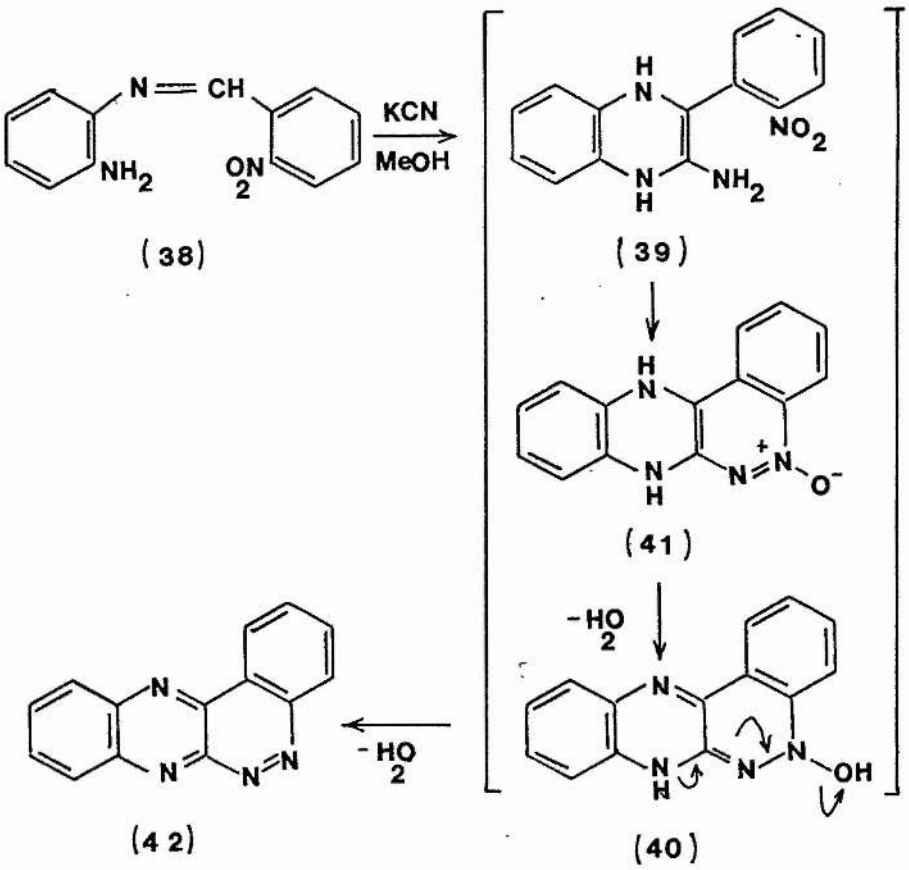
(30) (31)

(18), (21) and (20) may be made, taking into account the different distribution of products from different starting anils.

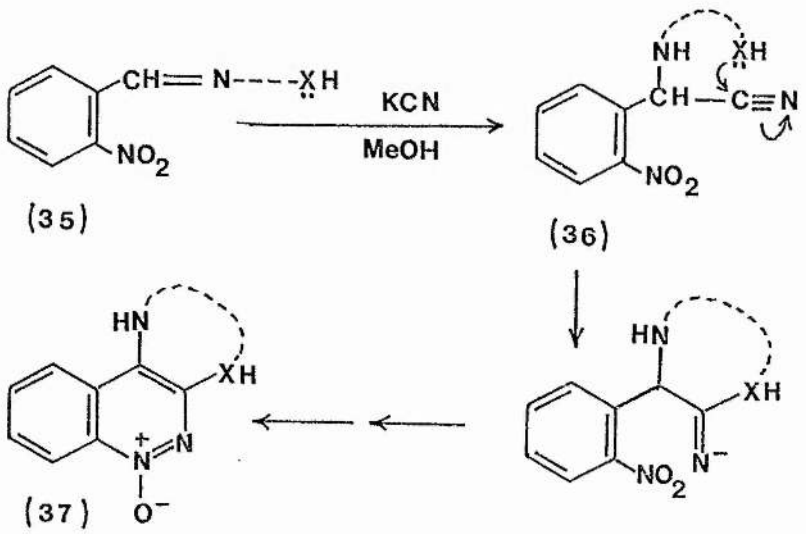
The reaction of N-o-nitrobenzylidene-o-nitroaniline (24:R=X=H) is of interest, since in principle cyclisation is possible involving either nitro group. Reaction of this compound with cyanide gives neither the indazole oxide (18:X=o-NO_2), nor the hydroxybenzimidazole (11:X=o-NO_2), but the 3-methoxy-4-(o-nitroanilino)cinnoline-1-oxide (21: Ar=o-$O_2NC_6H_4$), along with N-(o-nitrophenyl)-o-nitrobenzimidate (25: R=X=H). A route to these products and their derivatives is shown in scheme 3.

The proposed routes to cinnoline-1-oxides in schemes 2 and 3 have an analogy in the Arndt synthesis of 1,2,4- benzotriazine-1-oxides (26 to 27),[28] and related reactions (28 to 29).[29] There is also precedent for the cyclisation of imidates in sequence (30 to 31).[10] The scheme proposed for the formation of (25) from (24) is based on the work of Ogata and Kawasaki (figure 3).[15,16]

The reason for the absence of hydroxybenzimidazoles or indazole oxides among the products probably lies in the presence of electron delocalisation in intermediates (32),(33) and (34). In both cases the nucleophilic centres (charged atoms in (32) and (33), amino nitrogen in (34)) are attatched to ortho-nitrophenyl groups which will reduce the nucleophilicity of the respective sites. The possibility also exists of steric hindrance inhibiting attack by such a centre on the appropriate nitro group.


KCN
MeOH
(38)
(39)
(41)
(40)
(42)
- HO2
- HO2

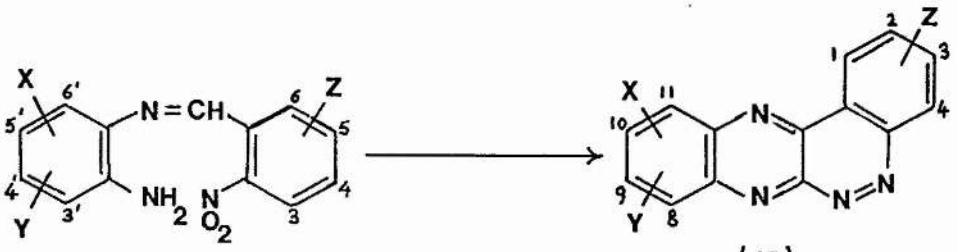
An extension of the reactions of o-nitrobenzylideneanilines with cyanide ion in methanol would in theory be possible if the N-aryl group in (17) included a nucleophilic centre, capable of acting as an internal nucleophile (35). In such a situation, a competitive reaction is envisaged where the internal nucleophile, rather than methoxide ion, attacks the cyano function of the HCN adduct (36) of (35). The product of such a reaction would be a polycyclic derivative of cinnoline-1-oxide (37). Steric factors would be expected to prevent formation of indazole derivatives.



(35) (36) (37)

A candidate for such a reaction is N-o-nitrobenzylidene-o-phenylenediamine (38). Reaction with cyanide in methanol might have been expected to yield the 7,12-dihydro-quinoxalino-[2,3-c]cinnoline-5-oxide (40). However, treatment of (38) with cyanide ion results in the formation of the fully aromatised quinoxalino[2,3-c]cinnoline (42), presumably by dehydration of the N-hydroxy species (41).[31]

Schiff base (38)	Quinoxalino[2,3-c]cinnoline (42); (yield%)	
unsubstituted	unsubstituted	(53)
5-Cl-	2-Cl-	(54)
4,5-(OCH_2O)-	2,3-(OCH_2O)-	(56)
4'-(or 5'-)Cl-	9-(or 10-)Cl-	(54)
5,4'-(or 5,5'-)Cl_2-	2,9-(or 2,10-)Cl_2-	(68)
4'-(or 5'-)CH_3-	9-(or 10-)CH_3-	(4)
4',5'-$(CH_3)_2$-	9,10-$(CH_3)_2$-	(0)
4-NO_2-	3-NO_2-	(0)
5'-NO_2-	10-NO_2-	(0)



(38) (42)

Table 1 Formation of quinoxalino[2,3-c]cinnolines (42) from N-o-nitrobenzylidene-o-phenylenediamines (38) (data taken from reference 30)

The cyanide-induced cyclisation of a number of substituted anils (38) to give substituted quinoxalinocinnolines (42) has been carried out with the results shown in table 1.[30,31] There are a number of features apparent in these results:-

(i) The failure of cyclisations when the aniline-derived ring of anils bears methyl substituents.

(ii) The failure of cyclisation of anils containing additional nitro groups in both rings.

(iii) The ambiguity of structure of the anil (and thus of the quinoxalinocinnoline) when an unsymmetrically substituted o-phenylenediamine is used as starting material.

In addition to the above, attempts to make the 9,10-dichloroquinoxalinocinnoline by this method results in the formation of a mono-chloro-mono-methoxy derivative.

The solution of problem (iii) is discussed in the following chapter, and the question of methoxydechlorination is considered in chapter 5.

CHAPTER 1

The formation and characterisation of 2-acetamido-N-(o-nitrobenzylidene)anilines

One of the entries in Table 1 of the introduction (p. 12) showed the cyclisation of `4-' (or 5-)' chloro-N-o-nitrobenzylidene-o-phenylenediamine to `9- (or 10-)' chloroquinoxalino[2,3-c]-cinnoline. The substitutional ambiguity is due to the use of an unsymmetrically substituted o-phenylenediamine in the formation of the anil. In principle, in an unsymmetrically substituted o-phenylenediamine, either amino function may be the site of condensation with carbonyl compounds. Thus 4-chloro-o-phenylenediamine (43) may form the 4- (or 5-) chloro-anil (44,45; X=H), or perhaps a mixture of both. Subsequent cyclisation of the anil (or anil mixture), results in the formation of one or other, or both, of the possible chloroquinoxalinocinnolines (46,47; X=H) (figure 5).

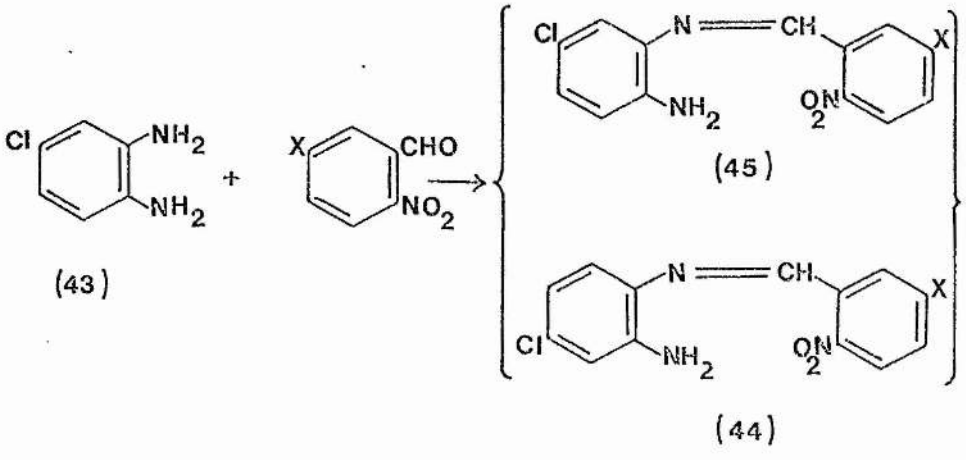
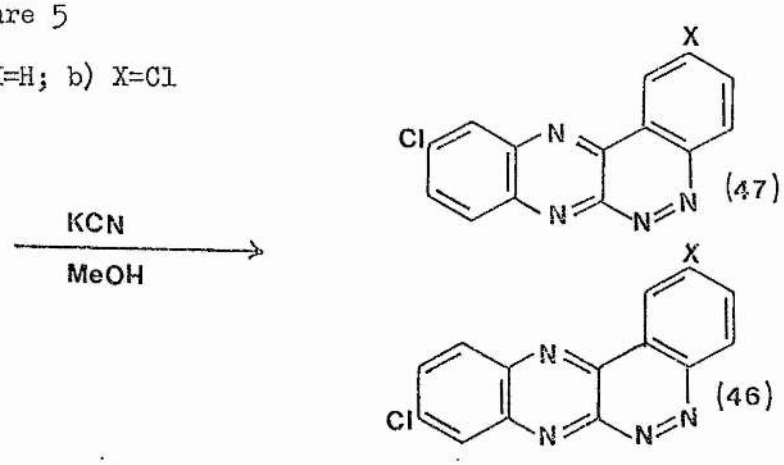


Figure 5

a) X=H; b) X=Cl



Similarly, condensation of 4-chloro-o-phenylenediamine with 5-chloro-o-nitrobenzaldehyde gives rise to the same problem concerning the site of condensation.

It is not possible to tell from the ^{1}H n.m.r. spectra of the mono- and di-chloro-anils, and the corresponding quinoxalinocinnolines, which isomer(s) is/are present, though in the case of the quinoxalinocinnoline products, it is known that they are single compounds rather than mixtures. Therefore, while it is possible that a mixture of anils is obtained from the condensation reaction, it is probable that minor components are lost in the isolation procedures.

In order to discover whether a mixture of anils is formed, the condensation of 4-chloro-o-phenylenediamine with o-nitrobenzaldehyde was repeated. The crude product from the reaction was examined by 360 MHz ^{1}H n.m.r. spectroscopy, revealing that a mixture of anils (44,45; X=H) is indeed formed, in the approximate ratio of 4:1. While the ^{1}H n.m.r. spectrum did identify two components, their identity cannot be inferred from the spectrum alone. It was also found on re-examination of the 100 MHz ^{1}H n.m.r. spectrum of the 5,5'-dichloro-anil obtained by a previous worker, that here too a product mixture is observed (44,45; X=Cl). The ratio of the components is again about 4:1. The assignment of identity of the components in the spectra is discussed in chapter 2, p.30, and the assigned spectra are found in tables 5 and 6, p. 30.

These mixtures were subjected to the cyclisation procedure, and

again only one quinoxalinocinnoline was isolated in each case. It was assumed that this arose from the major component of the anil mixture.

There is an alternative route to quinoxalino[2,3-a]cinnolines (42). This involves the reaction of 3,4-dibromocinnolines (48) with o-phenylenediamines to form dihydroquinoxalino[2,3a]cinnoline salts (49), which when basified undergo subsequent oxidation in air to give the products (42) (figure 6).[31,32] Several substituted quinoxalinocinnolines have been made by this method. Compared to the Schiff base route, this procedure is cumbersome due to the many steps and long reaction times required, and the substitutional ambiguity with unsymmetrically substituted o-phenylenediamines is not avoided.

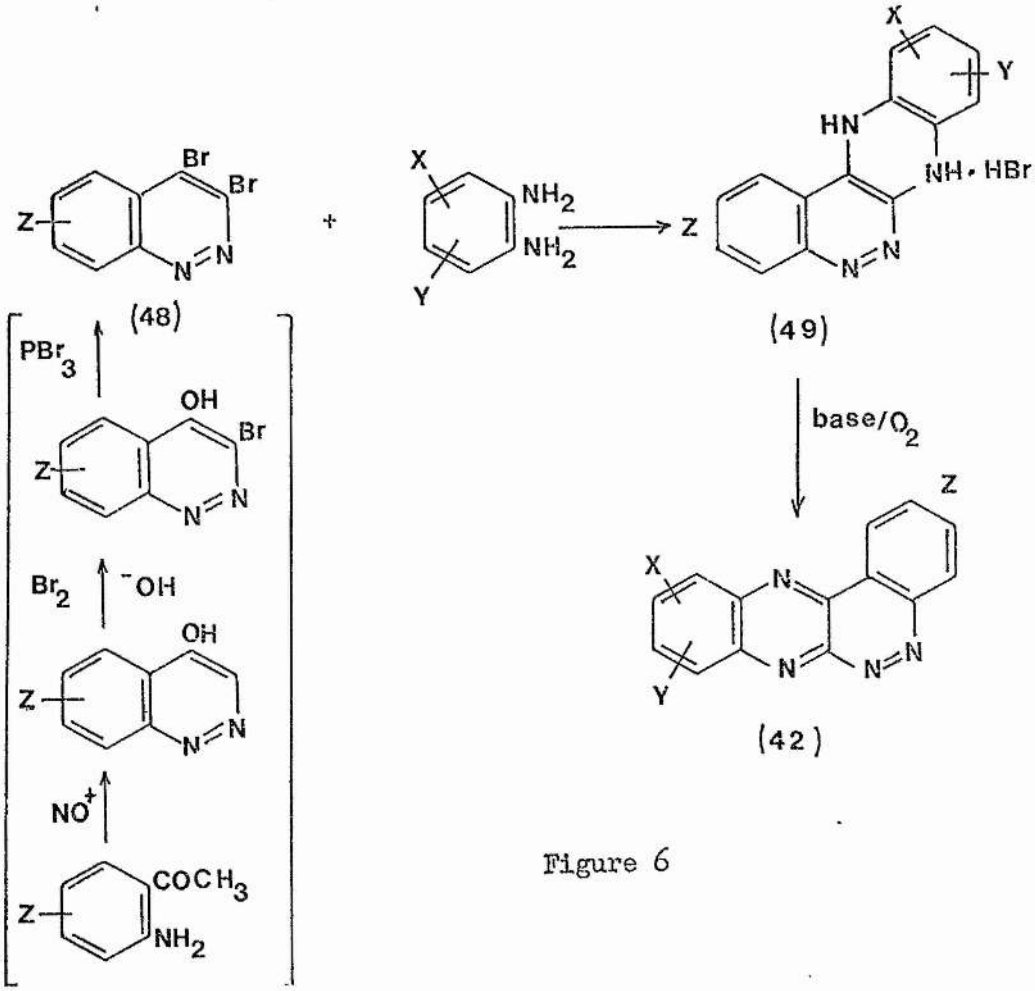
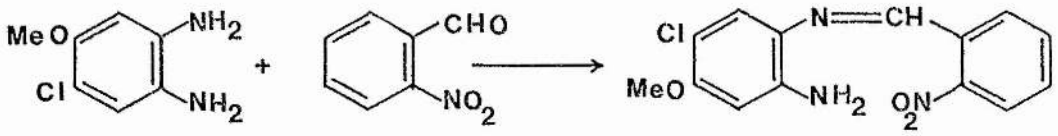


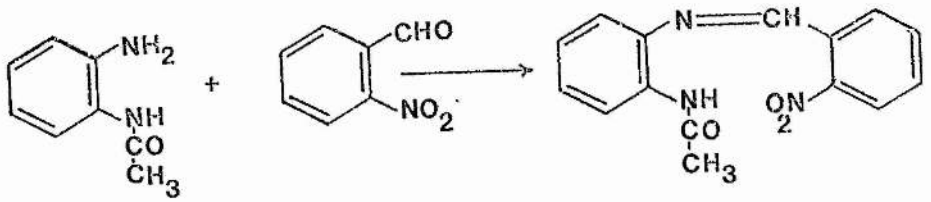
Figure 6

In order to resolve the problem of the substitutional ambiguity, it was necessary to develop an alternative synthetic route to quinoxalino[2,3-c]cinnoline and its derivatives, in which the positions of the substituents were known with certainty.



(51) (50)

A possible method would be to synthesise a Schiff base from a diamine in which one amino-group is substantially more nucleophilic than the other. For example, in 4-chloro-5-methoxy-o-phenylenediamine (51), the presence of the electron donating methoxy-group would be expected to activate the para-amino group enough to ensure that condensation with o-nitro-benzaldehyde occurs at that amino group, forming 4-chloro-5-methoxy-N-o-nitrobenzylidene-o-phenylenediamine (50)[31] (cf. p. 75). However, to be of general utility, such a synthetic route should not depend on the chemical or electronic interaction of the substituents in order to be successful. It was felt that a suitable method might be to protect one of the amino functions in the o-phenylenediamine with a good leaving group, permitting retention of substitution pattern during the formation of the anil. There are many available protecting groups for amino functions, and it was decided in the first instance, to proceed using an acetyl group as the protecting species, since the synthesis of o-aminoacetanilide and its derivatives should be relatively simple.

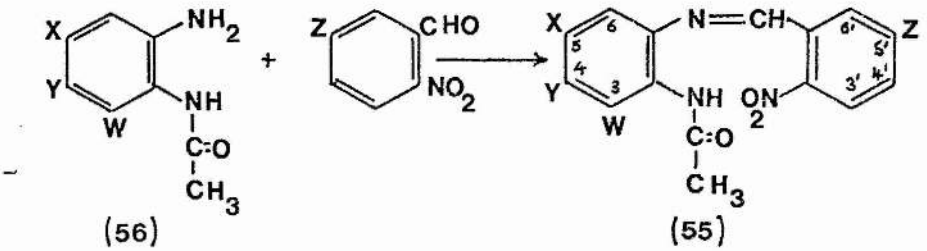


(52) (53)

When equimolar amounts of o-aminoacetanilide (52) and o-nitrobenzaldehyde in ethanol were heated gently on a water bath, after a short time a bright yellow solid precipitated out. The ^{1}H n.m.r. spectrum of this product showed a sharp singlet at $\delta 8.85$ corresponding to the benzylidene proton (c.f. $\delta 8.92$ for the same proton in N-o-nitrobenzylidene-o-phenylenediamine),[30] a broad singlet at $\delta 8.48$ for the amide proton, and a sharp intense singlet at $\delta 2.22$ for the acetyl methyl group. The protected anil, 2-acetamido-N-(o-nitrobenzylidene)aniline (53), and two mole equivalents of potassium cyanide in methanol, were heated under reflux for three hours. A bright orange crystalline product was obtained on cooling; on spectral examination it was found to be quinoxalino-[2,3-c]cinnoline (42 a), identical with samples produced from N-o-nitrobenzylidene-o-phenylenediamine.[30]

The success of this cyclisation at the first attempt was considered to be somewhat fortuitous, since it is known that the acetyl groups in a number of substituted acetanilides are not particularly labile in basic media, under relatively mild reaction conditions.[40] However, the acetyl function is obviously lost during the cyclisation process, perhaps resulting in the formation of the

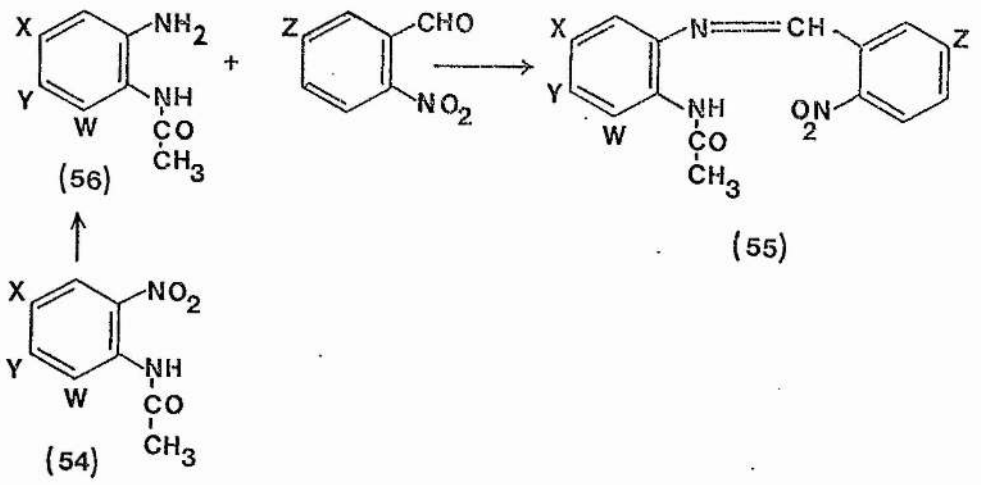
Substituents	Yield(%)	Melting point (°C); recrystallising solvent
(55 a) -	82	124-126 (EtOH)
(55 b) 5-Cl	82	152-154 (EtOH)
(55 c) 4-Cl	78	162-164 (EtOH)
(55 d) 5,5'-Cl_2	89	206-208 (EtOH)
(55 e) 5-CH_3	70	133-134 (EtOH)
(55 f) 5-OCH_3	77	137-138 (EtOH)
(55 g) 5'-Cl	74	200 (EtOH)
(55 h) 3,5-Cl_2	83	216-217 (EtCOMe)
(55 i) 3,5,5'-Cl_3	54	226-228 (EtCOMe)
(55 j) 3-Cl	68	216-217 (EtCOMe)
(55 k) 5-Br	84	160-161 (EtOH)
(55 l) 4-Br	72	165-167 (EtOH)



(56) (55)

Table 2 Formation of 2-acetamido-N-(o-nitrobenzylidene)anilines (55) from the condensation of appropriate o-amino-acetanilides (56) and o-nitrobenzaldehydes

unacetylated anil. The general usefulness of this synthetic route would depend on the successful cyclisation of substituted anils giving rise to specifically substituted quinoxalinocinnolines. Therefore in order to test the general utility of this reaction, a number of substituted anils (55) were synthesised by condensation of appropriate 2-aminoacetanilides (56) with o-nitrobenzaldehyde or 5-chloro-2-nitrobenzaldehyde, the results being shown in table 2.



All the anils, except those with a substituent at position 3, are bright yellow in colour. The latter anils are virtually colourless. The variation in colour is probably due to differing degrees of conjugation within the molecular structure, and will be discussed later in this chapter. All anils form needle-like crystals, being fibrous in 3- and 5-substituted anils, and more of a prismatic form in 4-substituted derivatives, perhaps illustrating that the crystal packing in 4-substituted compounds is more efficient. Where 4- and 5-substituted anils occur with the same substituent, the 4-substituted compounds have the higher melting point, again probably indicating more effective crystal packing. All anils are extremely

light-sensitive, darkening to a reddish-brown colour within a matter of minutes of their exposure to light. This is found to be particularly the case for those anils substituted at position 3, and is thought to be the reason why accurate analyses of these compounds were difficult to obtain. Indeed, while the analytical data for the mono-chloro- and dichloro- compounds is thought to be reasonably good considering their instability to light, it was not found possible to obtain a reasonable result for the trichloro-anil. The cyclisation reaction of the latter compound, is, however, included in the following chapter.

Compound	H - 3'	H - 4'	H - 5'	H - 6'	H - 3	H - 4	H - 5	H - 6	CH = N	NH	$COCH_3$	Others
(55 a) unsubstituted[a]	——— (7.5 - 8.1 (m)) ———				8.5 (d)	——— (6.9 - 7.4 (m)) ———			8.85 (s)	8.5 (bs)	2.22	-
(55 b) 5 - Cl[a]	——— (7.6 - 8.12 (m)) ———				8.47 (d)	——— (7.12 - 7.14 (m))[d] ———			8.85 (s)	8.35 (bs)	2.32	-
(55 c) 4 - Cl[a]	——— (7.65 - 8.15 (m)) ———				8.62 (d)	-	7.05 (dd)	7.2 (d)	8.9 (s)	8.5 (bs)	2.25	-
(55 g) 5' - Cl[a]	8.05 (d)	7.66 (dd)	-	8.16 (d)	8.59 (d)	——— (7.1 - 7.55 (m)) ———			9.0 (s)	8.49 (bs)	2.25	-
(55 d) 5,5'-Cl_2[a]	8.07 (d)	7.62 (dd)	-	8.06 (d)	8.51 (d)	7.3 (dd)	-	7.2 (d)	8.91 (s)	8.3 (bs)	2.25	-
(55 e) 5 - CH_3[a]	——— (7.7 - 8.23 (m)) ———				8.46 (d)	——— (7.08 - 7.3 (m))[d] ———			9.03 (s)	8.4 (bs)	2.27	2.37 (s)
(55 f) 5 - OCH_3[a]	——— (7.55 - 8.22 (m)) ———				8.47 (d)	6.92 (dd)	-	6.81 (d)	8.95 (s)	8.3 (bs)	2.25	3.86 (s)
(55 k) 5 - Br[a]	——— (7.67 - 8.17 (m)) ———				8.46 (d)	——— (7.52 - 7.37 (m))[d] ———			8.9 (s)	8.4 (bs)	2.25	-
(55 l) 4 - Br[a]	——— (7.6 - 8.17 (m)) ———				8.82 (d)	-	7.28 (dd)	7.1 (d)	8.95 (s)	8.47 (bs)	2.25	-
(55 j) 3 - Cl[b]	——— (7.85 - 8.3 (m)) ———				-	[7.43 or 7.12]	7.37	[7.12 or 7.43]	8.83 (s)	9.62 (bs)	2.02	-
(55 h) 3,5 - Cl_2[b]	——— (7.85 - 8.32 (m)) ———				-	[7.65 or 7.3]	-	[7.3 or 7.65]	8.87 (s)	9.7 (bs)	2.05	-
(55 i) 3,5,5' - Cl_3[b]	8.28 (d)	8.0 (dd)	-	8.16 (d)	-	as above	-	as above	8.87 (s)	9.75 (bs)	2.05	-

	J
(55 a)	$J_{3,4}$ = 7.8 Hz
(55 b)	$J_{3,4}$ = 8.2 Hz
(55 c)	$J_{3,5}$ = 2.5 Hz; $J_{6,5}$ = 8.2 Hz
(55 g)	$J_{3',4'}$ = 8.8 Hz; $J_{4',6'}$ = 2.4 Hz; $J_{3,4}$ = 8.4 Hz
(55 d)	$J_{3',4'}$, $J_{3,4}$ = 8.6 Hz; $J_{4',6'}$, $J_{4,6}$ = 2.3 Hz
(55 e)	$J_{3,4}$ = 8.4 Hz
(55 f)	$J_{3,4}$ = 8.6 Hz; $J_{4,6}$ = 2.5 Hz
(55 k)	$J_{3,4}$ = 8.6 Hz; $J_{4,6}$ = 2.2 Hz
(55 l)	$J_{5,6}$ = 8.6 Hz; $J_{3,5}$ = 2.2 Hz
(55 j)	-
(55 h)	$J_{4,6}$ = 2.4 Hz
(55 i)	$J_{3',4'}$ = 8.8 Hz; $J_{4',6'}$, $J_{4,6}$ = 2.4 Hz

a) In approximately 10% W/V $CDCl_3$ + TMS as internal standard; b) In approximately 10% W/V $(CD_3)_2SO$ + TMS as internal standard; c) By computer simulation; d) H - 4 and H - 6 signals overlap.

Table 3 ^1H n.m.r. of 2-acetamido-N-(o-nitrobenzylidene)anilines (55)

^{1}H n.m.r. spectra of 2-acetamido-N-(o-nitrobenzylidene)anilines (55)

The ^{1}H n.m.r. spectra of the 2-acetamido-N-(o-nitrobenzylidene)-anilines are shown in table 3. The benzylidene protons all come to resonance in the range δ8.83-9.03, which is very similar to that of benzylidene protons in unacetylated anils (δ8.88-9.02).[30,31] The most striking feature of the ^{1}H n.m.r. spectra of the acetylated anils (other than those with a 3-substituent), is the downfield shift of the resonances corresponding to proton 3 (δ8.46-8.42), compared to the corresponding protons in the unacetylated compounds. Comparison of the chemical shifts of proton-3 in the mono-chloro acetylated anils (55 b and 55 c, both at about δ8.5), with those of the corresponding protons-3' in the unacetylated anils (see table 5, both at about δ6.7), reveals that the downfield shift is about 1.8 p.p.m. The remaining protons come to resonance in the same ranges in both acetylated and unacetylated anils. Similarly, in the case of the 5,5'-dichloro acetylated anil and the corresponding unacetylated anil (table 6), the downfield shift is of about the same magnitude.[33] The most likely cause of such downfield shifts is the anisotropic deshielding of the proton in position 3 by the carbonyl group of the acetamido function, ortho to position 3.

The anisotropic shielding zones of the carbonyl group are shown in figure 7,[34] the deshielding effect being strongest in the plane of the carbon-oxygen bond, and just above the `surface' where the shielding effect changes sign. Thus protons which lie within the anisotropic deshielding zone due to their position within a molecular

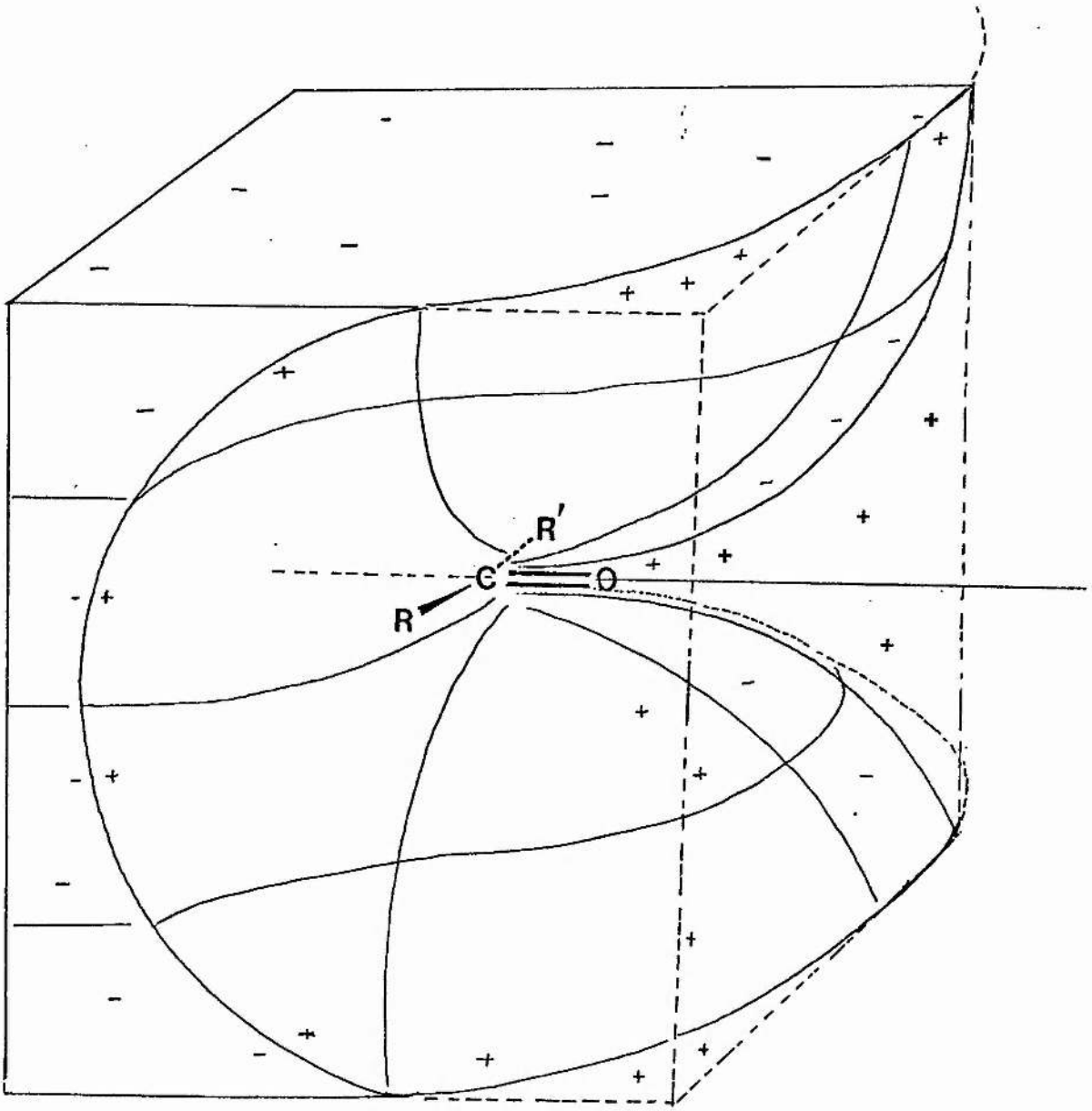
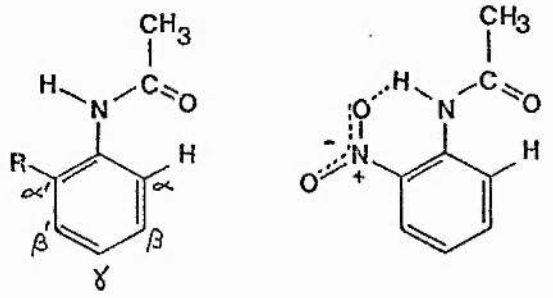


Figure 7 Anisotropic shielding zones of the carbonyl group.
Positive-zone-protons deshielded
Negative-zone-protons shielded

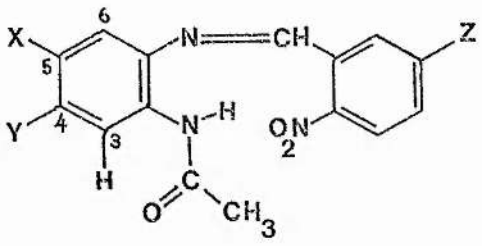
structure, experience an anisotropic deshielding effect of a magnitude dependent on their exact position within the zone. Anisotropic deshielding of aromatic protons by adjacent acetamido-groups has already been found in substituted acetanilides (57).[35,36] Calculated values for the chemical shift of proton H_α when compared with experimentally determined values, show chemical shift differences that generally increase with increasing size of the ortho-substituent R. Such differences are much less in compounds without such a substituent. Therefore there is also a steric effect: large bulky groups in the α' position tend to favour the correct alignment for anisotropic deshielding of the α-proton by the acetyl carbonyl group. Indeed, the effect is most pronounced in the case of the o-nitroacetanilides where, in addition, hydrogen bonding between the amide hydrogen and the nitro group holds the molecule in the correct conformation, the nitro-group acting as a conformational lock.[35] In o-nitroacetanilide (57:R=NO_2) the value of $\Delta\delta$ for proton 6 (i.e. position α) is 1.01 p.p.m.



(57)

In the case of the acetylated anils (55) there is unlikely to be any opportunity for intramolecular hydrogen bonding with the amide hydrogen atom. It is therefore probable that the bulk of the o-nitrobenzylidene group is sufficient to cause alignment of the acetamido-group in the correct position for anisotropic deshielding of

proton 3.



Another noticeable feature observed in the ^{1}H n.m.r. spectra of these anils is the downfield shift of the amide proton in compounds with chloro-substituents at position 3 (δ9.62-9.75), when compared to those of the rest of the series (δ8.3-8.5). A plausible reason for this anomaly is the steric interaction of the chlorine atom with the adjacent acetamido group, resulting in the latter being pushed out of the plane of the ring. Indeed, further indication of such an effect may be found by consideration of the colour of these compounds.

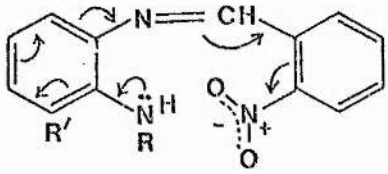


Figure 8

R=H, R'=H	colour: red
R=$COCH_3$, R'=H	colour: yellow
R=$COCH_3$, R'=Cl	colour: pale cream/ colourless

o-Amino-anils are orange red in colour; the acetylated anils are bright yellow (except for 3-chloro-derivatives), indicating different degrees of conjugation throughout the molecule (figure 8). The 3-chloro-acetylated anils are pale straw-coloured, or virtually

colourless, indicating a further diminution of conjugation, understandable if a planar conformation is disrupted by the chloro substituent.

The chemical shifts of protons 4,5 and 6 in the 3-chloro derivative (55 i) were estimated by computer simulation. In this case, and also in (55 h) and (55 j), it was not possible to establish whether H-4 or H-6 gave the lower field signal.

CHAPTER 2

The cyanide-induced cyclisation of 2-acetamido-N-(o-nitrobenzylidene)anilines

Compound	Substituents	From Anil no	Yield (%), Reaction time		Melting Point (°C), Recrystallising Solvent	By-products obtained on dilution of filtrates A) under air, B) under nitrogen[5]
			A) in air[2]	B) in nitrogen[3]		
42 (a)	-	55 (a)	40, 3 hours	52, 3 hours	A), B) 224-226 (DMF) (Lit. 228-230)	-
42 (b)	10-Cl-	55 (b)	(i) 7.5, 2½ hours (ii) 25, 1 hour (iii) 45, 25 minutes	(iv) 32. 35 minutes (v) 35, 50 minutes	A) 240-242 (DMF) B) 246-247	A) = Mixture of compounds, with a mass spectrum showing M^+; $(M + 16)^+$; $(M + 34)^+$ and $(M - 4/6)^+$ B) = Same as above
42 (c)	9-Cl	55 (c)	54, 1 hour	62, 25 minutes	A), B) 278 (DMF) (Lit. 274-276)	A) and B): trace of $(M + 16)^+$ in mass spectra of products of cyclisation, no dilution by products.
42 (g)	2-Cl	55 (g)	-	(i) 20, 50 minutes (ii) 43, 2 hours	B) ii) 260-261 (DMF) (Lit. 260 - 262)	B) (i): approximately 20% yield of $(M + 16)^+$ along with 42 (d) B) (ii): slight trace of $(M + 16)^+$ in mass spectrum of product. No dilution products.
42 (d)	2, 10-Cl_2	55 (d)	(i) 10, 40 minutes (ii) 7, 40 minutes[1]	-	A) 288-290 (DMF)	A): Mass spectrum of product shows a trace of $(M + 16)^+$ and $(M + 34)^+$ as well as $(M - 4/6)^+$. Dilution of filtrates yielded a mixture having mass spectral composition of M^+; $(M + 16)^+$; $(M + 34)^+$ and $(M - 4/6)^+$. A yellow solid was isolated in 6% yield m.p. 300 °C), molecular mass M + 34.
42 (e)	10-Me	455 (e)	0, 3 hours	0, 3 hours	-	A), B): The mass spectrum of the product obtained from dilution of reaction mixture shows the presence of M^+, while T L C shows the presence of five or six compounds.
42 (f)	10-OCH_3	55 (f)	-	(i) 35, 45 minutes (ii) 60, 2 hours	B) 264 (DMF)	B) i: approximately 35% yield of $(M + 16)^+$ along with 42 (g). No products on dilution.

Table 4 (continued overleaf)

Compound	Substituents	From Anil no	Yield (%), Reaction time under nitrogen	Melting Point (°C) Recrystallising Solvent	By-products
42 (k)	10-Br	55 (k)	(i) 50, 1 hour	263-265 (DMF)	-
42 (l)	9-Br	55 (l)	(i) 52, 1 hour	252-254 (DMF)	Brick red solution isolated from dilution of reaction mixture
42 (j)	8-Cl	55 (j)	20^4, 45 minutes	-	Approximately 20% yield of compound of mass M + 16
42 (h)	8, 10-Cl_2	55 (h)	25^4, 45 minutes	-	Approximately 25% yield of compound of mass M + 16
42 (i)	2, 8, 10-Cl_3	55 (i)	0, $1\frac{1}{2}$ hours	-	Approximately 35% yield of compound of mass M + 34

1 With DMF as co solvent

2 The mass spectra of these compounds showed a peak at $(M + 16)^+$ and traces of one at $(M + 34)^+$

3 The mass spectra of these compounds showed only a slight trace of $(M + 16)^+$

4 Estimated by chemical separation (see Chapter 4)

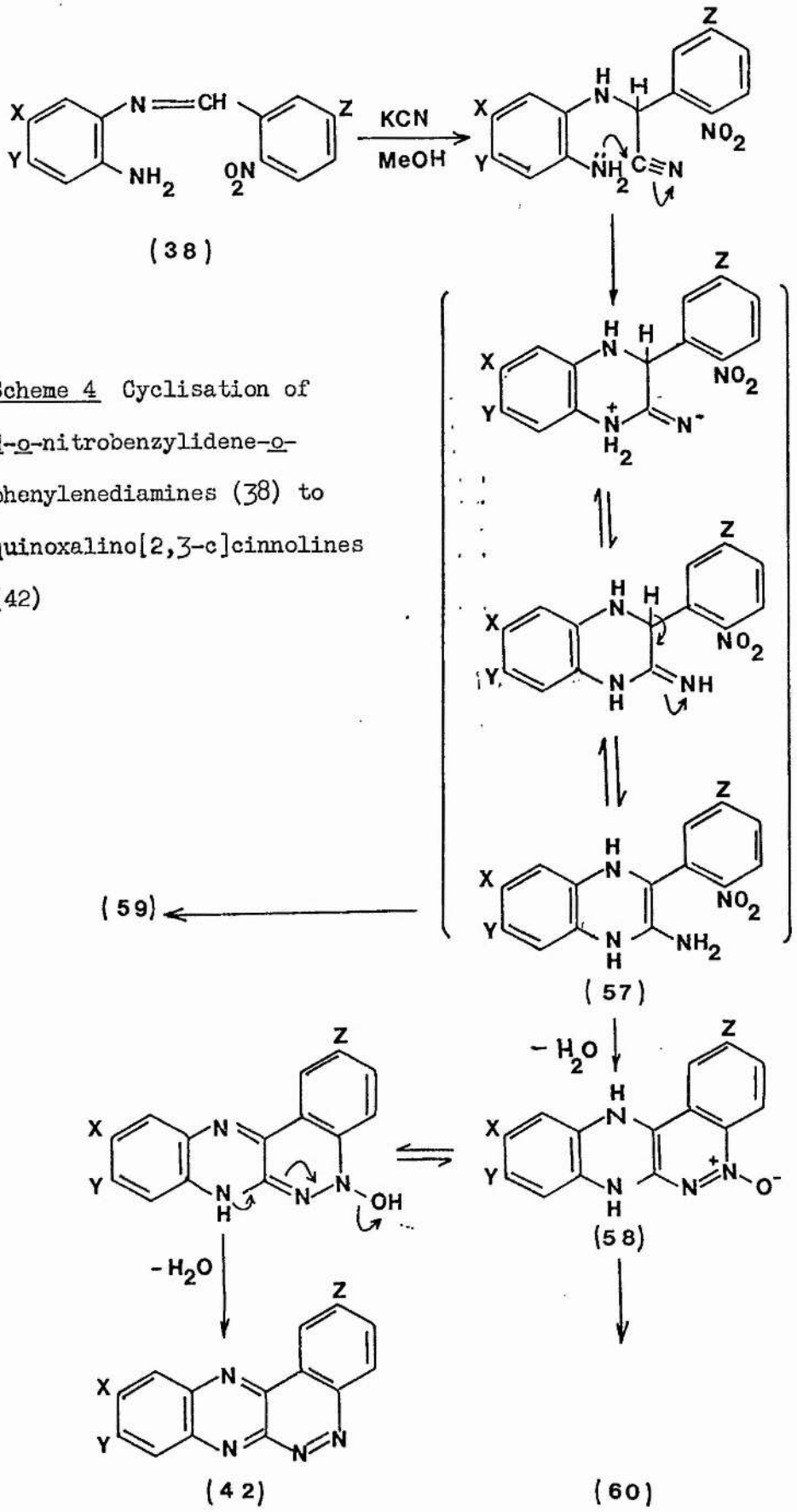
5 M^+ in this column represents the molecular mass of the product quinoxalino [2,3-c] cinnolines

Table 4 Cyclisation of 2-acetamido-N-(o-nitrobenzylidene) anilines (55) to give quinoxalino-[2,3-c]cinnolines and by-products.

The cyanide-induced cyclisation of 2-acetamido-N-(o-nitrobenzylidene)anilines

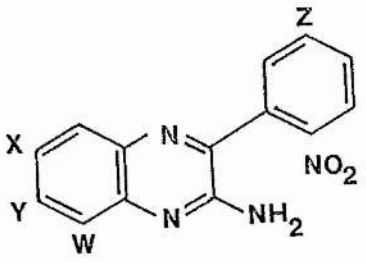
The o-acetamido-anils (55) were cyclised by heating under reflux with two mole equivalents of potassium cyanide in methanol (Table 4). On cooling, any precipitate was collected, and filtrates were then (if necessary) diluted with water to obtain more product. The cyclisations were initially carried out in air, but were later on carried out under nitrogen using degassed methanol as solvent.

Cyclisations of o-acetamido-anils in air gave an initial crop of product, consisting of the quinoxalino[2,3-c]cinnoline (42) and trace amounts of by-products, apparent in the mass spectrum as peaks at $(M+16)^+$ and $(M+34)^+$ (M refers to the parent quinoxalinocinnoline). On recrystallisation, the (M+34) component was generally removed, while the (M+16) component was significantly diminished. Neither by-product was evident in the ^1H n.m.r. spectra of the products. Dilution of reaction solutions after the removal of initial products yielded mixtures of quinoxalino[2,3-c]cinnolines and the two previously mentioned by-products in relatively low yields. When 10-chloroquinoxalino[2,3-c]cinnoline (42 b) and 2,10-dichloro-quinoxalino[2,3-c]cinnoline (42 d) were prepared by a cyclisation in air, low yields were obtained under the normal reaction conditions (viz, reflux for 3 hours), while a reduction in reaction time resulted in increased yield of (42 b). The mass spectra of (42 b) and (42 d) showed peaks at m/e 262, and m/e 296 respectively, corresponding to a

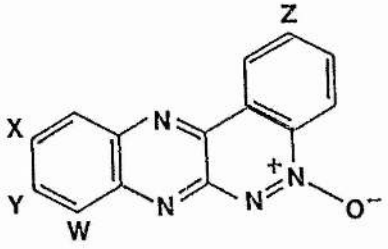


Scheme 4 Cyclisation of N-o-nitrobenzylidene-o-phenylenediamines (38) to quinoxalino[2,3-c]cinnolines (42)

by-product resulting from loss of halogen and replacement by methoxyl. Indeed, the ^{1}H n.m.r. spectra of these compounds showed small peaks at δ4.15, the correct chemical shift for methoxyl proton resonance. There was no evidence of such replacement in the case of formation of 9-chloroquinoxalino[2,3-<u>c</u>]cinnoline (44 c) from the appropriate anil.



(59)



(60)

Examination of the proposed reaction scheme for the cyclisation of unacetylated anils (scheme 4), shows that there are two intermediates (57) and (58), which on oxidation, might yield 2-amino-3-(<u>o</u>-nitrophenyl)quinoxalines (59) and quinoxalino[2,3-<u>c</u>]-cinnoline-5-oxides (60) respectively. The aminoquinoxalines (59) would have mass (M+34) while the <u>N</u>-oxides would have mass (M+16), where M is the molecular weight of the respective quinoxalino-cinnolines. In the mass spectra of mixtures containing these two by-products, they show retention of substituent (in the case of halogenated derivatives). In addition, mixtures of the 10-chloro-substituted quinoxalinocinnolines with the the previously mentioned methoxy by-products, show the corresponding chloro-substituted aminoquinoxalines and <u>N</u>-oxides, but no methoxyaminoquinoxalines or methoxy-<u>N</u>-oxides. If these compounds are oxidation products of intermediates formed during the reaction, it was thought that an

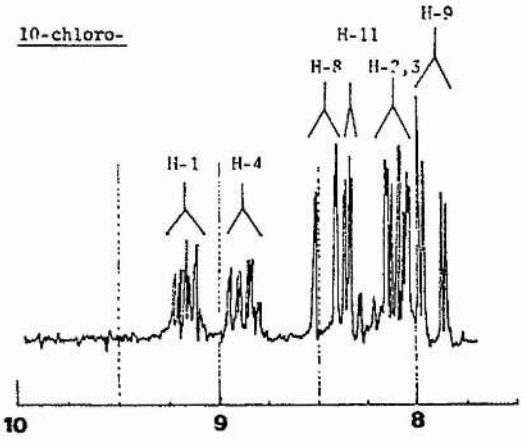
inert atmosphere might inhibit their formation. Consequently, cyclisations were subsequently carried out under nitrogen in degassed solvent.

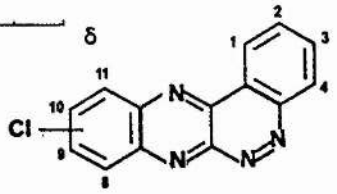
When the cyclisations were repeated under nitrogen, the yield of (42 a) and (42 c) increased, while that of (42 b) still showed a dependence on the length of reaction time. If the chlorine in (42 b) is being replaced by methoxide, then variation of yield with reaction time is not surprising. Cyclisation of the two bromo-anils (55 k) and (55 l) proceeded without difficulty to give 10- and 9-bromoquinoxalino[2,3-a]cinnolines (42 k) and (42 l) respectively, in reasonable yield. No displacement of the bromine was detected in either case. Cyclisation of anils leading to 10-methoxyquinoxalino-[2,3-a]cinnoline (42 f), and 2-chloroquinoxalino[2,3-a]cinnoline (42 g) showed a dependence on reaction time, both proceeding well in 2 hours, but giving a mixture of products in under one hour. These mixtures show the presence of $(M+16)^+$ in the mass spectra, possibly corresponding to the N-oxides of the respective quinoxalinocinnolines (60 f) and (60 g). Similarly, attempts to make the 8-chloro- (42 j) and 8,10-dichloroquinoxalinocinnolines (42 h) resulted in the formation of mixtures of these products and what appeared to be the corresponding N-oxides. In the case of the trichloro-anil (55 i), cyclisation appeared to give only the product of mass (M+34), the corresponding aminoquinoxaline. Attempts to cyclise the methyl-anil (55 e) under air and nitrogen were not successful. Solid precipitate was formed, but t.l.c. showed the presence of more than 5 components.

^{1}H n.m.r. spectra of chloroquinoxalino[2,3-c]cinnolines

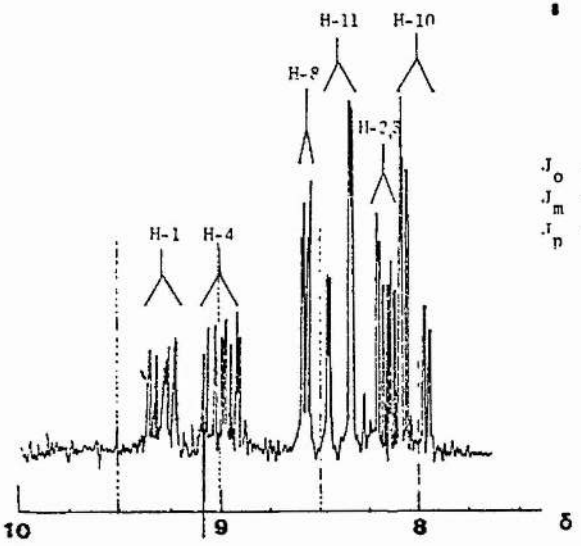
($CDCl_3$ solutions)

10-chloro-





9-chloro-

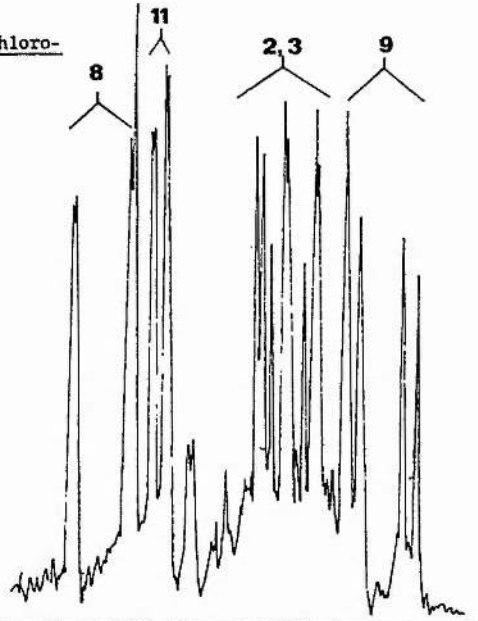


J_o = 9.2 Hz

J_m = 2.4 Hz

J_p = 0.5 Hz

10-chloro-



9-chloro-

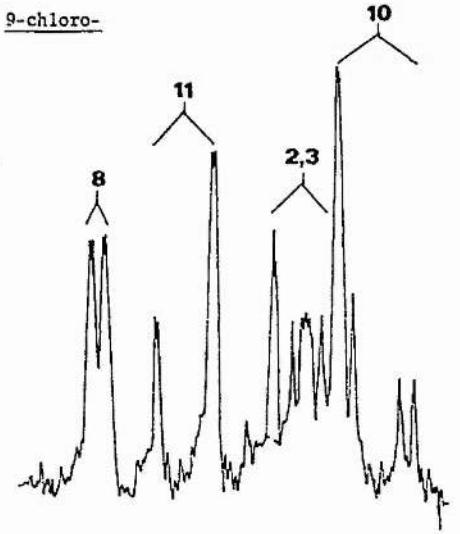


Figure 9

The ^{1}H n.m.r. spectra of 9-chloro- and 10-chloroquinoxalino-[2,3-*a*]cinnoline (42 b) and (42 c) are shown in figure 9. In (42 b), it appears that of the protons in the quinoxaline portion of the structure, H-8 is most deshielded, followed by H-11, with H-9 being the least deshielded. In (42 c), it appeares that the general order is the same, in this case H-10 (in place of H-9 in (42 b)) being the least deshielded. The clarity of the splitting patterns observed for these protons in both (42 b) and (42 c), make it easy to distinguish between the two isomers. The ^{1}H n.m.r. spectra or the quinoxalino-[2,3-*a*]cinnolines (42) are discussed in more detail in chapter 6.

Comparison of the ^{1}H n.m.r. spectrum of the mono-chloro-quinoxalinocinnoline produced from the cyclisation of 4'-(or 5'-)-chloro-*N*-*o*-nitrobenzylidene-*o*-phenylenediamine mentioned earlier, with those of 9- and 10-chloroquinoxalino[2,3-*a*]cinnoline produced from the corresponding *o*-acetamido-anils (55 b) and (55 c), revealed that the isomer produced from the unacetylated anil was the 9-chloro-quinoxalinocinnoline (42 c). Similarly, the 2,10-dichloroquinoxalino-cinnoline (42 d) was found to have a distinctly different ^{1}H n.m.r. spectrum to that of the `2,9-(or 2,10-)'dichloroquinoxalinocinnoline produced from the corresponding unacetylated dichloro-anil. Therefore it was assumed that the latter quinoxalino[2,3-*a*]cinnoline was the 2,9-dichloro-derivative.

Both of these results are consistent with the suggestion that in the formation of the unacetylated anils from 4-chloro-*o*-phenylene-diamine and the respective *o*-nitrobenzaldehydes, condensation occurred at the amino-group *para* to the chloro-substituent.

Table 5, X=H

Compound	CH	H-6'	H-5'	H-4'	H-3'
B	8.94(s)	7.04(d)	6.69(dd)*	-	6.74(d)
A	8.92(s)	7.09(d)	-	7.05(dd)	6.69(d)*
		H-4	H-5	H-3	H-6
B		(7.55 - 7.71(m))		7.99(m)	8.23(m)
A		(7.55 - 7.71(m))		7.98(m)	8.21(m)

$J_{3',4'}$, $J_{6',5'}$ 8.4Hz; $J_{5',3'}$, $J_{6',4'}$ 2.3Hz

* signals overlap exactly

Table 6, X=Cl

Compound	CH	H-6'	H-5'	H-4'	H-3'
B	8.96(s)	7.05(d)	6.69(dd)*	-	6.75(d)
A	8.95(s)	7.10(d)	-	7.06(dd)	6.69(d)*
		H-4	H-5	H-3	H-6
B		7.52(dd)	-	8.00(d)	8.22(d)
A		7.54(dd)	-	8.01(d)	8.22(d)

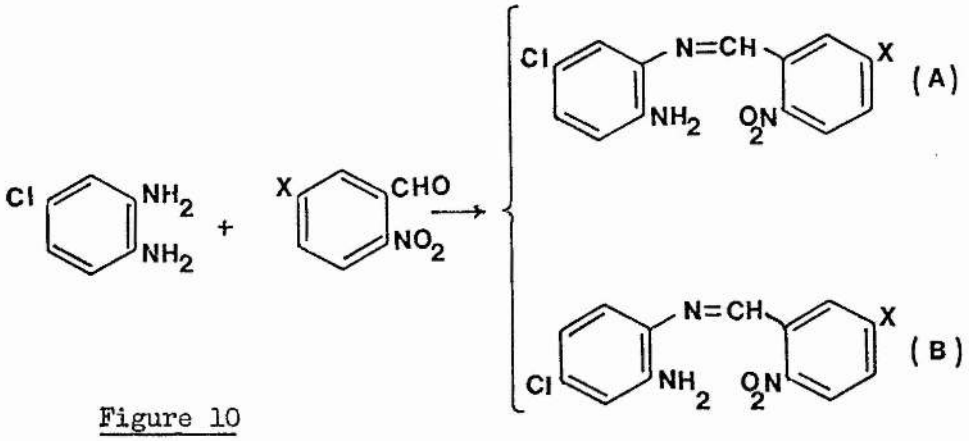


Figure 10

In order to investigate whether the condensation of 4-chloro-o-phenylenediamine with o-nitrobenzaldehyde gives a mixture of the two possible condensation products, the condensation was repeated, and the resultant product investigated, without recrystallisation, by 360 MHz ^{1}H n.m.r. spectroscopy. The 360 MHz ^{1}H n.m.r. spectrum shows a mixture of two products (table 5; figure 10, X=H), in the ratio of about 4:1. The major product is presumed to be isomer (B) in which condensation has occured *para* to the chlorine. Similarly, the 100 MHz ^{1}H n.m.r. spectrum of the products formed when 4-chloro-o-phenylenediamine is condensed with 5-chloro-2-nitrobenzaldehyde (table 6; figure 10, X=Cl), revealed that a mixture is also obtained in the same approximate ratio, and again isomer (B; X=Cl) is assumed to be the major product. The condensation of 4-bromo-o-phenylenediamine with o-nitrobenzaldehyde was carried out to give a mixture of anils in the ratio of approximately 5:1, (again presumably in favour of *para* condensation): this was deduced from the integration of the benzylidene protons in the ^{1}H n.m.r. spectrum. The rest of the spectrum could not be fully assigned due to the presence of contaminants.

Literature evidence concerning condensation reactions of 4-substituted o-phenylenediamines is confusing. A number of sources suggest that condensation occurs *para*- to electron donors and *meta*- to electron acceptors when carried out in approximately neutral conditions, and that the reverse is the case in acid conditions.[37,38] Theoretical studies indicate that the amino-group *para*- to electron donors is the more basic.[39] It appears that some of the structural

assignments in the literature may have been made on insufficient evidence, and that the reaction conditions vary over a wide range (neutral conditions, acid catalysis or strongly acid conditions). It is therefore not really possible to come to any clear conclusion from the literature concerning the behaviour of 4-substituted o-phenylenediamines. On the basis of the present results, however, the condensation of 4-chloro-o-phenylenediamine with o-nitrobenzaldehydes appears to conform with the suggestion that condensation occurs predominantly para- to the (weakly) electron donating substituent in neutral conditions.

The mechanism of the cyclisation of the o-acetamido-anils is probably similar to that proposed for the unacetylated anils (scheme 4). It is an obvious requirement that the acetyl group is lost during the cyclisation, the nucleophilicity of the amide nitrogen being too low for its direct involvement in the cyclisation process. Loss may occur before addition of the cyanide ion to the double bond, or once the adduct has formed.

The deacetylation of acetanilide derivatives by methoxide is known.[40] However, reaction times of up to 10 hours are required, and 2-acetamido-N-(o-nitrobenzylidene)aniline (55 a) when treated with methoxide in refluxing methanol, showed no appreciable degree of deacetylation (a colour change from yellow to red) after 4 hours. When the same anil was treated with cyanide in methanol under similar conditions, a red colour developed almost immediately, implying that it may be the adduct and not the anil which undergoes deacetylation. The nature of the deacetylating species is not known with certainty,

possibilities are methoxide (acting on the adduct), or intramolecular deacetylation by the adduct itself. No attempt has been made to identify deacetylation products.

CHAPTER 3

An investigation of the intermediates formed during the cyanide induced cyclisation of 2-acetamido-N-(o-nitrobenzylidene)-anilines

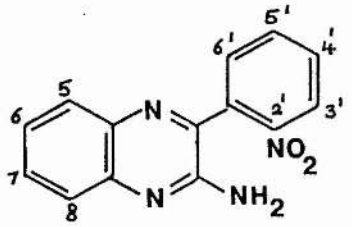
An investigation of the intermediates formed during the cyanide induced cyclisation of 2-acetamido-N-(o-nitrobenzylidene)-anilines

It will be recalled from the previous chapter, that the by-products formed during the cyclisation of the o-acetamido anils (55) were considered to be 2-amino-3-(o-nitrophenyl)quinoxalines (59) and quinoxalino(2,3-c)cinnoline-5-oxides (60) on the basis of mass spectral evidence. The amount of these compounds formed during cyclisation was generally low, and chromatographic separation processes were not successful, though small amounts of what was thought to be 2-amino-6-chloro-3-(5-chloro-2-nitrophenyl)quinoxaline (59 d) were isolated from the cyclisation of the 5,5'-dichloro-o-acetamido-anil.

In order to establish the identity of this intermediate, an attempt was made to synthesise it directly. It has been reported that treatment of N-o-nitrobenzylidene-o-phenylenediamine (38) with potassium cyanide in dimethylformamide results in the formation of 2-amino-3-(o-nitrophenyl)quinoxaline (59 a) in reasonable yield.[31] The acetylated derivative of the same anil (55 a) when treated with potassium cyanide in dimethylformamide, yielded a product identical with (59 a). Similarly, the 5,5'-dichloro-2-acetamido-anil (55 d) when treated with cyanide in dimethylformamide, yielded a compound found to be identical with the by-product isolated from the cyclisation of the same anil by cyanide in methanol.

Substituents	H-3'	H-(5 to 8); H-(4' to 6')	NH_2
none*	8.45(m)	(8.15 - 7.45(m))	6.65(bs)
none†	(8.19-8.23(m))	(7.61 - 7.93(m))	4.7(bs)
5',7-Cl_2*	8.38(d)	(8.02 - 7.65(m))	6.82(bs)
5',5,7-Cl_3*	8.47(d)	(8.10 - 7.92(m))	7.17(bs)

* in D_6-DMSO † in $CDCl_3$ $J_{3';4'}$ = 9.4Hz



(59)

Table 7 ^1H n.m.r. spectra of 2-amino-3-(2'-nitrophenyl)-quinoxalines (59)

The product obtained on cyclisation of the 3,5,5'-trichloro-2-acetamido-anil (55 i) was found to have ^{1}H n.m.r. and mass spectra consistent with an analogous structure (59 i).

The infra-red spectra of these compounds show the presence of a nitro-group and an amino-group [ν_{max} (NH_2) 3465, 3335 and 3105 cm^{-1}; (NO_2) 1520 and 1345 cm^{-1}], while the primary process observed in the mass spectra is loss of 46 (NO_2) from the molecular ion.[31]

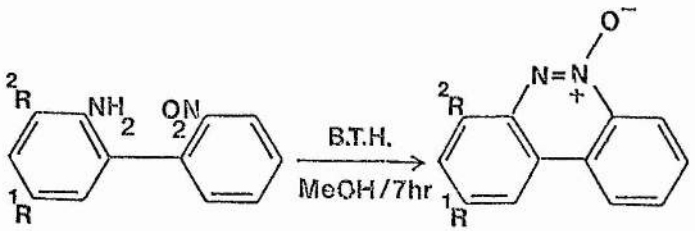
The ^{1}H n.m.r. spectra of these compounds are not completely first order, and are difficult to resolve (Table 7). However, there are a few features of particular note. The resonance between δ6.65 and δ7.17 observed in all spectra in D_6-DMSO is a broad two-proton singlet (NH_2). The amino-group in compound (59 a) resonates at δ4.47 in $CDCl_3$, and there is a general upfield shift in all protons, compared to the spectrum of the same compound run in D_6-DMSO.[31]

The second noticeable feature is that one proton in the aromatic region is considerably deshielded relative to the rest of the phenyl protons. The proton in question is likely to be that at position 3 in the o-nitrophenyl substituent (3' in structure (59)), which can experience deshielding by the adjacent nitro group.[35,36] The chemical shifts of the remaining protons are too similar to give a resolvable spectrum.

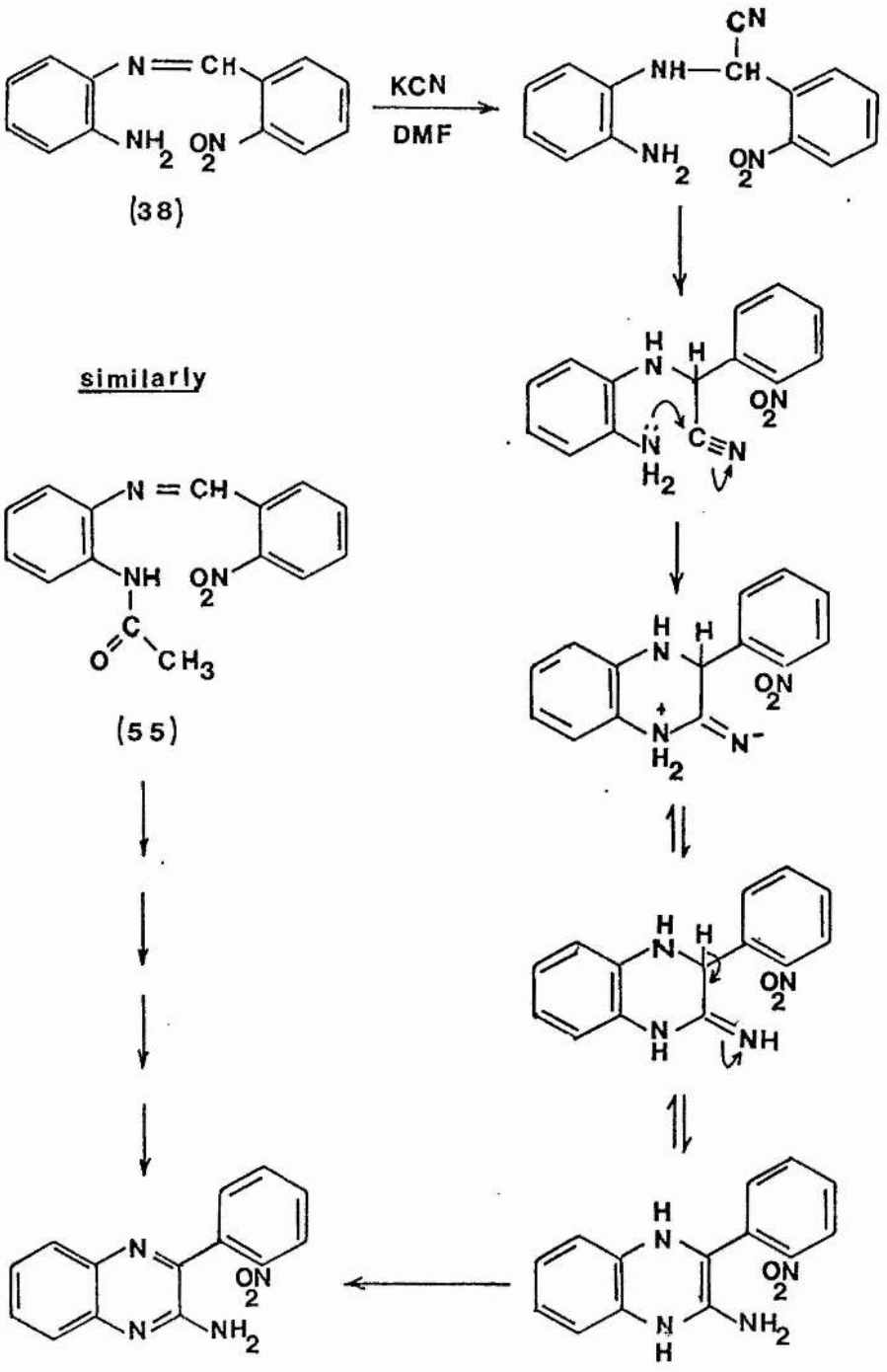
Protons in the carbocyclic ring of substituted quinoxalines generally come to resonance in the region of δ7.8-8.3,[31,41,42]

provided that the substituents do not cause any appreciable ortho-effects. Protons 6 and 8 in 5,7-dichloroquinoxaline resonate at δ7.85 and δ8.03 respectively,[42] shifts which correspond closely with those of the protons in 2-amino-6,8-dichloro-3-(5'-chloro-2'-nitrophenyl)quinoxaline (59 i).

The evidence suggests that these by-products are in fact the supposed aminoquinoxalines. Further indication that this is so would be given, if they could be cyclised to the corresponding quinoxalino[2,3-c]cinnoline-5-oxides. Previous attempts to cyclise (59 a) with sodium methoxide, potassium cyanide and a mixture of sodium cyanide and methoxide failed.[31] Therefore attempts were made to carry out the cyclisation using other bases, namely sodium hydroxide and benzyltrimethylammonium hydroxide. Solutions of the latter base in methanol have been used to cyclise a number of biphenyl derivatives (62),[43,44] especially when there are electron withdrawing substituents in the aminophenyl nucleus (eg. nitro) that will weaken the nucleophilicity of the amino-group. When the above mentioned bases were used, in both cases treatment of (59 a) with base was followed by substantial recovery of starting material. However, when benzyltrimethylammonium hydroxide was used, the mass spectrum of the product obtained indicated the presence of quinoxalino[2,3-c]cinnoline in very low yield.



(62)



(38)

(55)

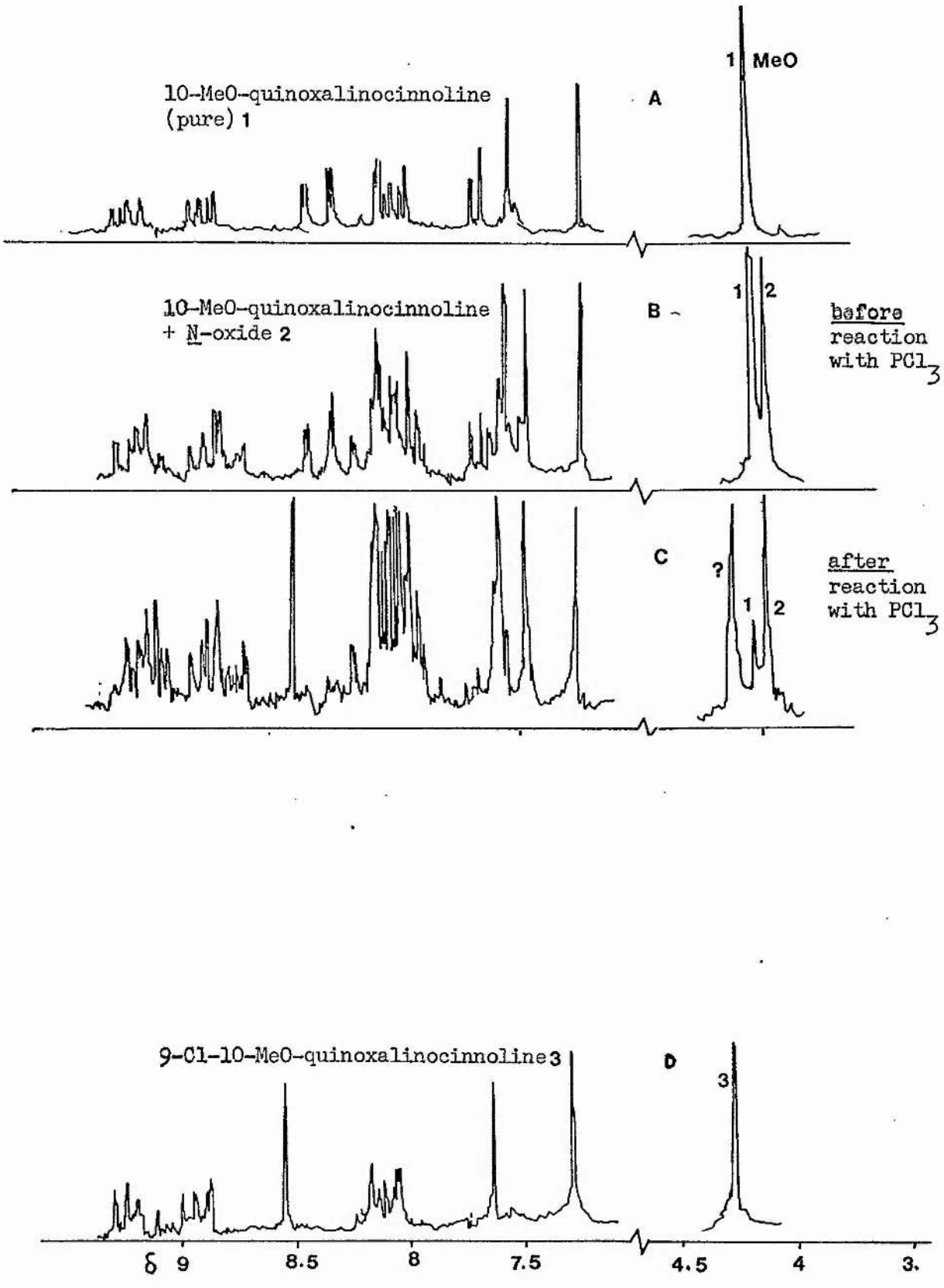
(59)

Scheme 5 Cyclisation of anils by potassium cyanide in DMF

In conclusion, although it was not possible to convert (59 a) to the quinoxalino[2,3-*c*]cinnolone-5-oxide to any measurable extent, the presence of trace amounts of quinoxalino[2,3-*c*]cinnoline (presumably by base induced deoxygenation of the *N*-oxide or as a fragmentation product of the *N*-oxide in the mass spectrum) indicates that cyclisation is possible. When considered together with the spectroscopic data, and the fact that compounds (59) have been isolated from the cyclisation of *o*-acetamido-anils, then it can be considered that the by-products observed are, very probably, the aminoquinoxalines (59) as suspected.

Formation of the aminoquinoxaline from the acetamido-anils in dimethylformamide presumably follows a route akin to that proposed for cyclisation of the unacetylated anils in dimethylformamide[31] (scheme 5). There is still a requirement for deacetylation of the anil during the cyclisation process, again probably after formation of the adduct.

The other type of by-product obtained from the cyanide-induced cyclisation of acetamido-anils was thought to be the 5-oxide (60) of the appropriate quinoxalino[2,3-*c*]cinnolines (42). This type of by-product was first encountered to an appreciable extent in the synthesis of 10-methoxyquinoxalino[2,3-*c*]cinnoline (42 f) from the methoxy-anil (55 f), and it was found possible to eliminate the by-product by increasing the reaction time. An attempt was made to convert the unwanted by-product in the initial mixture, into the



80 MHz ^{1}H n.m.r. spectra of 10-MeO-quinoxalinocinnoline its 5-oxide, and 9-Cl-10-MeO-quinoxalinocinnoline, along with mixtures of all three.

Figure 11

parent quinoxalinocinnoline by deoxygenation using phosphorus trichloride in chloroform.

The two components in the mixture, prior to treatment with phosphorus trichloride, were identified by their ^{1}H n.m.r. spectra (figure 11(B)), in particular by the signals due to the methoxy group protons at about δ 4.25. On completion of the reaction one might have expected to see substantial reduction in the height of one of the methoxy signals, with a corresponding increase in the height of the other, as N-oxide was converted into the parent compound. The ^{1}H n.m.r. spectrum of 10-methoxyquinoxalino[2,3-c]cinnoline (figure 11(A)) is present for comparison. Once the reaction had been carried out, however, the ^{1}H n.m.r. spectrum revealed three methoxy- signals (figure 11(C)). Comparison with figures 11(A) and (B) indicated that the signal due to the N-oxide component in the initial mixture had remained unchanged, while that due to the quinoxalinocinnoline itself had diminished, with appearance of a third signal. The concurrent appearance in the spectrum of two other signals (singlets) at δ 8.57 and δ 7.67, suggested that this new compound might be a 9,10-disubstituted quinoxalinocinnoline, and that these substituents were considerably different in character. The mass spectrum of the new product mixture indicated that the new component resulted from replacement of a hydrogen in 10-methoxyquinoxalino[2,3-c]cinnoline by chlorine, and that the new compound was probably the known 9-chloro-10-methoxyqinoxalino[2,3-c]cinnoline (figure 11(D)).[31]

Halogenation reactions of this type form the subject of the next chapter. In the course of this work, a method for isolation of the

N-oxide (60 f) was, fortuitously, discovered: this is described on page 48.

CHAPTER 4

The reaction of quinoxalino[2,3-c]cinnolines with hydrogen halides

1: The reaction of quinoxalino[2,3-c]cinnolines with phosphorus trichloride

In the previous chapter a reaction was described where phosphorus trichloride was used on a mixture of 10-methoxyquinoxalino[2,3-c]cinnoline (42 f) and its 5-oxide (60 f), in an attempt to deoxygenate the latter. The N-oxide was unaffected, but the parent base was transformed into another derivative by interchange of a chlorine atom for one of the hydrogens.

The reaction was repeated, using a pure sample of 10-methoxyquinoxalino[2,3-c]cinnoline. On isolation of the final product, it was found that 9-chloro-10-methoxyquinoxalino[2,3-c]cinnoline (42 m) had been formed in 79% yield.

When quinoxalino[2,3-c]cinnoline (42 a) itself was similarly treated with phosphorus trichloride, the final product was found to have a chlorine substituent at position 10. It was identical in all respects with authentic 10-chloroquinoxalino[2,3-c]cinnoline (42 b), formed from the Schiff base (55 b). The yield of the 10-chloroquinoxalinocinnoline formed by this direct halogenation procedure was 92%.

Treatment of 9-chloroquinoxalino[2,3-c]cinnoline (42 c) with phosphorus trichloride in an analogous manner, resulted in the formation of a product where one of the hydrogens was replaced by a second chlorine. The ^{1}H n.m.r. spectrum of the product showed the

presence of two sharp *para*-split doublets at δ 8.8 and δ 8.67, indicating that the product was the 9,10-dichloroquinoxalinocinnoline (42 n; yield, 83%). The structure was confirmed by comparison with the ^{1}H n.m.r. spectrum of a sample of 9,10-dichloroquinoxalino[2,3-*c*]cinnoline produced from the appropriate 3,4-dibromocinnoline and *o*-phenylenediamine.[31]

However, when 10-chloroquinoxalino[2,3-*c*]cinnoline (42 b) was treated with phosphorus trichloride, the final product isolated was found to be the starting compound (92% recovery).

Quinoxalino[2,3-*c*]cinnoline

Reactant	Product	(yield%)
unsubstituted	10-Cl	92
10-MeO	9-Cl-10-MeO	79
9-Cl	9,10-Cl_2	83
10-Cl	10-Cl	93

Table 8 Reaction of quinoxalino[2,3-*c*]cinnolines with phosphorus trichloride

These results (shown in Table 8) were somewhat surprising. In three out of four cases chlorination of a heterocyclic compound had occurred in high yield. In addition, the chlorination process appeared to occur at only one position: position 10 in two cases, and position 9 in the other. When position 10 was blocked, chlorination occurred at position 9 in the case of 10-methoxyquinoxalino[2,3-*c*]cinnoline, while apparently failing altogether in the

case of 10-chloroquinoxalino[2,3-a]cinnoline.

The reactions were carried out by dissolving the quinoxalino-[2,3-a]cinnolines in chloroform (to give an orange solution), adding phosphorus trichloride in chloroform, and heating under reflux for one hour. A dark precipitate formed, and on completion of heating and subsequent cooling, a mixture of aqueous sodium hydroxide and chloroform was added. The coloured precipitate dissolved, regenerating the orange colour in the solution. The products were isolated simply by evaporation of the chloroform layer.

Since it was obvious that the nature of the coloured intermediates formed during these reactions was of crucial importance to their final outcome, samples of the compounds were obtained by filtration for further investigation. Indeed, although the reaction of the 10-chloroquinoxalinocinnoline with phosphorus trichloride did not result in the formation of a dichloro-compound, as might have been expected from the other experiments, a coloured intermediate was formed during the reaction, and it was considered likely that an investigation of this intermediate might throw some light on the subsequent failure of chlorination.

It was found in all four cases, that the `dark precipitates' were in fact dark blue solids, consisting of tiny lustrous needles. Mass spectra of the blue solids were obtained, and in each case, showed a molecular ion equivalent to the parent base plus one molecule of hydrogen chloride. No obvious traces of phosphorus-containing fragments were observed in the mass spectra.

In order to prove the involvement of phosphorus trichloride in the reaction, quinoxalino[2,3-*a*]cinnoline was treated with redistilled and dried phosphorus trichloride in redistilled and dried chloroform as previously described. It was found that when the solution was heated under reflux, no precipitate of any nature was formed. However, on addition of approximately an equal volume of water to the reaction mixture, a deep-blue precipitate appeared. Similarly, when the experiment was repeated at room temperature, no solid formed until the addition of water. This suggested that the reactive species might not be phosphorus trichloride, but some hydrolysis product, possibly hydrogen chloride.

In order to test this hypothesis, a small amount of quinoxalino-[2,3-*a*]cinnoline was dissolved in chloroform, and a jet of gaseous hydrogen chloride was played across the surface of the liquid. A deep-blue precipitate was observed to form immediately at the surface, and spread throughout the solution. The blue solid was found to have a mass spectrum identical to that produced from the reaction of quinoxalino[2,3-*a*]cinnoline with phosphorus trichloride. These observations were taken to be clear indications that the reactive species was in fact hydrogen chloride.

Starting Compound	Blue adduct (42) + nHX , apparent value of n assuming 100% yield; Melting point (°C)	Product, Overall yield based on starting quinoxalino-[2,3-c] cinnoline (%)	Melting Point (°C), Recrystallising Solvent
(A) X = Cl			
42 (a) unsubstituted	n = 3.3 ; 280	42 (b) 10-Cl 75	250 - 252 DMF
42 (b) 10-Cl	n = 3 ; 274-276	42 (b) 10-Cl 90	250 - 252 DMF
42 (c) 9-Cl	n = 2.2 ; 283-286	42 (n) 9,10-Cl_2 72	257 - 258 $CHCl_3$
42 (g) 2-Cl	n = 2.8 ; 290	42 (a) 2,10-Cl_2 70	288 - 290 $CHCl_3$
42 (f) 10-OCH_3	n = 2 ; 275-277	42 (m) 9-Cl-10-OCH_3 76	242 - 243 $CHCl_3$
42 (k) 10-Br	n = 1.7 ; 278-281	42 (o) 10-Br-9-Cl Ca 40 ‡ 42 (k) 10-Br Ca 20 42 (n) 9,10-Cl_2 trace	- -
42 (l) 9-Br	n = 3.4 ; 300-302*	42 (p) 9-Br-10-Cl 70	274 - 276 $CHCl_3$
42 (j) 8-Cl	n = 4 ; 270	42 (h) 8,10-Cl_2 73	250 - 252 $CHCl_3$
42 (h) 8,10-Cl_2	n = 2.8 ; 315-317*	42 (n) 8,10-Cl_2 89	250 - 252 $CHCl_3$
(B) X = Br			
42 (a) unsubstituted	n = 1.7 ; 283-286	42 (k) 10-Br 70	261 - 263 DMF
42 (c) 9-Cl	n = 1.1 ; 279-281	42 (o) 10-Br-9-Cl Ca 45 ‡ 42 (c) 9-Cl Ca 25	- -
42 (b) 10-Cl	n = 1.8 ; 360	42 (b) 10-Cl 90 42 (p) 9-Br-10-Cl trace ‡	250 -253 $CHCl_3$

‡estimated from ^1H n.m.r. integrals

‡seen in the mass spectrum

*with decomposition

Table 9 Reaction of quinoxalino [2,3-c] cinnolines (42) with gaseous hydrogen chloride and hydrogen bromide

2. The reactions of quinoxalino[2,3-c]cinnolines with gaseous hydrogen chloride and hydrogen bromide

To investigate further the reaction of quinoxalino[2,3-c]-cinnoline and its derivatives with hydrogen halides, a series of experiments were carried out on a number of substituted quinoxalinocinnolines. Gaseous hydrogen chloride or hydrogen bromide was passed through a solution of the quinoxalinocinnoline in chloroform. The orange colour of the solutions (typically about 390nm) rapidly changed colour to deep red, then darkened further as blue precipitates (in some cases purple/red), were formed. On isolation, the blue solids were weighed, and portions retained for spectral examination. The remainder were treated with a mixture of aqueous sodium hydroxide and chloroform, the orange colour being regenerated in the organic layer. Separation and evaporation of the organic layer resulted in isolation of the products, which were subjected to ^{1}H n.m.r. and mass spectral analysis. The results of the reactions are seen in Table 9. Overall yields are based on the conversion of reactant quinoxalinocinnoline to product quinoxalino-cinnoline. Where product mixtures were obtained, the distribution of products is based on ^{1}H n.m.r. integrals. Where possible, the identities of the products were established by comparison with authentic samples, or by analysis, otherwise by their ^{1}H n.m.r. and mass spectra.

Treatment of quinoxalino[2,3-c]cinnoline (42 a) with hydrogen chloride as described, yielded a final product in which one hydrogen

atom had been replaced by a chlorine atom. It was identified as the 10-chloroquinoxalinocinnoline (42 b) by comparison of the ^{1}H n.m.r. spectrum with that of an authentic sample produced from the 5-chloro-anil (55 b).

Similarly, treatment of the 9-chloro- and 2-chloroquinoxalinocinnolines (42 c) and (42 g), resulted in the formation of dichloro compounds by replacement of one hydrogen for a chlorine atom. These compounds were identified as 9,10-dichloro- and 2,10-dichloroquinoxalinocinnolines (42 n) and (42 d), by spectral comparison with authentic samples.

Treatment of 9-bromoquinoxalinocinnoline (42 l) with hydrogen chloride resulted in formation of a mono-bromo-mono-chloro derivative, identified by ^{1}H n.m.r. spectroscopy to be the 9-bromo-10-chloro-derivative (42 p).

When quinoxalino[2,3-c]cinnoline was treated with gaseous hydrogen bromide, a mono-bromo- derivative was produced. This was found to be the 10-bromo-quinoxalinocinnoline (42 k). The reaction of the 9-chloroquinoxalinocinnoline (42 c) with hydrogen bromide resulted in formation of a mixture of products, consisting of the 10-bromo-9-chloro- derivative (42 o) and 9-chloroquinoxalinocinnoline (42 c) in the approximate ratio of 2:1.

In all the above cases, position 10 in the reactant quinoxalinocinnolines was unsubstituted. When the reactions were carried out on compounds already substituted at position 10, the results obtained

were different, depending on the nature of the 10-substituent. Thus, 10-chloroquinoxalinocinnoline (42 b) when treated with hydrogen chloride was not chlorinated at any position (although a blue intermediate was formed), and the starting material was recovered. Similarly, treatment of the same compound with hydrogen bromide resulted in very substantial recovery of the starting compound (42 b), though a small amount of a mono-bromo-mono-chloro- derivative was obtained, identified as the 9-bromo-10-chloro- derivative (42 p) by the ^{1}H n.m.r. spectrum of the final product.

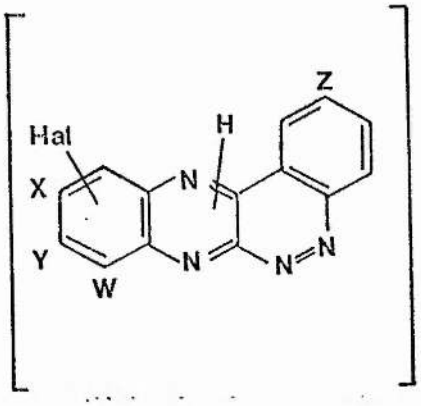
However, when 10-methoxyquinoxalino[2,3-a]cinnoline was treated with hydrogen chloride, it was found that chlorination took place at position 9, giving the 9-chloro-10-methoxy- derivative (42 m). The 10-bromo- derivative (42 k) on treatment with hydrogen chloride yielded a mixture, consisting of the 10-bromo-9-chloro- compound (42 o) and recovered 10-bromo- compound (42 k) in the ratio of 2:1 (a trace of a dichloro- derivative, presumably the 9,10-dichloro-quinoxalinocinnoline was also seen).

Therefore, some 10-substituted quinoxalinocinnolines fail to be halogenated, others are halogenated at position 9, and in some cases both processes appear to occur concurrently.

In addition to the above mentioned reactions, four further experiments were carried out, where a mixture of the quinoxalinocinnoline (42) and its 5-oxide (60) in chloroform were treated with hydrogen chloride as described. It was found in each case that the 5-oxide components were unaffected, and on completion of

the reaction, could be isolated by filtration of the coloured solids (formed from the quinoxalinocinnoline componenets), and subsequent evaporation of the filtrates. In this manner, samples of the 5-oxides of some of quinoxalinocinnolines were obtained for further investigation. The quinoxalinocinnoline portions of the mixtures reacted with hydrogen chloride. Thus, from 8-chloroquinoxalino[2,3-*c*]cinnoline (42 j) and its 5-oxide, both the 8,10-dichloro- derivative (42 h) and the 8-chloroquinoxalinocinnoline-5-oxide (60j) were obtained. The yield quoted in table 9 for the 8,10-dichloro- compound is based on the amount of the 8-chloro- compound in the initial mixture. Similarly, reaction of the mixture of 10-methoxyquinoxalino[2,3-*c*]cinnoline (42 f) and its 5-oxide (60 f) permitted isolation of the latter *N*-oxide, which was investigated by ^{1}H n.m.r. spectroscopy (see p. 89). A mixture of 2-chloroquinoxalino[2,3-*c*]cinnoline (42 g) and its 5-oxide (60 g) yielded on treatment with hydrogen chloride, 2,10-dichloroquinoxalinocinnoline (42 d) and the 2-chloroquinoxalinocinnoline-5-oxide (60 g). Finally, a mixture of the 8,10-dichloroquinoxalinocinnoline (42 h) and its *N*-oxide yielded 8,10-dichloroquinoxalinocinnoline (42 h) on treatment with hydrogen chloride.

In all the cases mentioned above, a coloured intermediate was formed. In all reactions except those of the 8-chloro- and 8,10-dichloro- compounds, the intermediates were dark blue, while in the latter cases they were purple/red in colour. Gravimetric studies of the blue compounds indicated that their formula can be considered as shown below, where n is between one and four.



		C	H	N
$C_{14}H_9ClN_4$	requires	62.6	3.4	20.85
$C_{14}H_{10}Cl_2N_4$	requires	55.1	3.3	18.3
$C_{14}H_{11}Cl_3N_4$	requires	49.2	3.2	16.4
	found	50.3	3.3	16.8

Table 10 Approximate analysis for quinoxalino[2,3-c]cinnoline+nHCl

The value of n may depend on the length of reaction time (and hence the amount of exposure of the reactants to hydrogen halide). The values of n given in table 9 for the intermediates, are calculated on the basis that the yield of blue compound obtained was considered to be 100%. Thus in the case of the reaction of quinoxalino[2,3-c]cinnoline (42 a) with hydrogen chloride, n=3.3, indicating that the blue intermediate is probably a mixture of compounds with differing values of n. This is further borne out by an approximate analysis carried out on the intermediate from this reaction. The results (shown in table 10, above) indicate that the intermediate is a mixture of components with different values of n.

The mass spectra of the blue solids in most cases show the

presence of only one hydrogen halide molecule, which is retained in some of the fragmentation processes observed (see section on mass spectra, chapter 7). The implication of this is that one of the hydrogen halide molecules is covalently bound in the blue intermediates, the remainder probably being ionically associated; thus the blue compounds are regarded as salts.

The melting points quoted in table 9 for the adducts are the temperatures at which the bulk of the solid appeared to melt, in most cases small amounts solid or semi-solid material being left at temperatures above 360°C. This may be a consequence of the presence of more than one compound in the adducts, therefore the melting points are probably not of great diagnostic value, since they may not be repeatable to within a few degrees.

The adducts are only slightly soluble, or totally insoluble in a wide range of solvents. They were found to be most soluble in dimethylformamide, dimethylsulphoxide, alcohols and acetone. They are insoluble in hydrocarbon solvents, halogenoalkanes, ethers, higher ketones and acetonitrile. Attempts to make up ^{1}H n.m.r. solutions (eg. in D_6-DMSO, TFA etc.) of sufficient concentration to show ^{1}H n.m.r. spectra were unsuccessful; even after two thousand scans on a Fourier transform instrument no recognisable spectra were obtained.

Even using the solvents in which the adducts did, to some extent dissolve, it was not possible to recrystallise them, except in one case where a sample of recrystallised material was obtained after evaporation of a dilute ethanol solution over a period of weeks. This

sample was used to obtain the analytical data presented above in table 10.

Solutions of sufficient concentration for an essentially qualitative ultraviolet/visible study were obtained by using ethanol or aqueous acetone. The results of these studies are shown on pages 65-68 as part of the discussion of the reaction mechanism of halogenation. Relatively weak absorptions are observed in the range 546-610nm, undoubtedly giving the compounds their blue colouration.

Group 1 : position 10 vacant

Reactants	Products
unsubstituted	10-Cl; (10-Br)
9-Cl	9,10-Cl_2; (9-Cl-10-Br)
9-Br	9-Br-10-Cl
2-Cl	2,10-Cl_2
8-Cl	8,10-Cl_2

group 2 : position 10 blocked

10-Cl	10-Cl; (10-Cl, 9-Br-10-Cl (trace))
8,10-Cl_2	8,10-Cl_2
10-Br	10-Br, 10-Br-9-Cl, dichloro (trace)
10-OCH_3	9-Cl-10-OCH_3

compounds in parentheses are the products of the reactions with hydrogen bromide

Table 11 Classification of the reactions of quinoxalino-[2,3-c]cinnolines (42) with gaseous hydrogen halides

3. Consideration of a possible reaction mechanism for the halogenation of quinoxalinocinnolines by gaseous hydrogen halides

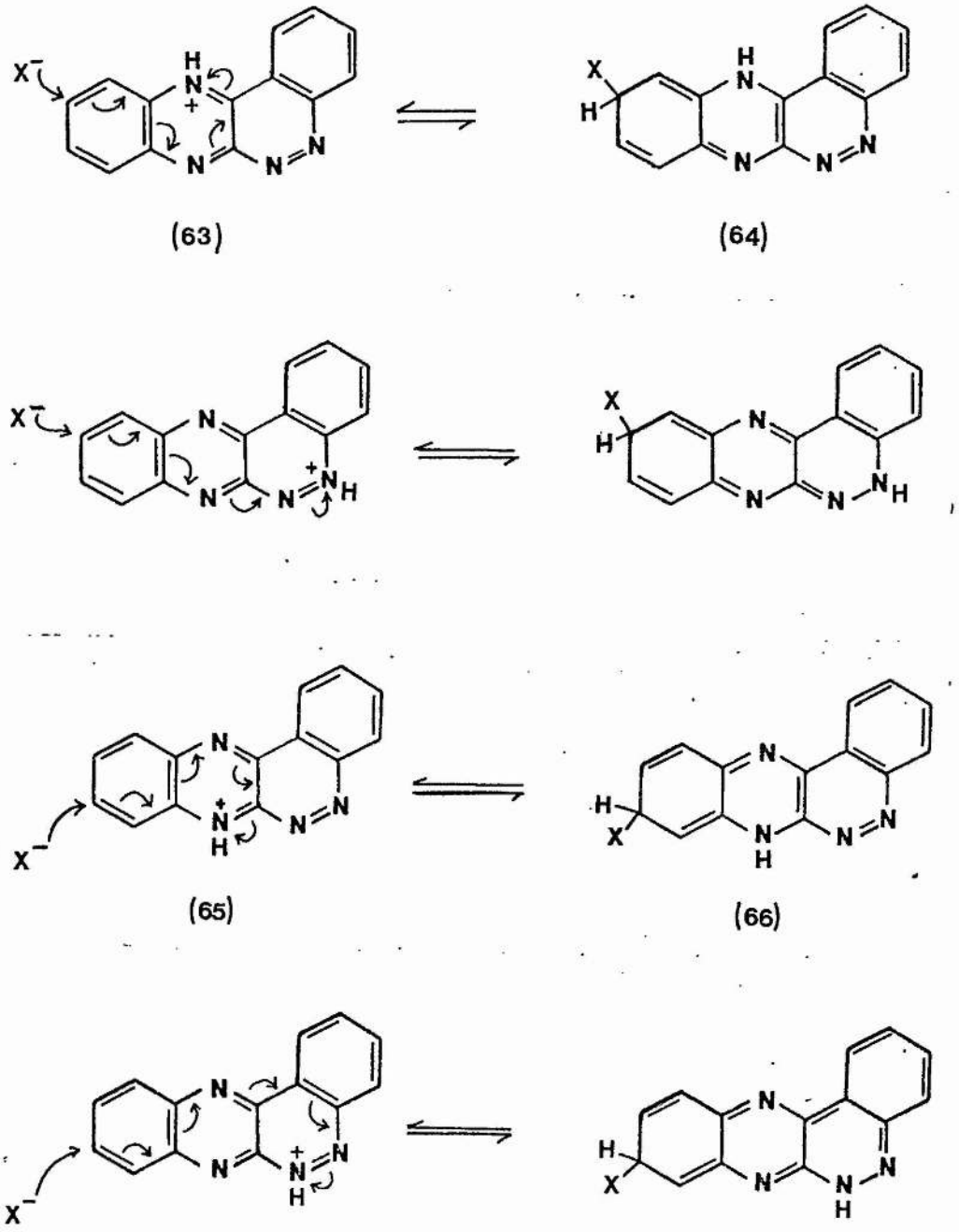
Since it has proved difficult to obtain structural information concerning the adducts, then the reaction mechanism and structure of the adducts must be inferred by consideration of the nature of the reaction, distribution of products, and by use of theoretical methods.

The reaction of quinoxalino[2,3-*c*]cinnoline (42 a) and its derivatives with gaseous hydrogen halides can be separated into two groups (Table 11), those where position 10 in the reactants is unoccupied by substituents, and those where position 10 is blocked.

Any mechanism must account for these facts:-

(i) Where position 10 is unsubstituted, the incoming halogen atom replaces the hydrogen atom at position 10. If position 10 is blocked, the reactant is either recovered unchanged; substituted at position 9; or a mixture of products is obtained.

(ii) The mass spectra of the adducts show the presence of one hydrogen halide molecule covalently bound in each case. In addition, the mass spectrum of 10-bromoquinoxalinocinnoline.n(HCl) shows the presence of an adduct where there are <u>two</u> covalently bound hydrogen chloride molecules, and the mass spectrum of 10-chloro-quinoxalinocinnoline.n(HBr) shows a fragment that may be a breakdown product of an adduct with two covalently bound hydrogen bromide



(63) (64)

(65) (66)

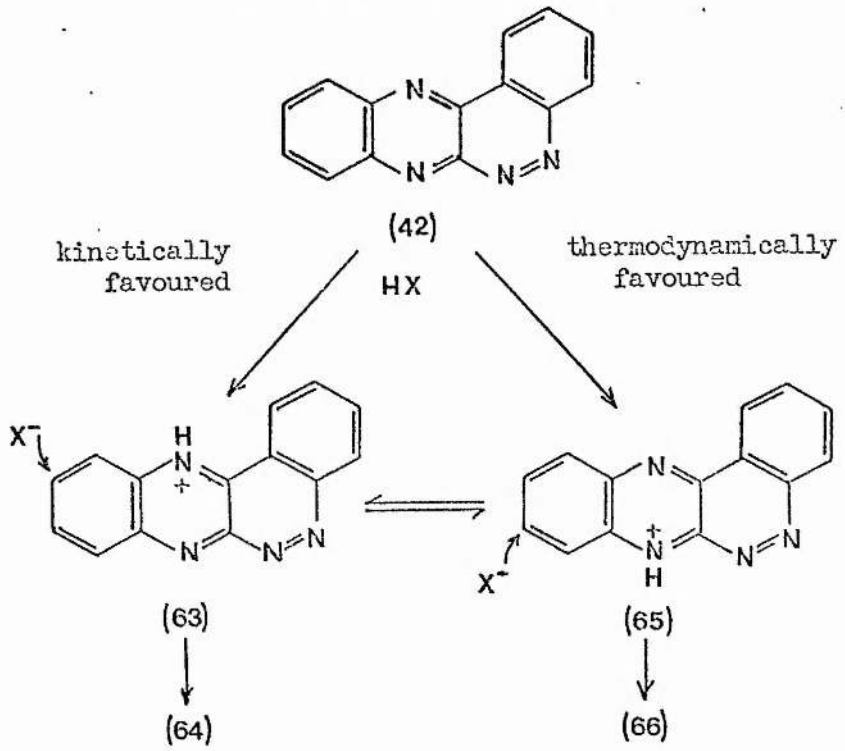
Figure 12

molecules.

The adducts were obtained by the reaction of gaseous hydrogen halide with the heterocyclic bases in chloroform, the position of halogen substitution in the final product being known. Therefore it is reasonable to assume that the initial event will be protonation of one of the ring nitrogens. This would create a charged species which would be susceptible to nucleophilic attack by chloride ion at the appropriate site. A covalent species would result, which could then be protonated again, providing the ionic adduct. During the basification of the adducts to obtain the final products, excess hydrogen halide would be neutralised, leaving a covalent species that could either lose a further hydrogen halide molecule, or undergo aerial oxidation, resulting in product formation. Consideration of the effect of protonation at each of the four ring nitrogens results in the conclusions illustrated in figure 12. Protonation at positions 12 and 5 permits attack of halide at position 10, while protonation at positions 7 and 6 permits attack at position 9. Protonation might reasonably be expected at the most basic nitrogen atom.

MNDO studies[47] on quinoxalino[2,3-c]cinnoline (42 a) and a few of its derivatives,[46] have been carried out by Dr. C. Glidewell at the Deparment of Chemistry, St. Andrews University. Such calculations are approximations, applying to isolated molecules in the gas phase. However, they should also be valid if considered as occurring in very dilute solutions of the subject molecules in non-polar solvents. These calculations can give information about the structure and reactivity of these heterocycles, adding to that obtained from ^{1}H

n.m.r. and mass spectral data. The optimised geometry of the molecule confirms that in the absence of substituents, the structure is planar. The calculated partial charges (figure 13) on the nitrogen atoms suggest that N-12 is the site of highest electron density (presumably the most basic), and initial protonation there would allow attack by halide ion at position 10. Calculation also indicates, however, that protonation at position 7 gives the cationic species with the lowest heat of formation. Therefore, if attack by halide ion at position 10 is fast, an adduct with halogen at position 10 results, while inhibition of attack at position 10 would in principle allow a proton shift from N-12 to N-7 to form the thermodynamically more stable cation, allowing subsequent attack of halide at position 9, giving an adduct with halogen at position 9.

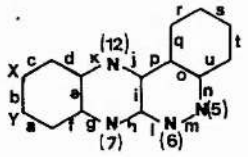


Calculations have also been carried out on a number of substituted quinoxalino[2,3-c]cinnolines, namely the 9-chloro-, 10-chloro-, and 10-methoxy- derivatives.[46] These indicate that the

Charges on nitrogen

	Parent	5-Oxide	Y=Cl	X=Cl	X=MeO
N-12	-0.157	-0.144	-0.161	-0.159	-0.172
N-7	-0.101	-0.155	-0.118	-0.112	-0.112
N-6	-0.004	-0.182	-0.008	-0.008	-0.004
N-5	-0.034	+0.360	-0.020	-0.023	-0.030
(O)	-	-0.310	-	-	-

Figure 13



Parent X=Y=H bondlengths

a) 1.377	b) 1.439	c) 1.378	d) 1.448	e) 1.554
f) 1.450	g) 1.370	h) 1.340	i) 1.448	j) 1.339
k) 1.370	l) 1.433	m) 1.225	n) 1.428	o) 1.430
p) 1.469	q) 1.418	r) 1.402	s) 1.410	t) 1.400
u) 1.421				

Parent bond orders X=Y=H

a) 1.664	b) 1.175	c) 1.662	d) 1.136	e) 1.242
f) 1.133	g) 1.321	h) 1.498	i) 1.157	j) 1.502
k) 1.314	l) 1.007	m) 1.865	n) 1.037	o) 1.328
p) 1.036	q) 1.343	r) 1.455	s) 1.359	t) 1.460

Figure 15 (i)

Heat of formation of N-protonated species (KJ mol^{-1})

Protonation at	Parent	X=MeO	Y=Cl	X=Cl
N-12	1144.09	963.9	1132.8	1135.6
N-7	1121.3	957.2	1112.8	1111.5
N-6	1160.6	-	-	-
N-5	1183.6	-	-	-

Figure 14

Bond orders in adducts (first protonation)

X=Cl

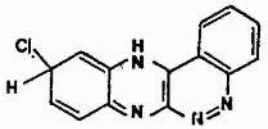
a) 1.883	b) 0.985	c) 0.994	d) 1.758	e) 0.981
f) 0.998	g) 1.758	h) 1.097	i) 1.394	j) 1.100
k) 1.019	l) 1.148	m) 1.717	n) 1.130	o) 1.330
p) 1.147	q) 1.224	r) 1.577	s) 1.252	t) 1.573
u) 1.219				

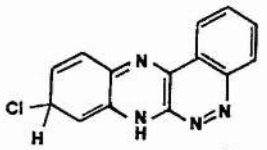
Figure 15 (ii)

Y=Cl

a) 0.996	b) 0.984	c) 1.881	d) 1.000	e) 0.980
f) 1.747	g) 1.032	h) 1.096	i) 1.393	j) 1.108
k) 1.748	l) 1.138	m) 1.691	n) 1.163	o) 1.313
p) 1.130	q) 1.227	r) 1.579	s) 1.242	t) 1.589
u) 1.202				

Figure 15 (iii)





orders of the partial negative charges on the four ring nitrogens are the same as those of the parent compound. These are shown together in figure 13. In each case, N-12 carries the largest partial negative charge, followed by N-7, while the charges on N-5 and N-6 are very small in comparison. Similarly, it is indicated by calculation that the orders of the heats of formation for the four cationic species (corresponding to protonation at each of the ring nitrogens) also occur in the same order as those of the parent compound. These are shown together in figure 14. In each case, protonation at N-7 gives a marginally more thermodynamically stable cation when compared with protonation at N-12. Protonation at N-5 and N-6 give species that are considerably more thermodynamically unstable, therefore, protonation at the latter two sites is considered to be highly unlikely.

These calculations therefore indicate that the position of initial protonation appears to be independent of the position and type of substituents in the above mentioned compounds, when considered solely from a thermodynamic viewpoint. As will become apparent, thermodynamic considerations alone appear to be insufficient to explain the distribution of products in the reactions that have been carried out.

Depending on the site of initial protonation, the second step in the mechanism is considered to be attack by halide at either C-10, or C-9, to give the adducts (64) and (66). Calculations have been carried out on the corresponding adducts of the parent compound (64 a) and (66 a). Figure 15 represents the calculated bond orders of both of these adducts, along with the calculated bond orders of the parent

Bond orders in cinnoline

a) 1.605 b) 1.227 c) 1.605 d) 1.190 e) 1.324

f) 1.202 g) 1.211 h) 1.590 i) 1.197 j) 1.672

k) 1.174

Bond orders in quinoxaline

a) 1.611 b) 1.222 c) 1.611 d) 1.182 e) 1.302

f) 1.181 g) 1.214 h) 1.650 i) 1.137 j) 1.649

k) 1.174

Figure 16

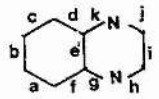
Bond orders in adduct of quinoxaline+HCl

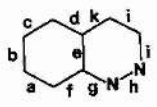
a) 1.876 b) 0.987 c) 1.000 d) 1.728 e) 1.002

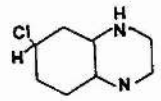
f) 1.002 g) 1.722 h) 1.142 i) 1.661 j) 1.090

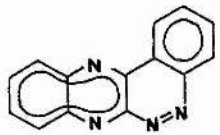
k) 1.635

Figure 17

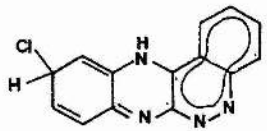








(67)



(68)

Heat of formation of diprotonated species, second protonation (KJ mol^{-1})

N-12	N-7	N-6	N-5
1193.9	1083.7	1104.8	1097.7

Figure 20

X=Cl second protonation at N-5

a) 1.874 b) 0.981 c) 0.978 d) 1.812 e) 0.968

f) 1.003 g) 1.775 h) 1.048 i) 1.103 j) 1.300

k) 0.954 l) 1.543 m) 1.220 n) 1.204 o) 1.272

p) 1.201 q) 1.184 r) 1.607 s) 1.226 t) 1.563

u) 1.228

X=Cl second protonation at N-12

a) 1.870 b) 0.984 c) 0.972 d) 1.824 e) 0.961

f) 0.996 g) 1.765 h) 1.078 i) 1.475 j) 0.916

k) 0.960 l) 1.119 m) 1.743 n) 1.140 o) 1.286

p) 1.148 q) 1.259 r) 1.534 s) 1.273 t) 1.543

u) 1.231

Figure 21

X=Cl second protonation at N-6

a) 1.856 b) 0.982 c) 0.979 d) 1.792 e) 0.984

f) 1.016 g) 1.693 h) 1.103 i) 1.243 j) 1.100

k) 1.030 l) 1.220 m) 1.321 n) 1.357 o) 1.204

p) 1.130 q) 1.185 r) 1.605 s) 1.194 t) 1.633

u) 1.426

Bond orders in adducts (second protonation)

X=Cl second protonation at N-7

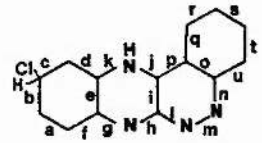
a) 1.800 b) 0.985 c) 0.986 d) 1.755 e) 1.016

f) 1.060 g) 1.529 h) 0.989 i) 1.914 j) 1.107

k) 0.998 l) 1.114 m) 1.760 n) 1.102 o) 1.284

p) 1.130 q) 1.271 r) 1.516 s) 1.302 t) 1.500

u) 1.281



compound (42 a). Examination of the bond orders in quinoxalino[2,3-a]cinnoline (42 a), indicates that the structure should be represented by (67). In particular the bonds 4a-5, 6-6a and 12a-12b are all of the order <1.04, whereas examination of the bond orders of the hydrogen chloride adduct (64 a), indicates that this should be represented by structure (68). In (67) and (68) the bond orders of the isolated 10π fragments are very similar to those calculated for isolated molecules of quinoxaline and cinnoline respectively (figure 16). Despite the disruption of the 10π system in (67) upon addition of hydrogen chloride, a cyclic 10π system is still present in the adduct (68). In comparison, when calculations are done on the formation of a similar adduct between quinoxaline and hydrogen chloride, it is found that the 10π system is totally disrupted (figure 17). The calculated heat of reaction for the addition of hydrogen chloride to quinoxalino[2,3-a]cinnoline is 24.6 KJ mol^{-1} (calculated from $\Delta^{\circ}H_{adduct}-(\Delta^{\circ}H_{quinoxalinocinnoline}+\Delta H^{\circ}_{hydrogen\ chloride})$, while that for addition of hydrogen chloride to quinoxaline is 43.8 KJ mol^{-1}. The proton affinities for protonation at N-12 in quinoxalinocinnoline and for protonation of quinoxaline are virtually identical, being 835.8 KJ mol^{-1} and 838 KJ mol^{-1} respectively. Therefore, the driving force behind the formation of the adduct in the case of quinoxalinocinnoline and hydrogen chloride is the addition of chloride ion to the protonated species (64 a), which does not result in disruption of the 10π system, whereas quinoxaline will not form an adduct with hydrogen chloride due to disruption of the 10π system.

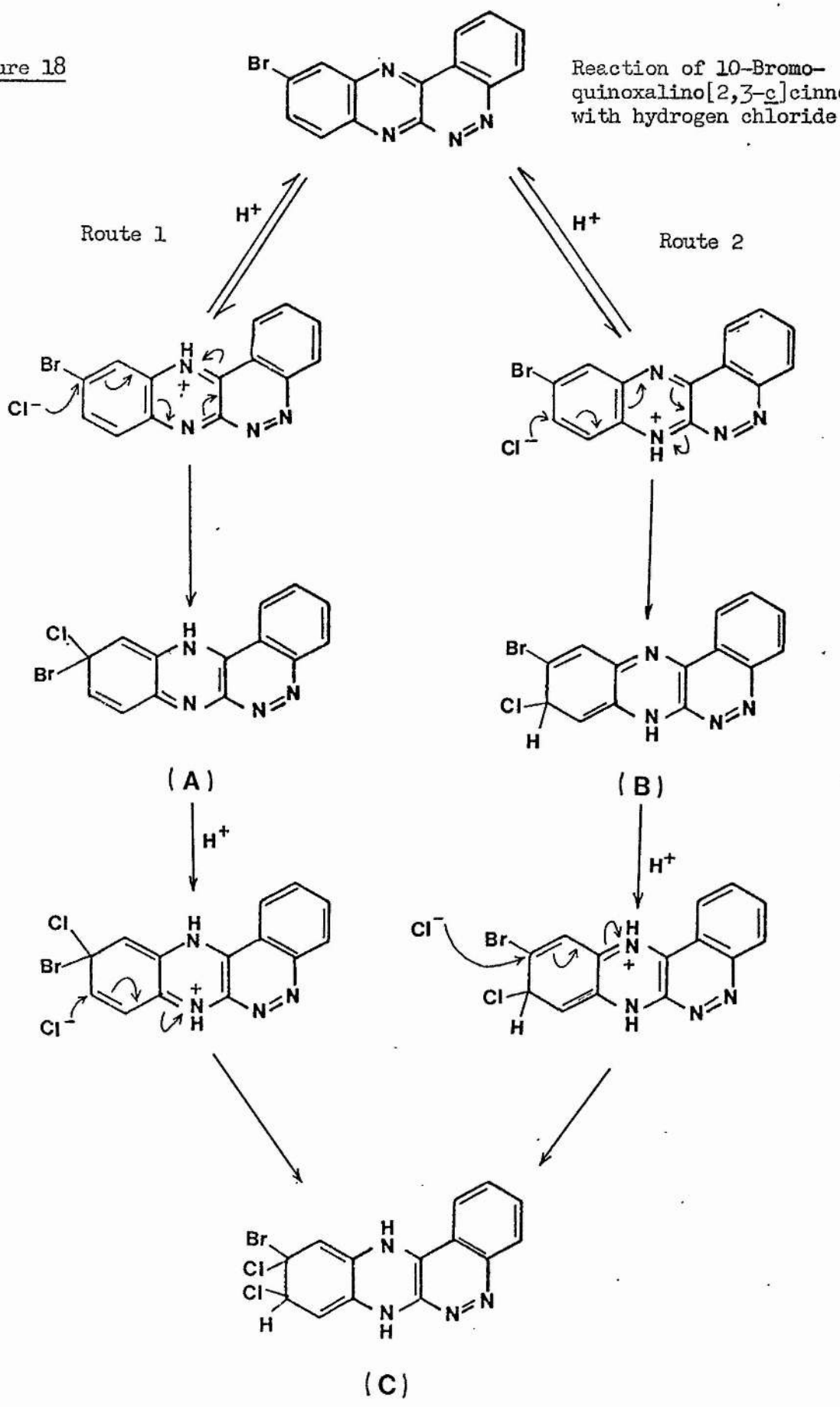
The scheme as proposed, can account for the reactions of quinoxalinocinnolines with no substituents at position 10. The

mechanism involves the reaction of essentially ionic species, and is probably reasonable for the reaction of hydrogen chloride. Hydrogen bromide however, is known to be more prone to undergo radical reactions, and therefore the possibility of a radical mechanism for the reactions of quinoxalinocinnolines must be considered. A sample of quinoxalino[2,3-c]cinnoline was treated with hydrogen bromide in the dark using degassed chloroform as solvent, the reaction being carried out under an inert atmosphere (nitrogen). Also present in the solution was a small amount of 2,6-di-t-butyl-para-cresol, a known radical inhibitor. On completion of treatment with hydrogen bromide, the solution was found to contain a dark blue solid, which gave the same mass spectrum as the adduct of quinoxalinocinnoline and hydrogen bromide under 'normal' conditions. Basification of the adduct yielded 10-bromoquinoxalino[2,3-c]cinnoline as before, in comparable yield. This result would tend to suggest that a radical mechanism for bromination reactions is unlikely, although cannot be completely ruled out.

It will be recalled that the calculated values for the heats of formation of the cationic species formed by protonation at nitrogens 7 and 12 are very similar. Therefore, in situations where for some reason or other attack by halide at position 10 is inhibited, the possibility of a proton shift is great, resulting in the formation of the more stable cation (protonation at N-7). Where there is more than one possible reaction pathway, then it is likely that kinetic effects have a considerable impact on the final outcome of the reaction. Such considerations may explain why in the case of 10-methoxy-quinoxalinocinnoline, chlorination occurs exclusively at C-9, instead

Figure 18

Reaction of 10-Bromo-quinoxalino[2,3-c]cinnoline with hydrogen chloride

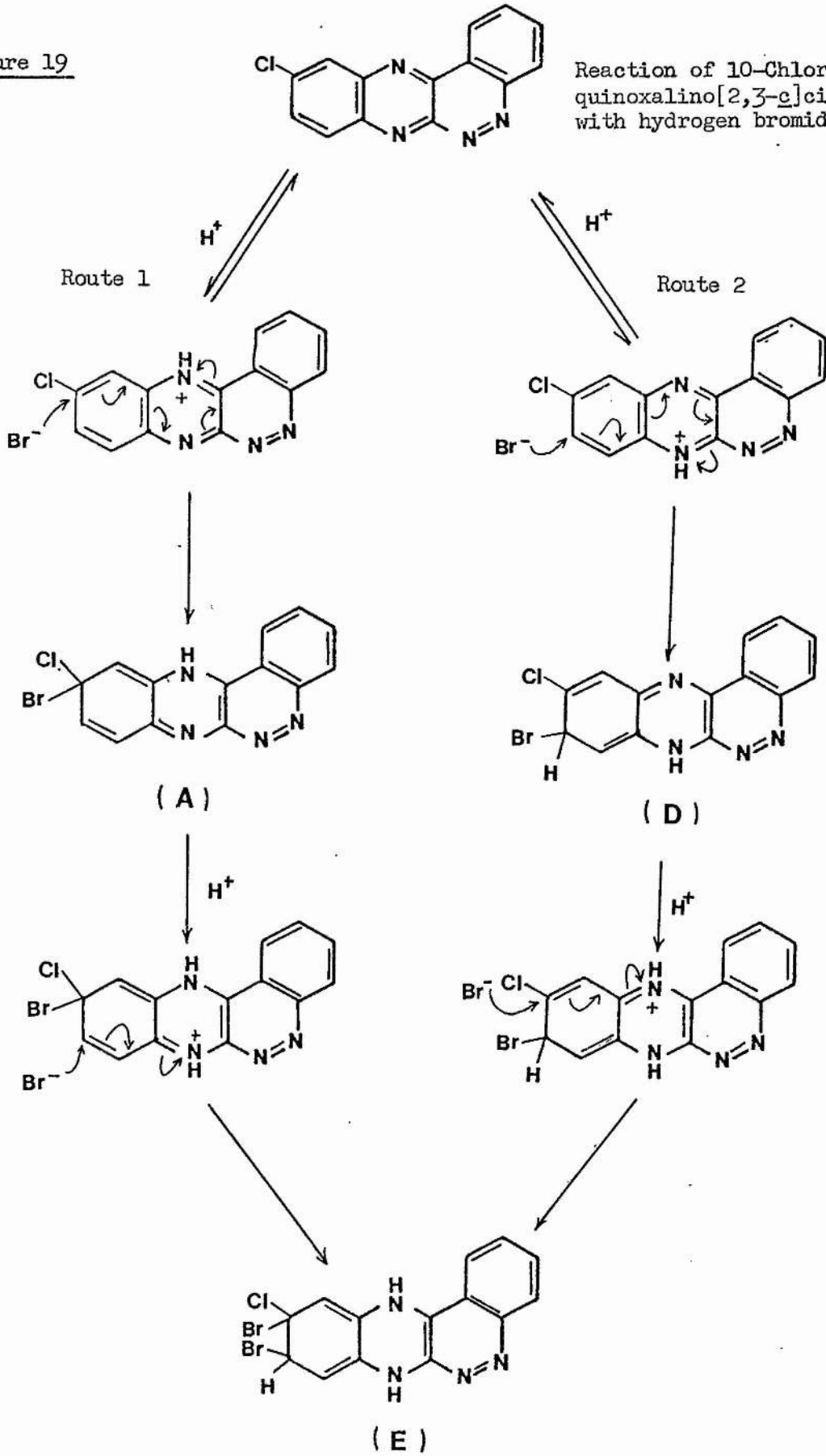


of formation of an adduct at C-10. In those cases where the starting material is recovered in virtually quantitative yield (10-chloroquinoxalinocinnoline with hydrogen chloride and hydrogen bromide, 8,10-dichloroquinoxalinocinnoline with hydrogen chloride), then it would appear highly probable that halogenation does occur at C-10, giving adducts with geminal di-halogeno- substituents at C-10. These adducts would then lose a molecule of hydrogen halide during work-up, rather than undergo aerial oxidation. However, it is obvious that in a few cases the situation is somewhat more complex.

When 10-bromoquinoxalino[2,3-a]cinnoline is treated with hydrogen chloride, three products are obtained. The major products are the 9-chloro-10-bromo- and 10-bromoquinoxalinocinnilines (42 o) and (42 k) respectively, in the ratio of about 2:1. There is also a small amount of what is thought to be the 9,10-dichloro- derivative. The mass spectrum of the blue material formed during this reaction shows the presence of a mono-bromo-mono-chloro adduct, and also a mono-bromo-dichloro adduct. The latter compound would be formed by reaction with a second molecule of hydrogen chloride, in such a way that it is covalently incorporated into the adduct. Possible routes for the formation of the above mentioned adducts are shown in figure 18. Route 1 involves initial protonation at N-12, followed by attack of chloride at C-10 to give adduct A. This is envisaged as being followed by a second protonation at N-7, which is susceptible to attack by chloride at C-9 to give adduct C. The alternative route 2 involves initial protonation at N-7, followed by attack of chloride at C-9, giving adduct B. Further protonation and attack by chloride yielding adduct C. It must be considered likely that the initially

Figure 19

Reaction of 10-Chloro-quinoxalino[2,3-c]cinnoline with hydrogen bromide



formed mono cations are in equilibrium with each other, and that both pathways may be involved. Also, it is likely that the rates of the various reactions occurring have a decisive influence on the final outcome. Adduct C would be the source of the small amount of dichloro compound, while the bromo-chloro- compound could come from either adduct B or C. Adduct A and C would be the most likely sources of the mono-bromo product.

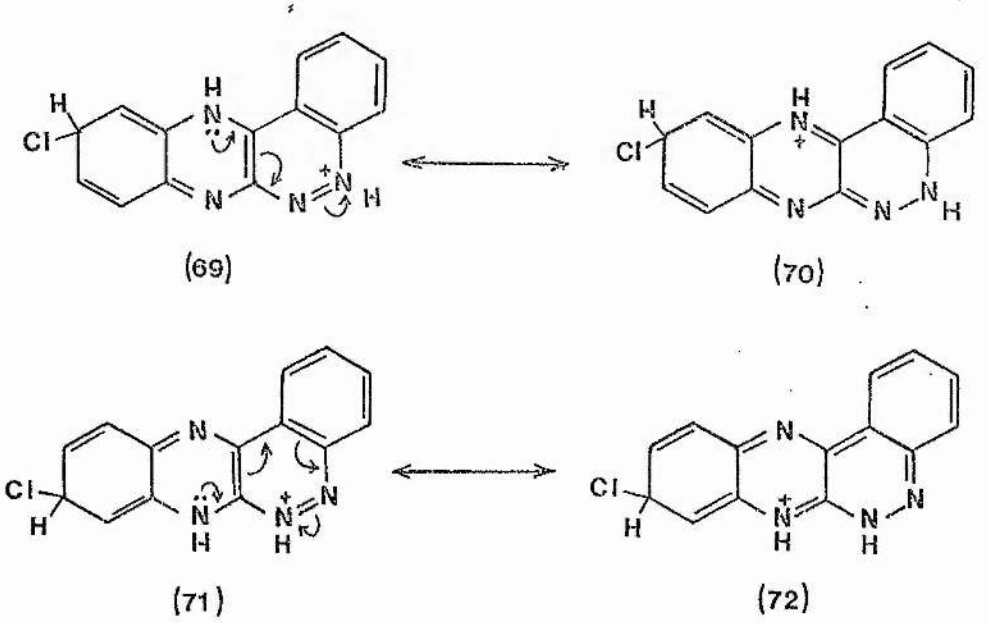
The similar reaction, that of 10-chloroquinoxalinocinnoline with hydrogen bromide gives a final product consisting of mainly 10-chloroquinoxalinocinnoline (42 b) and a small amount of the 9-bromo-10-chloro- derivative. A scheme for this reaction is shown in figure 19. It is similar in nature to that shown in figure 18 for 10-bromoquinoxalino[2,3-a]cinnoline and hydrogen chloride. Again, there are two competing routes, initial protonation at N-12 giving adduct A on attack by bromide while initial protonation at N-7 eventually gives adduct D. The mass spectrum of the blue intermediate obtained during this reaction shows a mono-bromo-mono-chloro adduct, and what may be a fragmentation product of a chloro-dibromo adduct E, though the presence of the latter adduct is by no means certain. If it is present, then it is so in low quantity. The small amount of bromo-chloro compound detected in the final product would most likely come from adduct D or E, while adduct A would most likely give the major component of the product, the 10-chloro derivative.

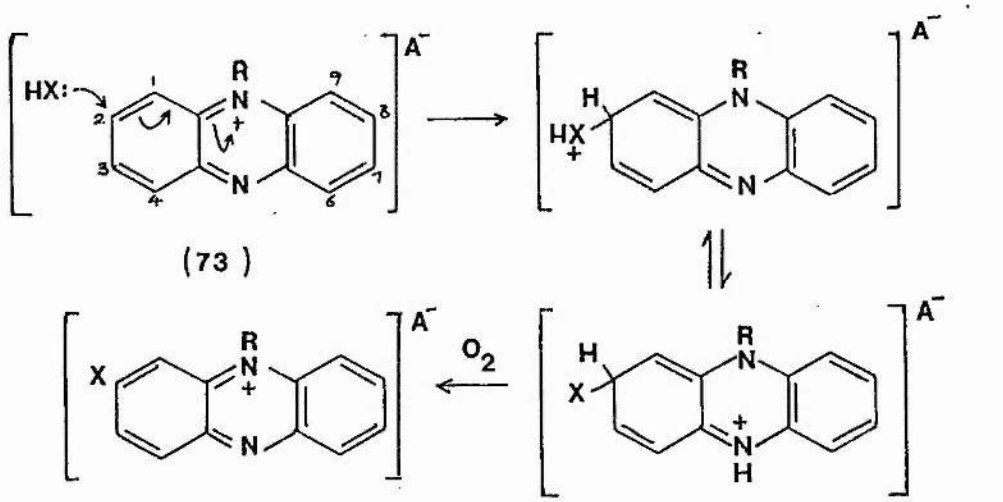
It can be seen that in both of the schemes shown in figures 18 and 19, that an adduct appears that is common to one of the pathways in each (adduct A). If both adducts were present in the respective

blue intermediates, then it might be expected that there be some similarity in the distribution of products. This is clearly not so, therefore it is reasonable to assume that in at least one of the schemes, the pathway involving adduct A is of minor significance. The production of a mono-chloro-mono-bromo product in major yield would tend to favour route 2 in both schemes, while the relative absence of such a compound, and the high return of starting material would tend to rule out route 2. Therefore, in the reaction of 1-bromo-quinoxalinocinnoline with hydrogen chloride, the production of 10-bromo- 9-chloroquinoxalinocinnoline suggests that route 2 in figure 18 is the major pathway, while in the reaction of 10-chloro-quinoxalinocinnoline with hydrogen bromide, the formation of the mixed halide in low yield in conjunction with a nigh recovery of starting material. suggests that route 1 in figure 19 is the major pathway. If this is the case, then the recovery of the 10-chloro compound from adduct A in figure 19 implies that hydrogen bromide is preferentially lost, from the adduct on work up. In the scenario described, route 1 would be thermodynamically favoured, while route 2 would be important if the reaction was under kinetic control. The results also imply that attack by chloride at C-10 when C-10 carries a bromine atom is in some way inhibited, while attack of bromide at C-10 when the carbon atom is chloro substituted is not inhibited. Whether the inhibition is steric in origin, or whether some form of electronic interaction between the bromine substituent and ring system and/or chloride ion is occurring, is difficult to say.

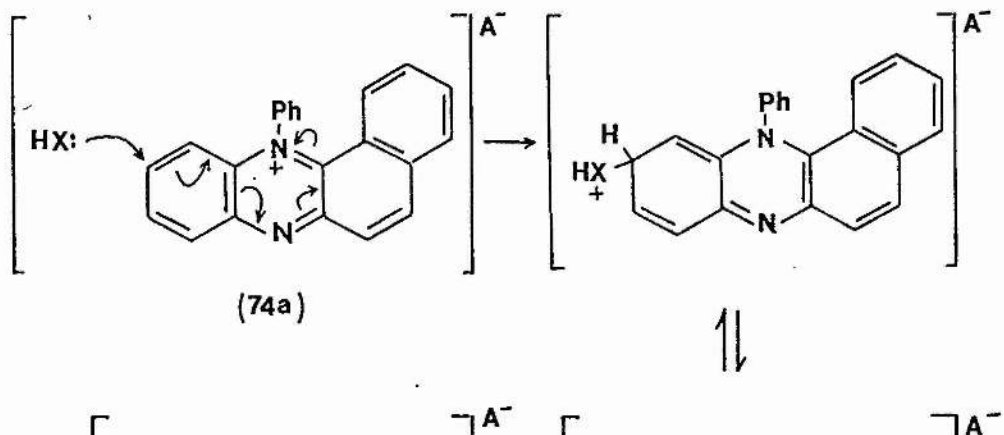
Formation of a covalent adduct between a quinoxalinocinnoline and a hydrogen halide molecule is considered to be followed by further

protonation. MNDO studies[46] carried out on the adduct formed between quinoxalino[2,3-a]cinnoline and hydrogen chloride, indicate that second protonation at N-7 and N-5 would give the thermodynamically more stable cationic species (protonation at N-7 giving the cation of marginally lower energy), while protonation at N-6 or N-12 is thermodynamically unfavoured (figure 20). Protonation at N-12 is by far the least favoured process, which is understandable, since the electron lone pair on N-12 will lie perpendicular to the plane of the adduct, while those on the others will lie in the plane of the adduct. The protonation of the adduct at N-5 has some analogy with the protonation of 4-aminocinnoline, which is protonated preferentially at N-1[48]. Protonation at N-5 allows extension or conjugation into the cinnoline portion of the molecule as shown below. Second protonation at N-5 would give species (69), while extension of the conjugation would give species (70). Similarly, initial protonation at N-7, followed by second protonation at N-6, would also allow extension of congugation, the protonated species (71) giving species (72) on extension of conjugation.

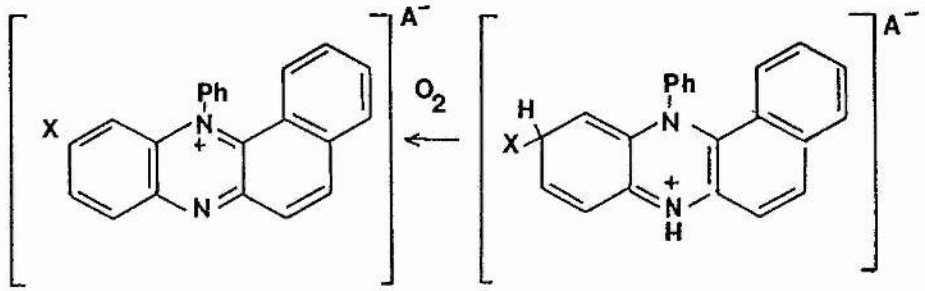


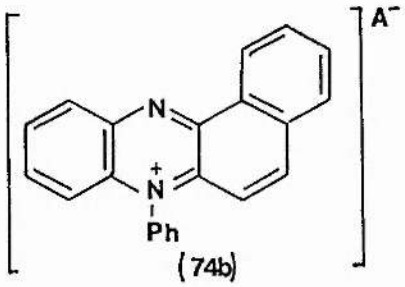


(73)

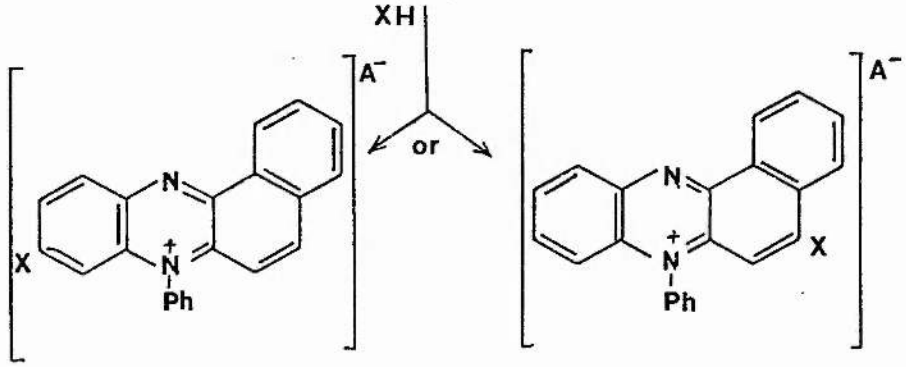


(74a)





(74b)

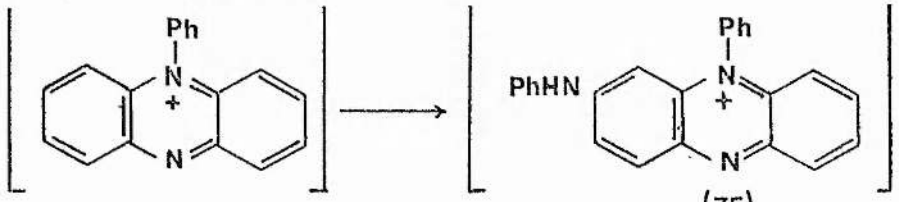


The total bond orders for the diprotonated species (second protonation at N-7 and N-5) are shown in figure 21. These figures indicate that extension of conjugation into the cinnoline portion of the molecule, is to some extent predicted by the MNDO calculations done for second protonation at N-5. In the species with protonation at N-5, the bond order of bond 12-12a is 1.3, while that of bond 6-6a is 1.54.

When a solution of quinoxalino[2,3-c]cinnoline in chloroform is treated slowly with gaseous hydrogen chloride, the solution is seen to darken from deep orange to deep red before precipitation of the blue adduct commences. Similarly, if a solution of the adduct in ethanol is shaken with chloroform and aqueous base, the colour changes from blue to red, then to orange-yellow. The neutralisation of excess hydrogen halide in the adduct is considered to result in the reformation of the adducts (64) and (66). The initial adducts (64) and (66) are thought to be totally covalent, and therefore might be expected to be chloroform soluble. In which case, the red colour in the chloroform (mentioned above) might be due to these adducts, while the blue colour might be due to the species showing extended conjugation ((70) and (72)).

The overall process of the proposed reaction scheme has some analogy in the reactions of phenazinium salts (73)[49] and benzo[a]phenazinium salts (74)[49] with nucleophiles. The sites of nucleophilic attack in these compounds is shown opposite. Attack by nucleophiles upon (73) occurs at position 2,[49,50,51] while in (74)

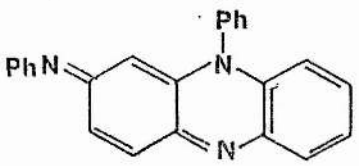
attack occurs at position 10 in 12-phenyl salts (74 a),[49,52] and at positions 5 or 9 in 7-phenyl salts (74 b).[49,52] Phenazinium salts and benzophenazinium salts are not, however, reactive towards chloride ion (chloride is often the counterion in the salts themselves). Phenazinium salts are represented in the ortho-quinonoid forms shown in (73). However, they will readily undergo reactions in which they are converted to compounds with para-quinonoid structures. Thus 10-phenylphenazinium chloride (73: R=Ph, $A^{-}=Cl^{-}$) reacts with aniline to form tha anilino compound (75). When the salt is recrystallised from ethanol, the compound (76), with the para-quinonoid structure, is formed by loss of HCl.[49]



(73, R=Ph; $A^{-}=Cl^{-}$)

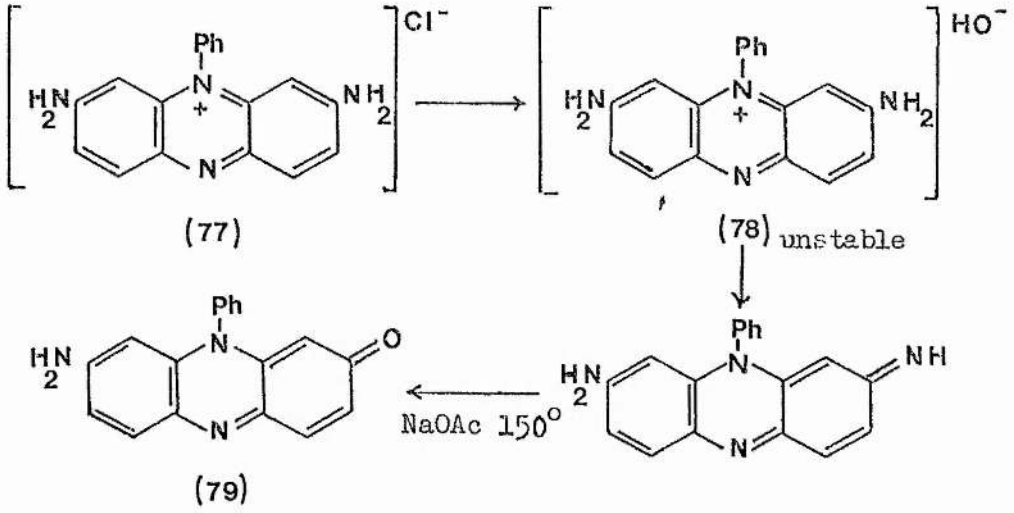
(75)

Recrystallised from ethanol



(76)

Similarly the safranine salt (77), if visualised as having only the ortho-quinonoid structure shown, might be expected to yield a strong quaternary base on treatment with alkali, undergo diazotisation at both amino groups and to be resistant to hydrolysis. Such is not the case. Upon neutralisation with aqueous ammonia it forms a weak base (78)[53] which can only be diazotised at one amino group, and readily undergoes hydrolysis to form an aminosafranone (79).[53] The aminosafranone, having a para-quinonoid structure is then resistant to further hydrolysis.



In the proposed mechanism for the conversion of quinoxalinocinnolines to the hydrogen halide adducts, the simple adduct (64) has a partially para-quinonoid structure, while the adduct (70) has an extended para-quinonoid structure. Preference for a structure such as this is supported by the behaviour of phenazinium salts.

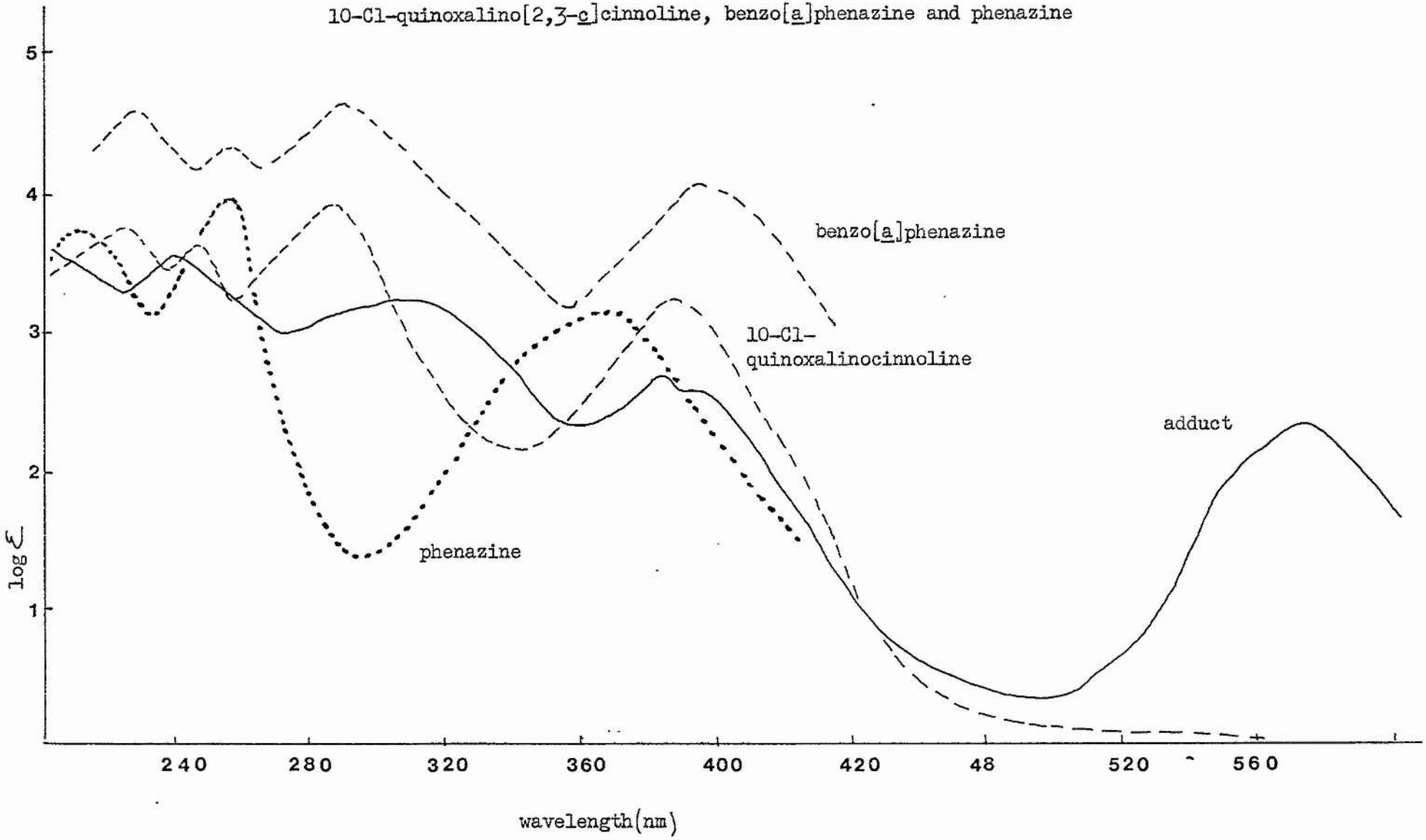
Compound	λ_m nm (log ε in parentheses)
10-Chloroquinoxalino[2,3-c] cinnoline	227(3.66) 242(3.47) 383(3.65) 390(3.17)
Benzo[a]phenazine	225(4.57) 252(4.3) 278(4.65) 384(4.02)
Adduct, quinoxalino[2,3-c] cinnoline+HCl	232(3.44) 302(3.3) 386(2.82) 569(2.76)
Adduct, 10-chloroquinoxalino [2,3-c]cinnoline+HCl	235(3.42) 320(3.3) 392(2.8) 610(2.73)

Figure 22

Quinoxalino[2,3-c]cinnoline+HCl	λ_m
10-Cl+HCl	570
10-Br+HCl	569
9-Br+HCl	568
2-Cl+HCl	594
8-Cl+HCl	546
10-MeO+HCl	610
10-Cl+HBr	581

Figure 25

Figure 23 Ultra-violet/visible spectra of the adduct of quinoxalino[2,3-c]cinnoline+HCl, 10-Cl-quinoxalino[2,3-c]cinnoline, benzo[a]phenazine and phenazine



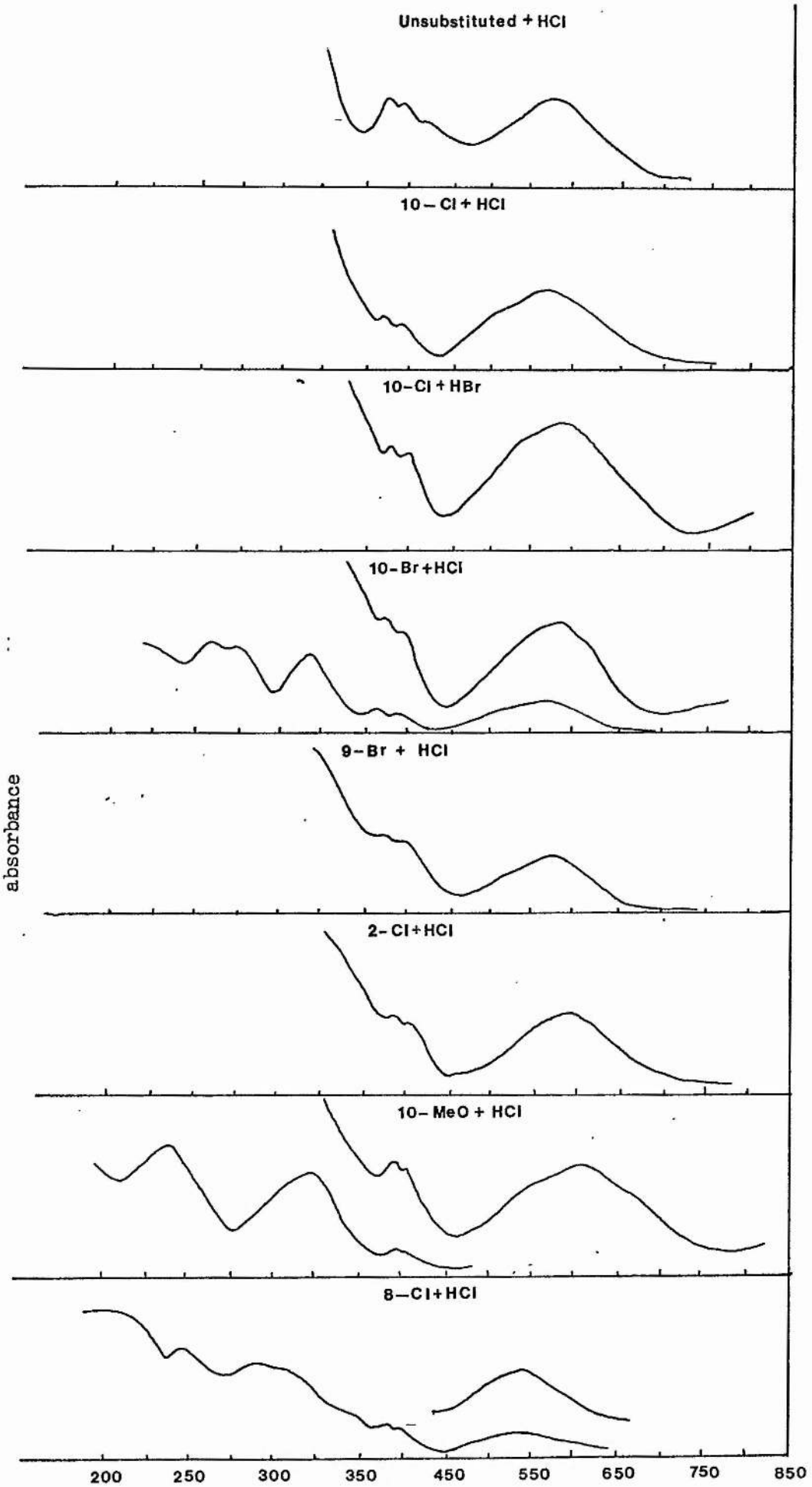

Unsubstituted + HCl
10 – Cl + HCl
10–Cl + HBr
10–Br + HCl
9–Br + HCl
2–Cl + HCl
10– MeO + HCl
8–Cl + HCl
absorbance
200
250
300
350
450
550
650
750
850
wavelength (nm)

Figure 24

4. Ultra violet/visible spectra of the adducts formed from quinoxalino[2,3-c]cinnolines and hydrogen halides

The absorption spectra of quinoxalino[2,3-c]cinnoline (42 a) and its derivatives over the range 200-500nm shows a profile similar to that of benzo[a]phenazine.[55] The adducts formed between quinoxalino[2,3-c]cinnoline (42 a) and hydrogen halides show weak absorptions generally greater than 550nm that are totally absent from the parent heterocycles, although below 400nm the spectra are not unlike those of quinoxalino[2,3-c]cinnoline and benzo[a]phenazine. The absorptions in the adducts above 550nm are those responsible for the intense blue colour of these compounds. The ultra-violet/visible absorption spectra of the adduct of quinoxalino[2,3-c]cinnoline and HCl, along with the spectra of 10-chloroquinoxalinocinnoline, phenazine[56] and benzo[a]phenazine are shown in figures 22 and 23. The spectra of the remainder or the adducts are shown in figure 24, and the position of the absorption maxima in the region 550nm are shown in figure 25 (spectra are recorded in ethanol). The hydrolysis and oxidation processes that the adducts appear to undergo in basic media can be followed, either by making up solutions in water, or in some cases by using solutions in propan-2-ol. It was found that several adducts, in particular those of quinoxalino[2,3-c]cinnoline and the 10-chloro derivative with hydrogen chloride, underwent hydrolysis and oxidation resulting in the formation of 10-chloro-quinoxalino[2,3-c]cinnoline in propan-2-ol. Presumably propan-2-ol either de-protonates the adduct (70) in dilute solution, and this is followed by oxidation of the resultant adduct (64); or the propan-2-ol

Figure 26 Adduct of quinoxalino[2,3-c]cinnoline+HCl

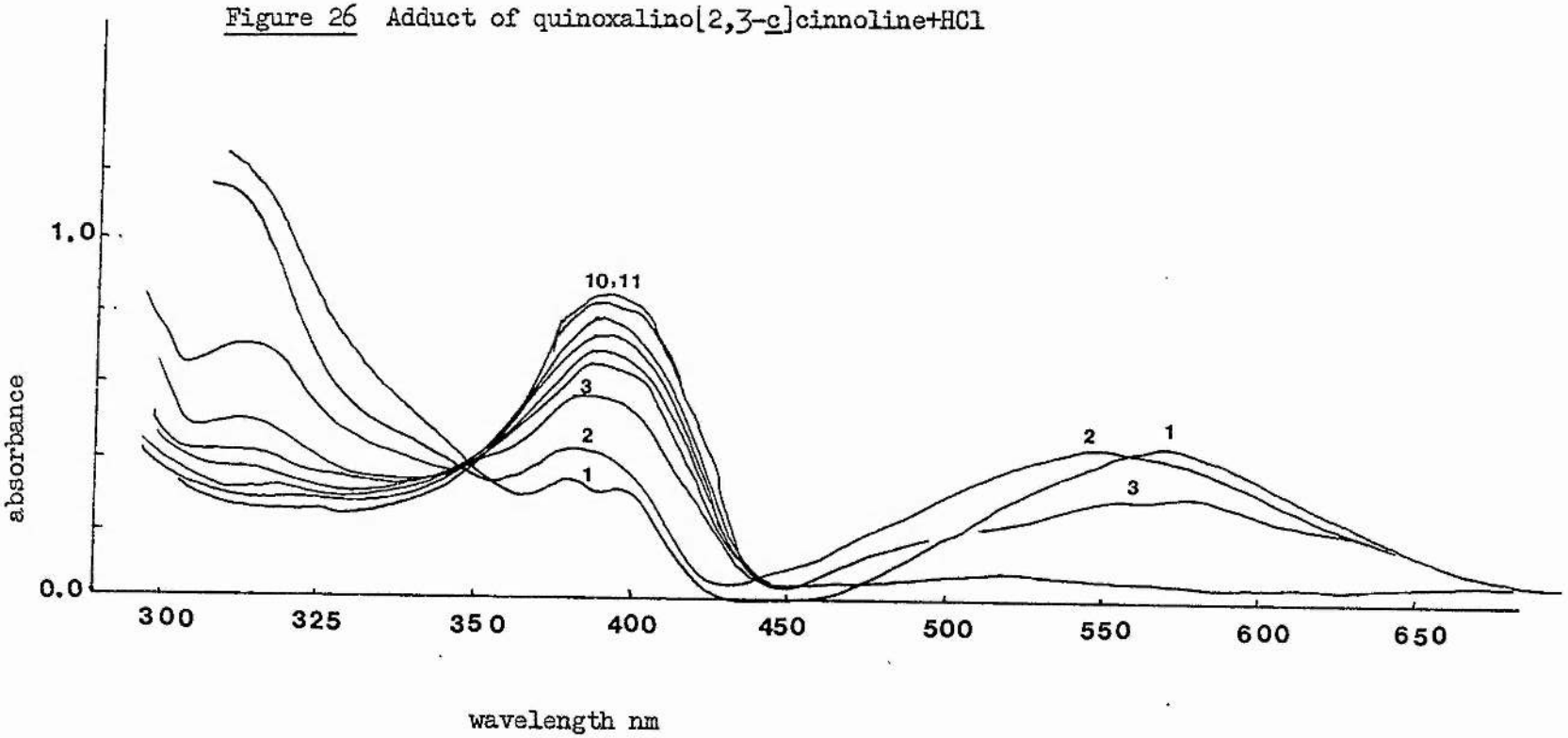
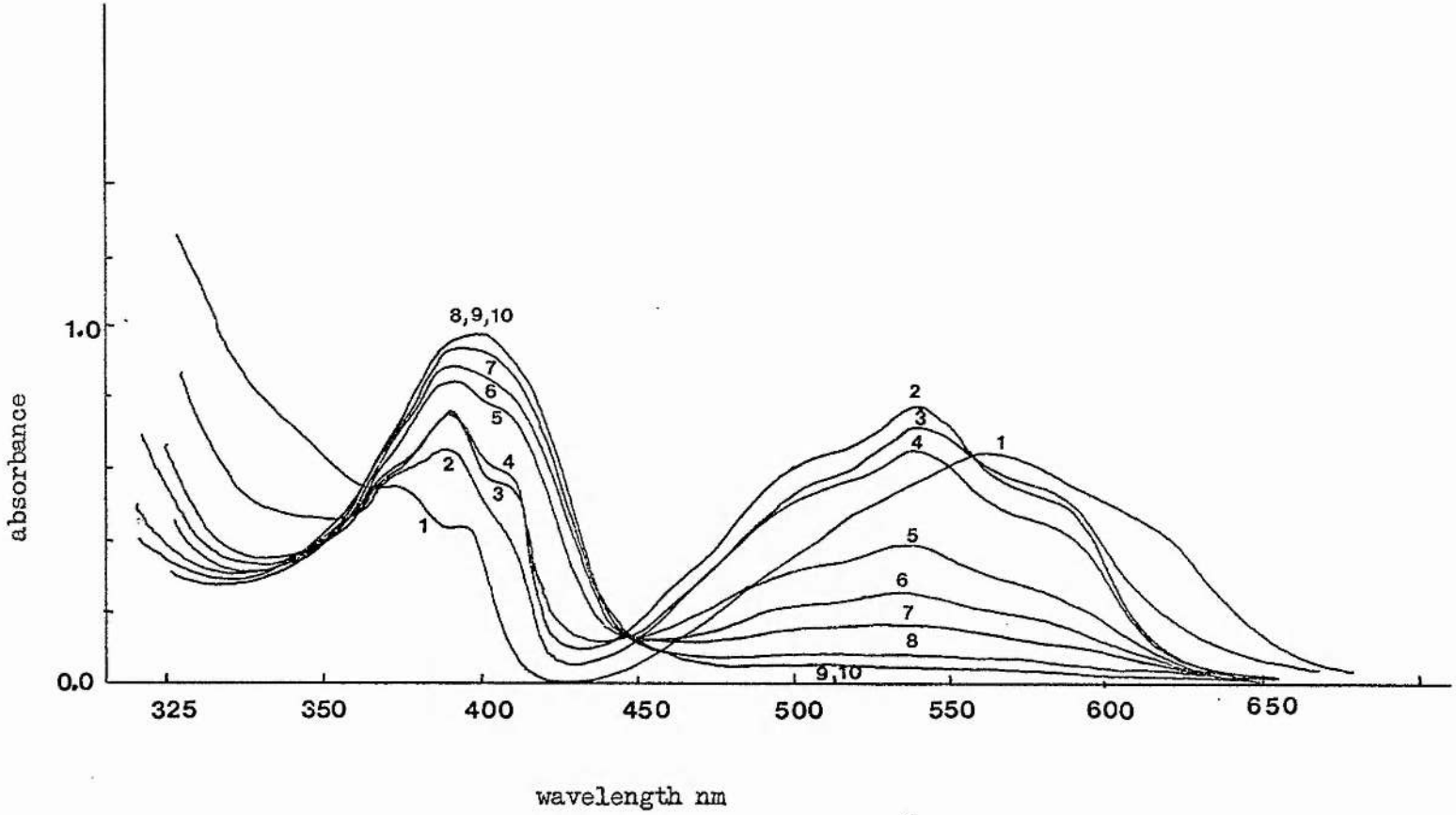


Figure 27 Adduct of 10-Cl-quinoxalino[2,3-c]cinnoline+HCl in acetone



acts as an oxidising agent itself. The extinction coefficients of the adducts of quinoxalino[2,3-a]cinnoline with HCl and the 10-chloro derivative with HCl were determined by the following method: Solutions of each in ethanol were diluted and the ultra-violet/visible spectra recorded. Solutions of the same concentration in an ethanol/propan-2-ol mixture were made up, and the ultra-violet/visible spectra recorded over a period of time until hydrolysis and oxidation were complete. The solutions that provided the final spectra were therefore solutions of 10-chloro-quinoxalino[2,3-a]cinnoline of the same concentration as the initial adduct solutions. Since the extinction coefficient of 10-chloro-quinoxalinocinnoline had previously been determined, the extinction coefficients of the absorption maxima in the adducts could be determined.

Figure 26 shows the change in the absorption spectra of the quinoxalino[2,3-a]cinnoline-HCl adduct in propan-2-ol/ethanol solution. Spectrum 1 represents the adduct in ethanol (and also in propan-2-ol). Profiles 2 to 11 show the changes that occur on changing from the adduct to 10-chloroquinoxalinocinnoline, and were recorded over equal time intervals. Similarly, figure 27 shows the change that occurs to the spectrum of the 10-chloro-quinoxalinocinnoline-HCl adduct in an aqueous acetone solution. Here, profile 1 is the spectrum of the adduct in neat acetone, although a solution of equal concentration in aqueous acetone is initially the same. Again the product is 10-chloro- quinoxalinocinnoline. Both spectra show similar features, with isosbestic points at approximately 350 and 450nm. A feature of note is that in both series of spectra there is an initial rapid shift in the position of the absorption

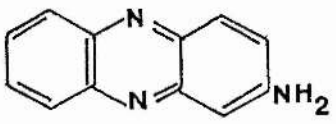
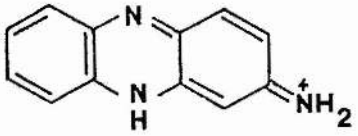
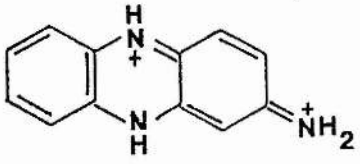
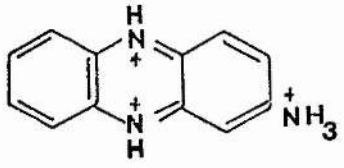
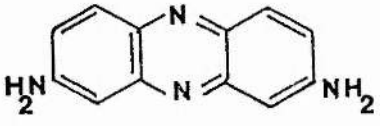
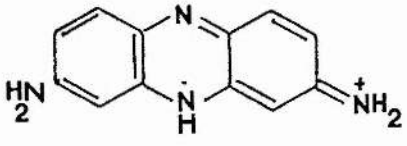
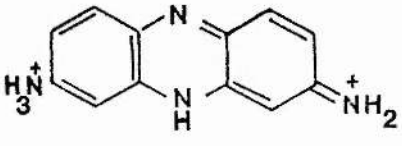
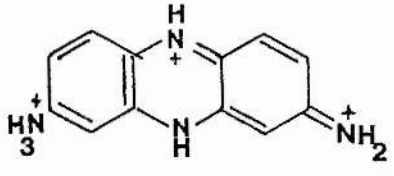
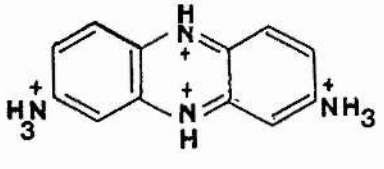
	colour	λ_m	acid strength
 base	orange	472nm	-
 mono-salt	cerise	520nm	1 drop HCl
 di-salt	pure green	705nm	conc HCl
 tri-salt	brown/red	541 nm (506)	conc H_2SO_4
 base	yellow/ orange	447nm	-
 mono-salt	cerise	520nm	1 drop HCl
 di-salt	violet	580nm	dil HCl
 tri-salt	blue/ green	650nm	conc H_2SO_4
 tetra-salt	red/brown	540nm	fuming H_2SO_4

Figure 28

maxima in the visible region from about 570nm to 545nm (profiles 1 to 2), and that the observed change is the reduction of the maxima at 545nm and increase of the maxima at 390-400nm (due to formation of 10-chloroquinoxalinocinnoline). This may represent the initial change from adduct (70) to (64) via deprotonation, followed by oxidation, which is the major process observed. Certainly if species (64) is deep red, a shift in the absorption maximum to a shorter wavelength would be expected.

Examples of changes in absorption wavelength with changes in the degree of conjugation in heterocyclic bases are shown by a group of phenazine derivatives, the safranines.[49,57] Such changes are brought about by the differing extent of protonation in media of variable acidity. Figure 28 shows a series of such compounds and the change in the position of absorption maximum. It is interesting to note that compounds with a para-quinonoid structure generally show absorption maxima above 520nm, while those with ortho-quinonoid structures absorb below 500nm. Also, in those compounds with para-quinonoid structures, the position of the absorption maximum changes with degree of protonation. Often increased protonation moves the absorption maximum towards the red end of the spectrum (i.e. colour changes from red/orange through violet and blue to green) up to a point, then increased protonation disrupts the conjugation in the molecules, and the wavelength of absorption drops.

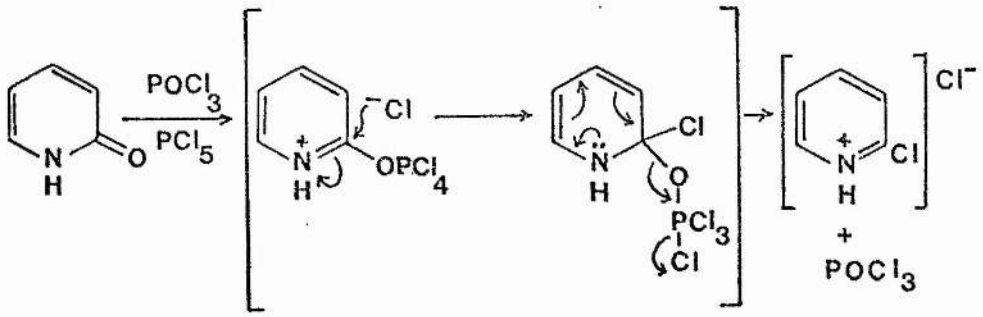
The adducts (64) and (70) are respectively considered to be dark red and blue in colour, and this change in colour coupled with the difference in proposed structure, is similar to the effects observed

in the safranines.

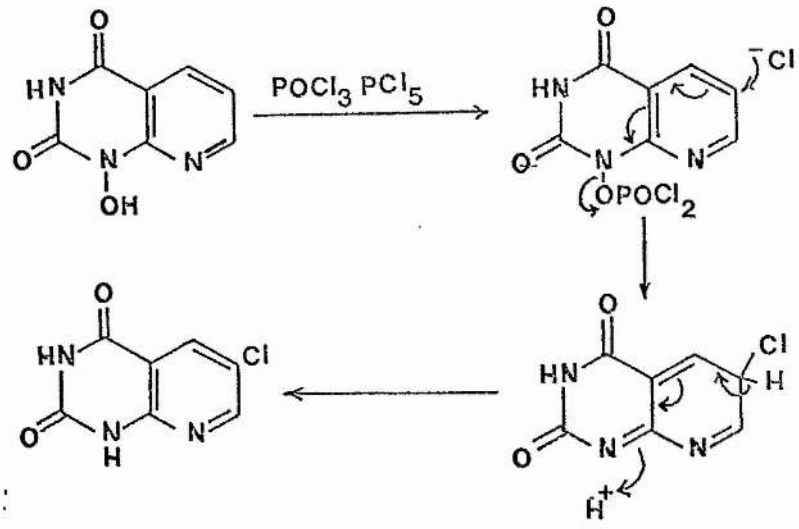
5. Chloride ion as a nucleophile in substitution reactions of heterocyclic systems

Chloride ion is not generally considered to be a strong nucleophile, and therefore will only take part in a few specific types of nucleophilic substitution reaction. These generally involve the reaction of a halogen containing reagent such as acetyl chloride, phosphoryl chloride, phosphorus pentachloride and hydrogen chloride, with heterocycles bearing an oxy-substituent such as N-oxide, keto or hydroxy groups. The oxygen atoms in such compounds undergo electrophilic attack by the reagent, furnishing a chloride ion which can then attack the positively charged species formed. The site of chloride attack depends both on the nature of the heterocyclic compound, and its substituents if any; since the addition of chloride ion is followed by elimination of a good leaving group (and often a proton as well). The chloride ion need not attack at the site of the leaving group. Examples of the various types of reaction follow:

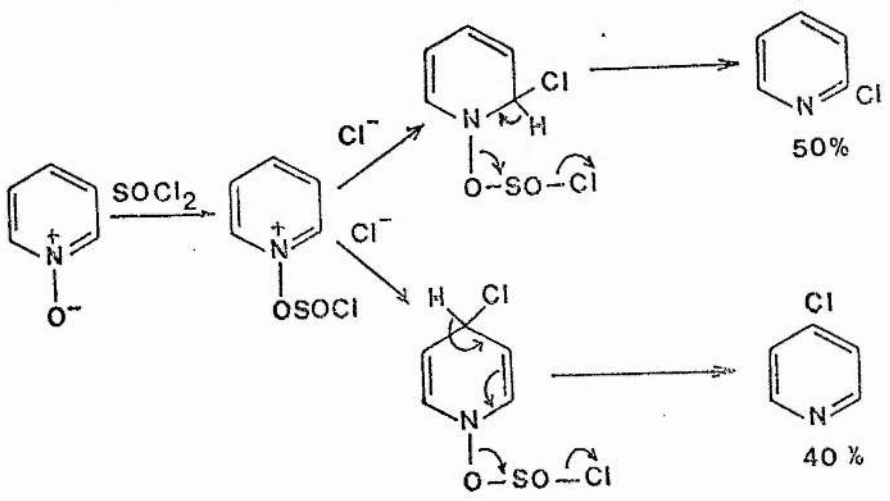
There are many reactions where keto compounds are deoxygenated and chlorinated at the same site. For example, the reaction of phosphoryl chloride and phosphorus pentachloride with pyridones:[58]

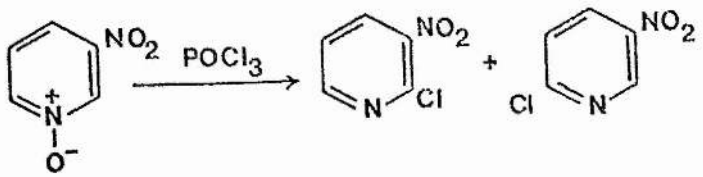


Chloride need not attack at the site of the leaving group, as illustrated by the reaction of pyrido[2,3-d]pyrimidin-2,4-(1H,3H)-dione-1-N-oxide with phosphorus pentachloride and phosphoryl chloride to give 6-chloropyrido[2,3-d]pyrimidin-2,4-(1H,3H)-dione:[59]

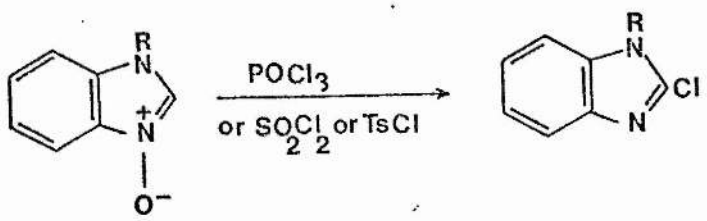


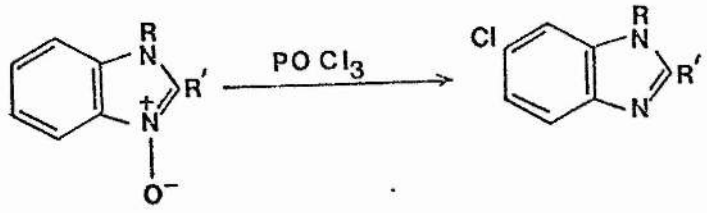
Many other heterocyclic N-oxides may be deoxygenated by reagents such as phosphoryl chloride and thionyl chloride, being substituted with chlorine at the same time:[60,61]

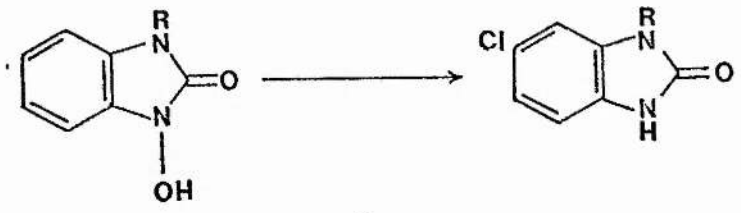




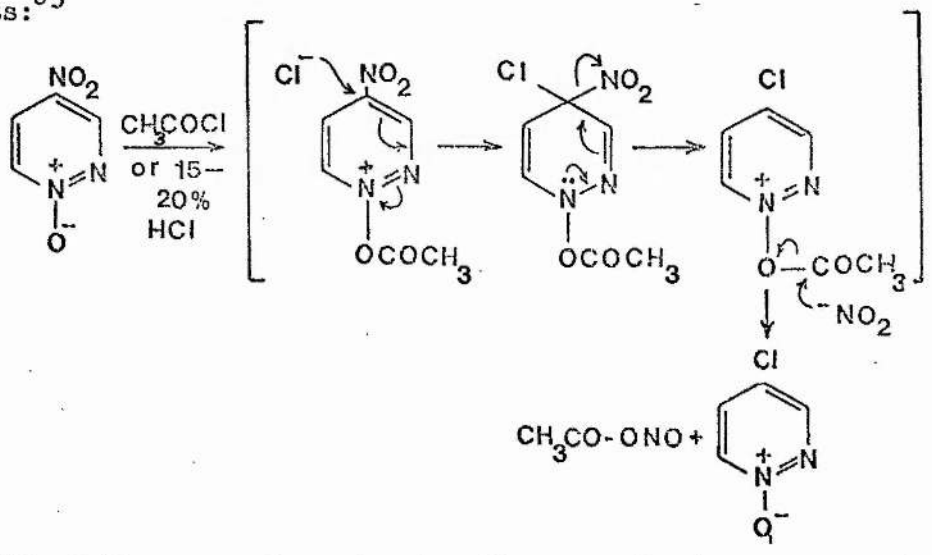
Similarly, benzimidazole-N-oxides can be chlorinated and deoxygenated at the same time:[62]







Other functional groups can become involved in the displacement process:[63]



All of these reactions involve the removal of an oxygen atom, or

some other functional group, and are considered to be addition and elimination reactions, though of an abnormal type, since *cine*-substitution occurs. They are referred to as AE_a reactions.

The reaction of quinoxalino[2,3-*a*]cinnoline and its derivatives with hydrogen halides is of a type similar to the above mentioned, in that halide ion is considered to attack a positively charged species at a site remote from the charge. It differs however, in that it is not strictly an addition-elimination process, rather when considered overall, it is an addition-oxidation process. Under the reaction conditions it is envisaged that the adduct formed initially is stabilised by further protonation. There is however, reason to believe that the initial adduct is itself susceptible to oxidation, and therefore overall, the further protonation need not be considered essential to the reaction.

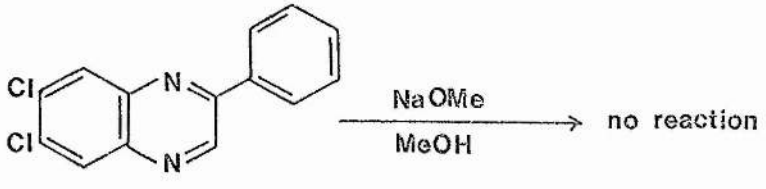
Within the study of quinoxalino[2,3-*a*]cinnolines the ease of introduction of chlorine into position 10 is of great synthetic value, since as will be mentioned in the following chapter, chlorine in position 10 is labile to nucleophilic reagents, opening up synthetic routes to other compounds. Further investigation of this reaction is required in order establish firmly the identity of the adducts and the mechanism. Indeed, investigation of the application of this type of reaction to other heterocyclic species is an obvious further extension of the present work.

CHAPTER 5

The reactions of halogenated quinoxalino[2,3-c]cinnolines with nucleophiles

1. Nucleophilic displacement reactions of halogenated quinoxalino[2,3-c]cinnolines

It will be recalled from the introduction (p. 12), that when 4,5-dichloro-*N*-*o*-nitrobenzylidene-*o*-phenylenediamine was reacted with potassium cyanide in an attempt to form the 9,10-dichloroquinoxalino[2,3-*c*]cinnoline (42 n), a mono-chloro-mono-methoxy derivative was formed.[31] In addition it had been found that a sample of the 9,10-dichloroquinoxalinocinnoline (42 n) prepared by the 3,4-dibromocinnoline route (p. 16), when treated with sodium methoxide, underwent methoxydechlorination of one of the chloro substituents. The product from this reaction had a ^{1}H n.m.r. spectrum virtually identical to that of the product of the cyclisation of the 4,5-dichloro-anil mentioned above. In both cases, it had not been possible to determine with certainty which chlorine atom had been replaced. It had also been found that a model compound, 6,7-dichloro-2-phenylquinoxaline (80) showed no reaction with methoxide.[31]



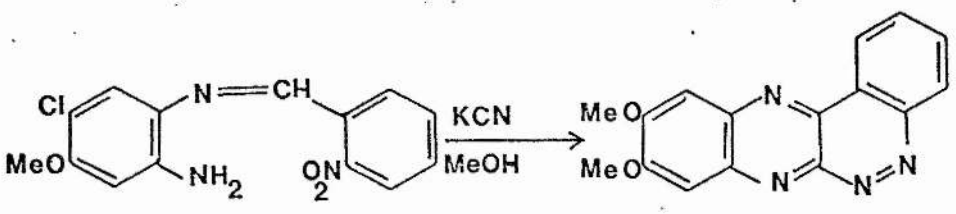
This suggested that the nitrogen atoms in the cinnoline portion of the quinoxalinocinnoline structure (N-5 and N-6) were structurally

Reactant (quinoxalino-[2,3-c]cinnoline)	Reaction time	Product (quinoxalino-[2,3-c]cinnoline); yield(%)		
(42 b) 10-Cl	1 hour	(42 f)	10-MeO	(83)
(42 c) 9-Cl	8 hours	(42 c)	9-Cl	(92)
	10 hours	(42 c)	9-Cl	(90)
(42 k) 10-Br	10 hours	(42 f)	10-MeO	trace*
		(42 k)	10-Br	(90)
(42 l) 9-Br	10 hours	(42 l)	9-Br	(95)
(42 n) 9,10-Cl_2	1 hour	(42 m)	9-Cl-10-MeO	(90)
		(42 q)	9,10-$(MeO)_2$	trace*
	2.5 hours	(42 m)	9-Cl-10-MeO	(50) **
		(42 q)	9,10-$(MeO)_2$	(35)
	10 hours	(42 m)	9-Cl-10-MeO	(13) **
		(42 q)	9,10-MeO_2	(68)

* from mass spectrum; ** estimated from ^1H n.m.r. integrals

Table 12 Reactions of halogenated quinoxalino[2,3-c]cinnolines with sodium methoxide.

involved in the substitution process. Finally, it had been found that the cyclisation of 5-chloro-4-methoxy-N-o-nitrobenzylidene-o-phenylenediamine (50) with cyanide resulted in the formation of a dimethoxyquinoxalinocinnoline, presumably the 9,10-dimethoxy derivative (42 q). This suggested that the chlorine atom at position 10 of the 10-chloro-9-methoxyquinoxalinocinnoline (42 r) was labile to methoxide.



(50)

Further evidence of the occurrence of methoxydechlorination of chloroquinoxalinocinnolines was observed during the cyclisation reactions of some chloro-substituted 2-acetamido-anils. It has already been mentioned in chapter 2 (p. 26), that when the 5-chloro- and 5,5'-dichloro-2-acetamido-anils (55 b) and (55 d) were cyclised with cyanide in methanol, the expected 10-chloro- and 2,10-dichloroquinoxalinocinnolines (42 b) and (42 d) were formed, but the presence of methoxy-derivatives was also detected in the spectra of the reaction products. Indeed, it was found that increased reaction time resulted in a larger yield of the methoxy compounds.

To investigate the methoxydehalogenation of halogeno-quinoxalinocinnolines, a number of such compounds were reacted with excess of methanolic sodium methoxide for several hours. The results of these

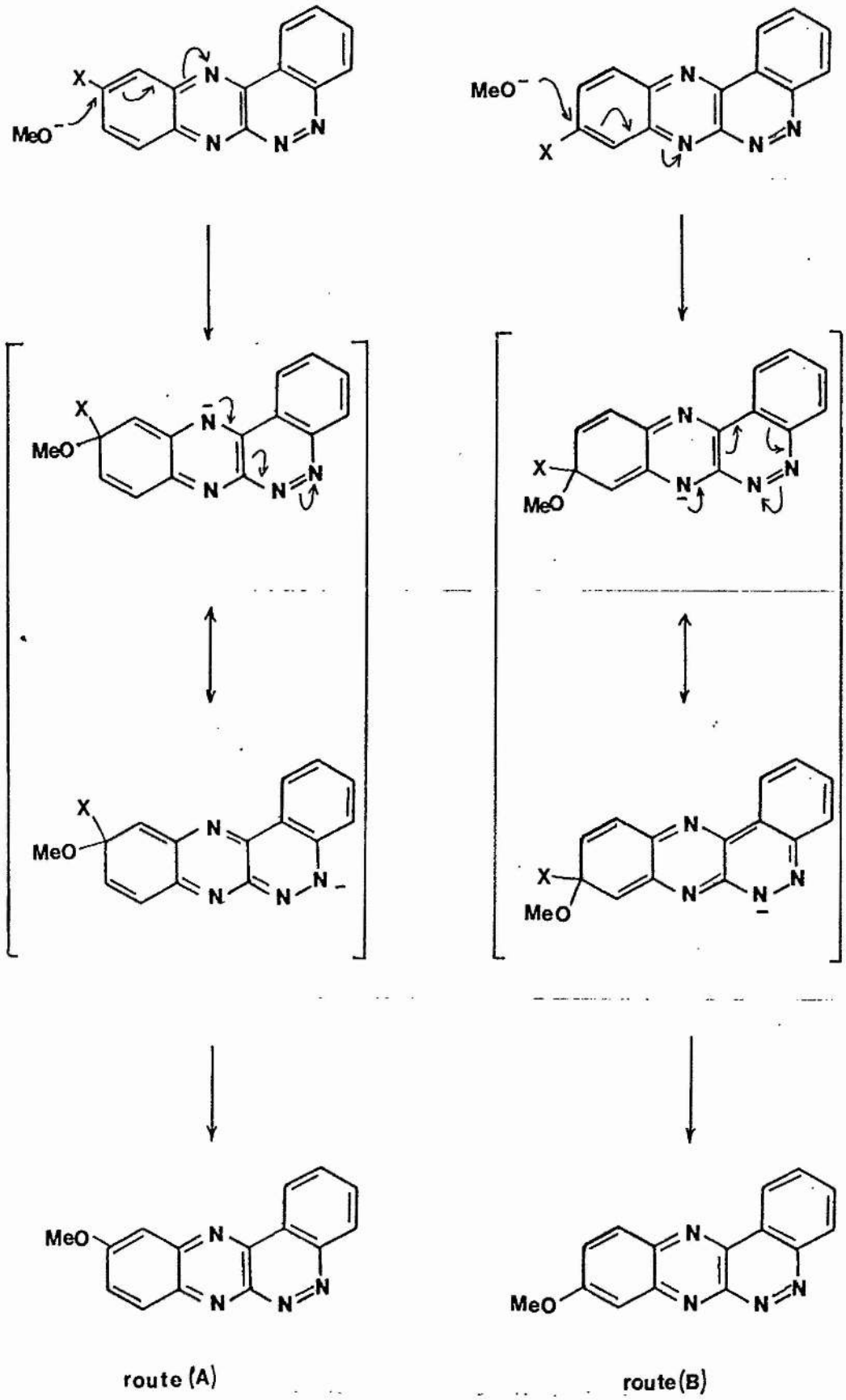


Figure 29

experiments are shown in Table 12.

These results show a number of interesting features:

(i) 10-chloroquinoxalino[2,3-c]cinnoline (42 b) underwent methoxy-dechlorination with relative ease (in high yield). Under similar conditions, 9-chloroquinoxalino[2,3-c]cinnoline (42 c) was unaffected, even after longer reaction time.

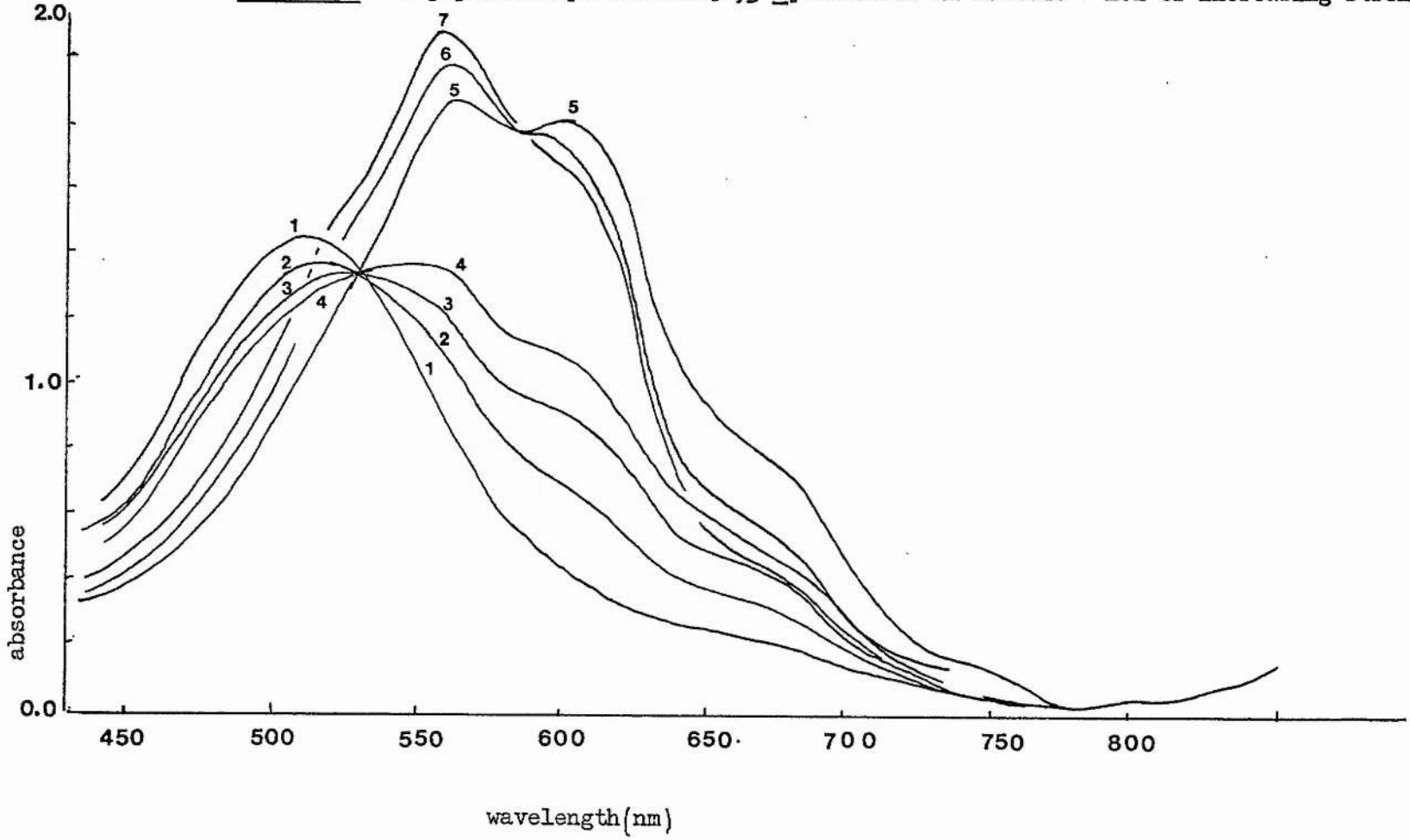
(ii) 10-Bromoquinoxalinocinnoline (42 k) showed only a very slight trace of bromine replacement, after 10 hours. 9-Bromo-quinoxalinocinnoline (42 l) was completely unaffected over the same reaction time.

(iii) When 9,10-dichloroquinoxalino[2,3-c]cinnoline (42 n) was reacted with sodium methoxide, one chlorine atom was replaced after one hour. Increasing reaction time, up to 10 hours, resulted in apparent replacement of the other chlorine atom with methoxide, presumably forming the 9,10-dimethoxyquinoxalinocinnoline (42 q). This compound was identified by its ^{1}H n.m.r. spectrum, which shows two sharp singlets (H-11 and H-8) at δ7.65 and δ7.78, and by its mass spectrum, with a molecular ion at m/e 292.

A mechanism for the dehalogenation process should take all the above features into account. A suggestion for the mechanism is shown in figure 29, showing attack by methoxide at both positions 9 and 10. The charged intermediates can be represented in more than one form. One of the intermediates in route A has a conjugated 10π system, while the other has a benzenoid like 6π system. In route B, one of the intermediates has a delocalised 10π system, while in the other the conjugation is extended, resulting in disruption of the 10π fragment.

Therefore, it may be considered that for attack of methoxide on 10- and 9—chloroquinoxalinocinnolines, route A (figure 29, X=Cl) gives the most stabilised intermediate. This would mean that replacement of chlorine at position 10 is easier than replacement of chlorine at position 9. The relative unreactivity of the bromo-derivatives is understandable, since it fits the observation that for S_N2 addition-elimination reactions of various heterocyclic and benzenoid aromatic compounds, the order of mobility of the leaving group is F>>Cl>Br>I, for anionic nucleophiles (where the nucleophilic centre is an element from the first row of the periodic table).[64] In the case of the 9,10-dichloroquinoxalinocinnoline, there is no obvious reason why the chlorine atom at position 9 should be replaceable upon formation of the 9-chloro-10-methoxy- derivative, although it is likely that in this case (as well as the others mentioned), the rates of the various processes that can occur will have a decisive effect on the outcome of the reaction.

Figure 30 10-piperidinoquinoxalino[2,3-c]cinnoline in acetone + HCl of increasing strength



2. The reactions of 10-chloroquinoxalino[2,3-c]cinnoline with nitrogen nucleophiles

A number of reactions were carried out on 10-chloroquinoxalino-[2,3-c]cinnoline in attempts to displace the chlorine atom with a nitrogen nucleophile. With piperidine, using the base as both solvent and reactant, the chlorine atom was replaced to yield the 10-piperidino derivative along with piperidine hydrochloride. The piperidino compound is bronze in colour, and like the hydrogen halide adducts mentioned in the previous chapter, was very insoluble in most solvents. In acetone, it formed a deep purple/red solution, the visible spectrum being shown in figure 3 0 The mass spectrum of this compound shows the breakdown pattern common to other quinoxalinocinnolines.

With diethylamine, using the base as solvent and reactant as above, no reaction took place. This is probably due to the temperature of the boiling solvent and reactant being too low for reaction to occur.

With benzylamine, again using the base as solvent and reactant at 100°C, a blue product was obtained. This solid was extremely insoluble in most solvents, but its mass spectrum indicates that it is a 1:1 adduct of benzylamine and 10-chloroquinoxalinocinnoline. This information, in conjunction with the observed colour indicates that the solid might have the structure represented below. When the reaction was repeated at boiling point of benzylamine (180°C),

10-chloroquinoxalino[2,3-c]cinnoline was recovered in high yield.

A possible reaction scheme for the reaction of piperidine with 10-chloroquinoxalino[2,3-c]cinnoline is shown in figure 31.

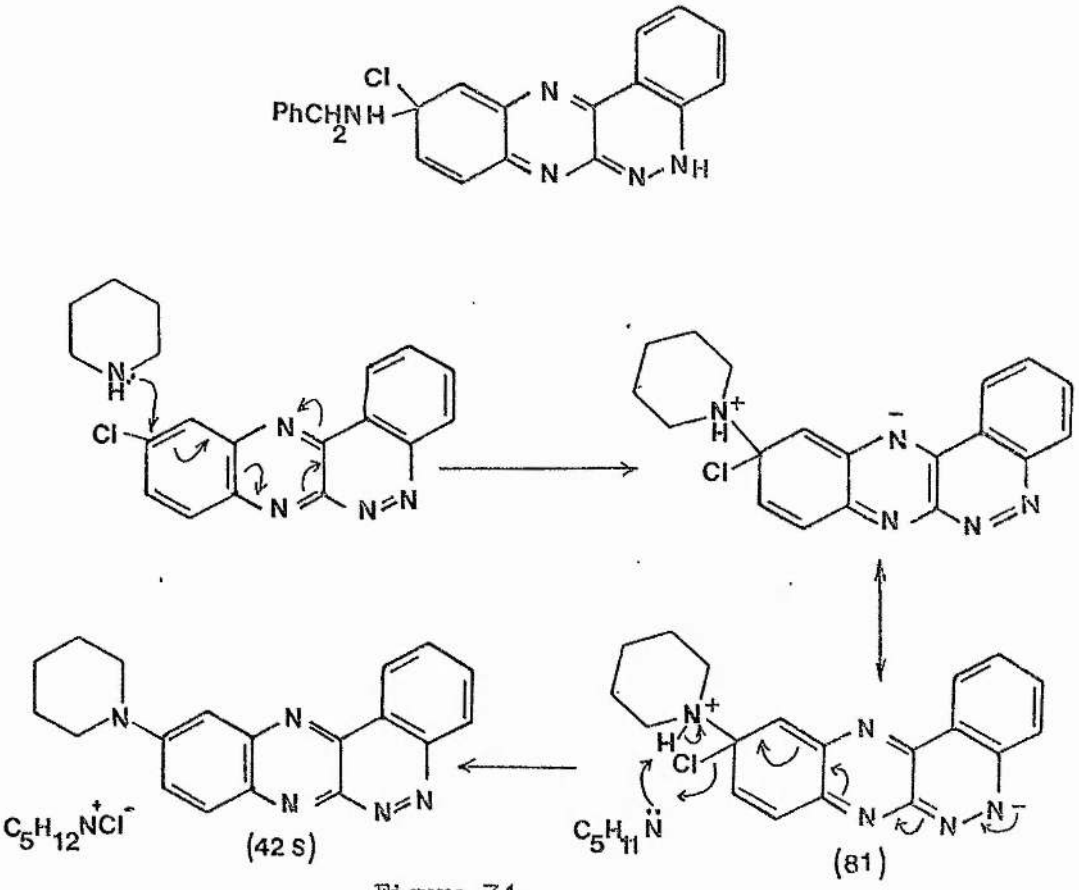
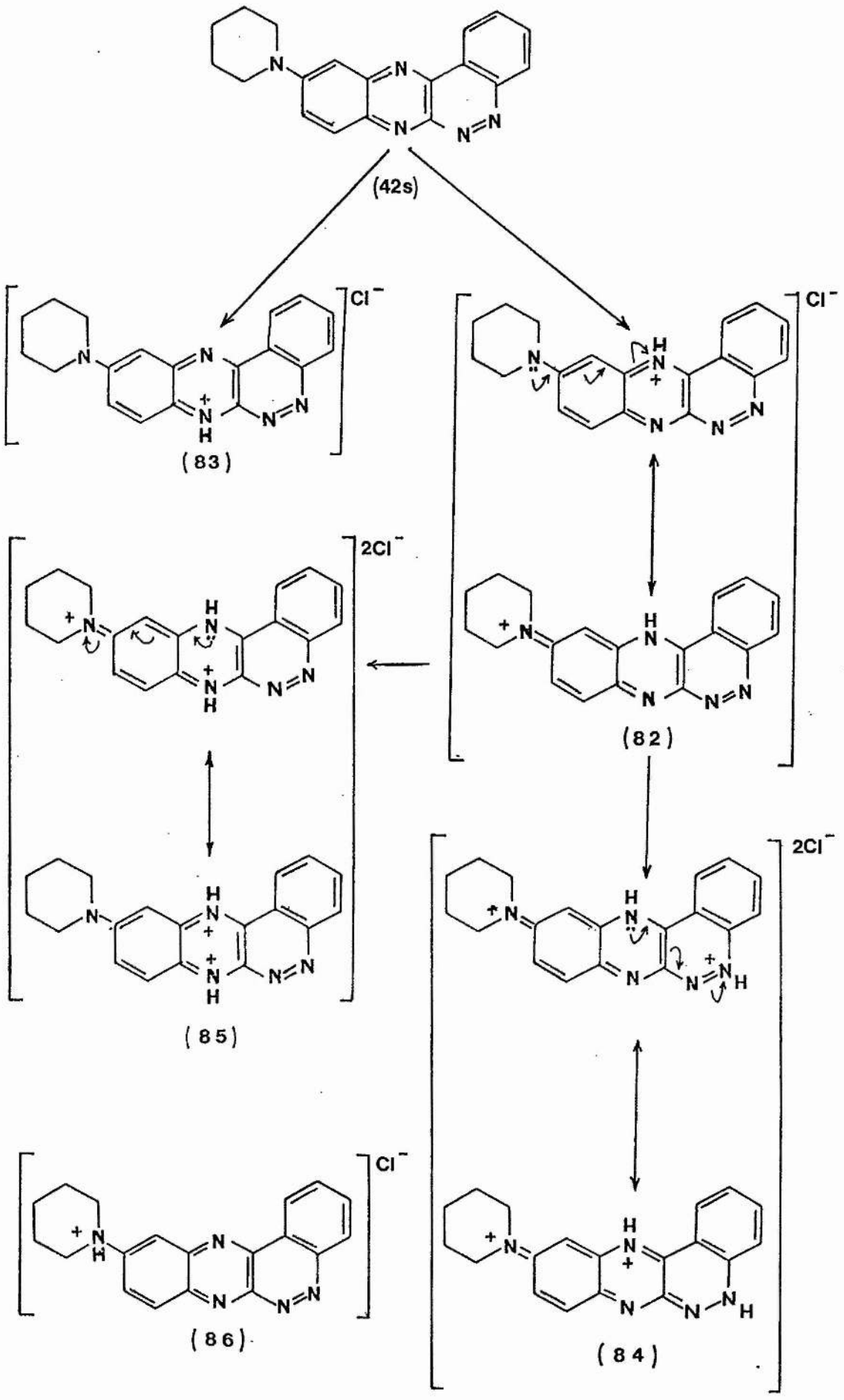


Figure 31

The formation of the blue compound with benzylamine may represent the above sequence being terminated at the equivalent of species (81) or its uncharged tautomer shown above.

This would be due to protonation of the intermediate rather than benzylamine to give the 1:1 adduct of 10-chloroquinoxalinocinnoline and benzylamine. Attempts to deprotonate the blue compound with dilute aqueous sodium hydroxide and concentrated sodium hydroxide were not successful.


(42s)
Cl⁻
(83)
Cl⁻
(82)
2Cl⁻
(85)
2Cl⁻
(84)
Cl⁻
(86)

The 10-piperidino compound (42 s) shows interesting acid/base behaviour. If a dilute solution in acetone is treated with increasingly concentrated acid, a series of colour changes are observed, from red/purple to blue, then to red/purple again. These changes can be followed spectrophotometrically, and the changes from 10-piperidinoquinoxalinocinnoline to a blue species, then to a purple/red species, occur through two series of isosbestic points. This is shown in figure 30. Since the changes occur with each profile passing through an isosbestic point, then they probably represent successive protonations of (42 s). First protonation at N-12 would allow extension of the conjugation, giving a species such as (82), whereas protonation at N-7 (83) would not permit further extension of the conjugation. The observation that the absorption maximum moves towards longer wavelengths (profiles 1 to 5) would therefore agree with protonation at N-12, rather than at N-7. Further protonation at N-5 would allow further extension of conjugation to give a species such as (84), while protonation at N-7 could possibly result in disruption of conjugation (85). Likewise, initial protonation on the piperidino nitrogen (86) would inhibit extension of conjugation. The second change observed (profiles 5 to 7) show a slight shift back to a shorter wavelength, but not to one as low as that of the unprotonated species (42 s). Therefore, it is possible that the successive formation of species (82) and (84) cause the changes in the position of absorption maxima observed. Indeed, structures (82) and (84) both contain para-quinonoid bond arrangements, and would be expected to absorb at longer wavelengths than (42 s) and (85), which both have ortho-quinonoid arrangements. This behaviour has some analogy in that

of the phenazine derivatives (the safranines) mentioned in the previous chapter.[51,52]

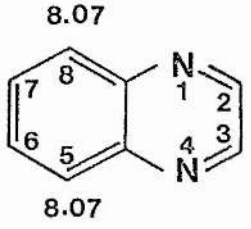
In conclusion, 10-chloro-substituted quinoxalinocinnolines are good substrates for methoxydechlorination reactions, and potentially also for nitrogen nucleophiles. Thus in conjunction with the various chlorination reactions possible at position 10 by gaseous hydrogen chloride, nucleophilic displacement reactions open up routes to compounds that would otherwise be difficult to make, or totally inaccessible.

CHAPTER 6

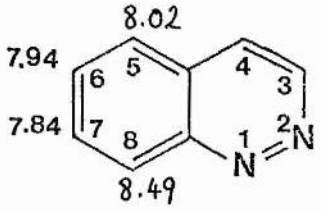
The ^{1}H n.m.r. spectra of quinoxalino[2,3-c]cinnoline and its derivatives

The ^{1}H n.m.r. spectra of quinoxalino[2,3-c]cinnoline and its derivatives

The 80 MHz ^{1}H n.m.r. spectrum of the parent quinoxalino[2,3-c]-cinnoline (42 a) shows two protons at low field, one at δ9.2-9.35 and one at δ8.85-9.05. Both signals are complex multiplets. These protons are considered to be protons 1 and 4 respectively. They come to resonance at lower field than the corresponding protons 5 and 8 in cinnoline (87)[65,66] and quinoxaline (88).[66] A similar effect is seen in the spectrum of 9-chloro-2,3-dimethylpyrazino[2,3-c]cinnoline (89),[67] where protons 10 and 7 come to resonance at δ 8.87 (meta-coupled doublet) and δ8.71 (ortho-coupled doublet).

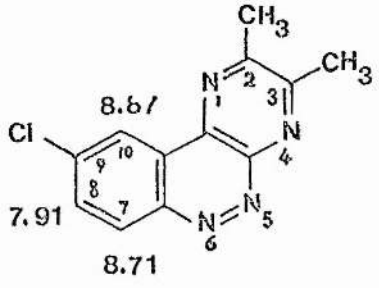


(88)



(87)

Figure 32



(89)

The spectrum of benzo[h]cinnoline (90)[68] shows proton 10 to be furthest downfield (corresponding to proton 1 in (42 a). Similar effects are seen in the spectra of benzo[h]quinoline (91),

benz[a]acridine (92) and naphtho[2,1-h]quinoline (93).[69]

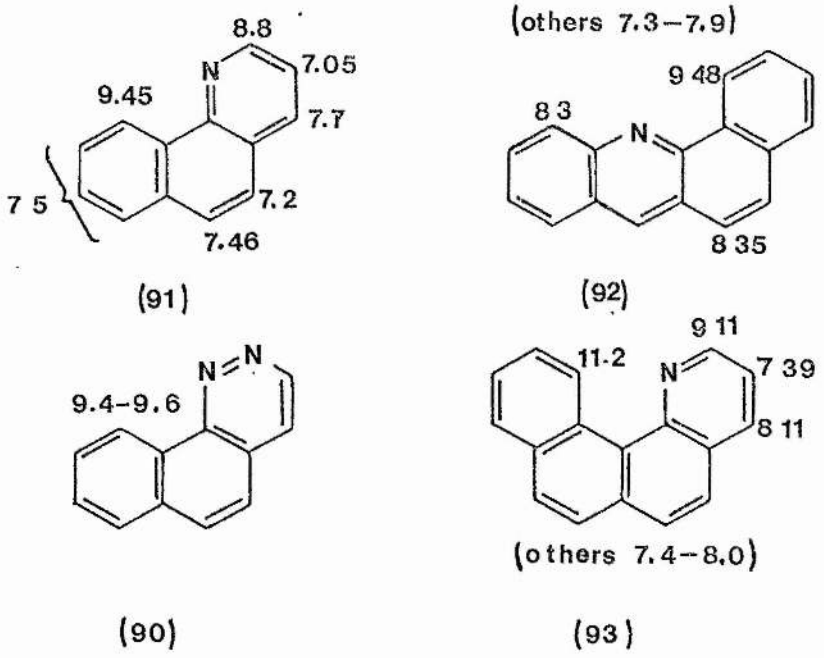


Figure 33

The cause of this is probably a deshielding effect on the protons concerned by the lone pair of electrons on the nearby nitrogen atoms (N-2 in (90), N-12 in (42 a) etc.). Indeed the effect is most pronounced in (93) where the steric arrangement required for such interaction is particularly favourable. The case of quinoxalinocinnoline (42 a) is illustrated in figure 34.

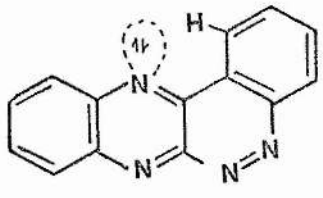


Figure 34

Protons 2 and 3 in quinoxalino[2,3-c]cinnoline (42 a) come to

Positions of protons in the ^1H n.m.r. spectra of quinoxalino[2,3-c]cinnolines

Figure 35(a)

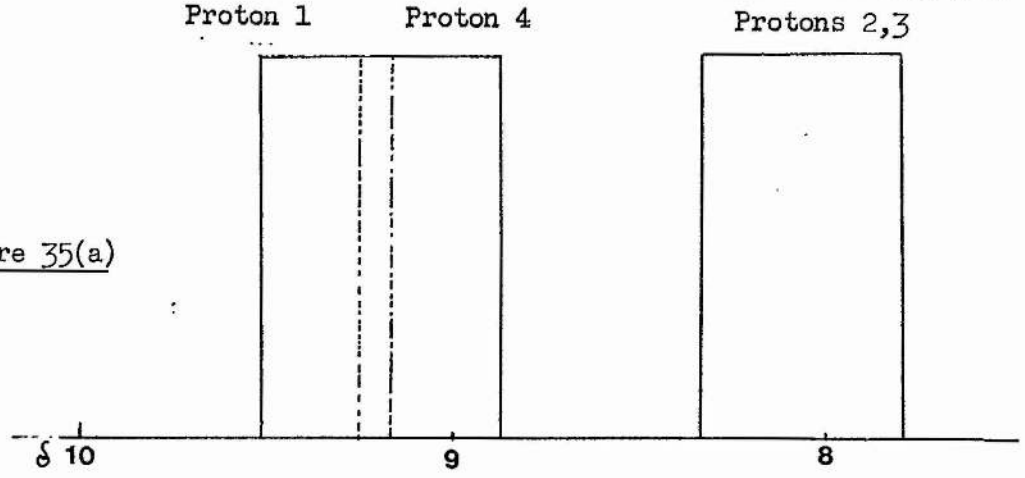


Figure 35(b)

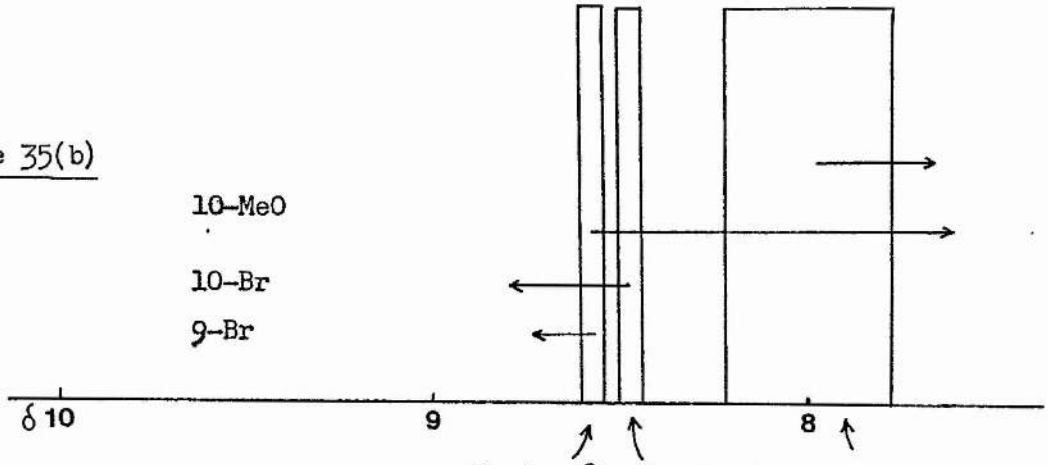
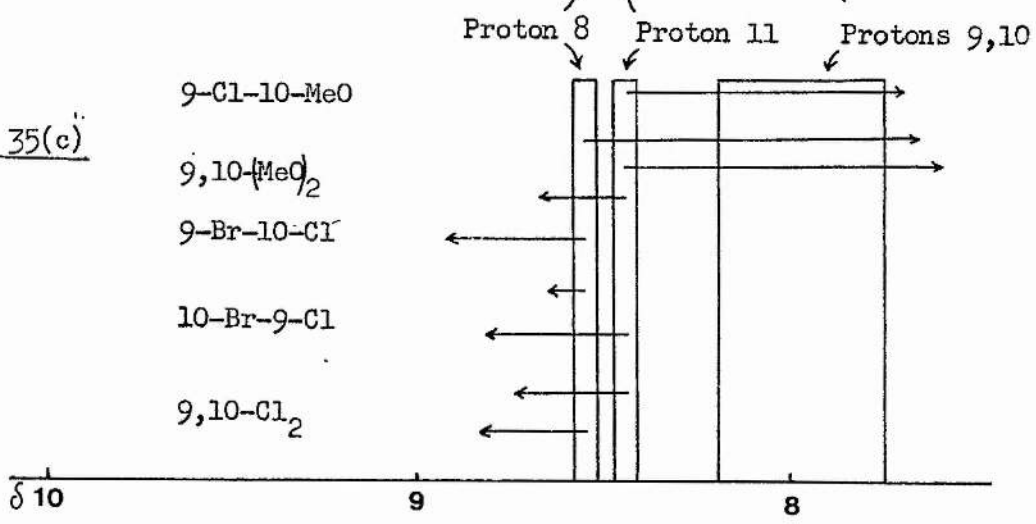


Figure 35(c)



resonance at δ7.92-8.25, compared to protons 6 and 7 in cinnoline which resonate at δ7.89 and δ7.94 respectively. Similarly, proton 8 of (89) has a chemical shift of δ7.91. Protons 8 and 11 come to resonance in (42 a) at δ8.32-8.7, compared to δ8.07 for H-5 and H-8 in cinnoline. Protons 7 and 10 in (42 a) resonate at δ7.92-8.25.

When the parent ring system is substituted, assignment of protons in the ^{1}H n.m.r. spectrum is simplified, since for substitution at positions 9 and/or 10 the quinoxaline-derived protons give a first order spectrum, while the same is also true for the cinnoline-derived protons in 2-substituted compounds.

By comparison of the compounds listed in table 13, it can be seen that in all cases proton 1 falls into the range δ9.14-9.48, proton 4 in the range δ8.83-9.15, and protons 2 and 3 in the range δ7.92-8.32 (shown diagramatically in figure 35(a)). Indeed, the chemical shift differences between signal groups H-1, H-4 and H-(2,3) are always approximately the same throughout the series.

A similar trend is apparent for protons in the quinoxaline portion of the structure, which is generally substituted. Thus in most cases of monosubstitution in the quinoxaline portion, proton 8 resonates at approximately δ 8.5, proton 11 at approximately δ8.4, and protons 9 and 10 come to resonance in the range δ7.88-8.2. This is shown in figure 35(b).

There are three exceptions to the above trends, involving shifts away from the general positions. In 9-bromoquinoxalinocinnoline

Compound	Substituent	H - 1	H - 2	H - 3	H - 4	H - 8	H - 9	H - 10	H - 11	Others	J (Hz)
42(a)‡	unsubstituted	9.2-9.35(m)	7.92-8.25(m) (with H-9,10)		8.85-9.05(m)	8.32-8.7(m)	7.92-8.25(m) (with H-2,3)		8.32-8.7(m)	-	-
42(b)‡	10-Cl-	9.14-9.28(m)	8.05-8.2(m)		8.83-9.0(m)	8.52(dd)	7.88(dd)	-	8.42(dd)	-	(8,9),9.2;(8.11),0.5; (9,11),2.4.
42(c)‡	9-Cl-	9.24-9,36(m)	8.25-8.5(m)		8.92-9.12(m)	8.55(dd)	-	8.06(dd)	8.41(dd)	-	(8.10),2.4;(10,11),9.2; (11,8),0.5.
42(g)‡	2-Cl-	9.26(d)	-	8.07(dd)	8.87(d)	8.41-8.62(m)	8.02-8.17(m)		8.41-8.62(m)	-	(3,4),8.6;(1,3),2.2
42(d)‡	2,10-Cl_2	9.22(d)	-	8.10(d)	8.9(d)	8.5(d)	8.0(dd)	-	8.45(dd)	-	(3,4),8.6;(1,3),2.2; (8,9),9.2;(8,11),0.5; (9,11),2.4.
42(f)‡	10-OCH_3	9.23(m)	8.13-8.25(m)		8.95-9.07(m)	8.5(dd)	7.74(dd)	-	7.64	4.14 (-OCH_3)	(8,9),8.8;(8.11),1.2; (9,11),2.8.
42(k)‡	10-Br	9.27-9.45	8.2-8.32(m)		8.99-9.17(m)	8.52(dd)	8.15(dd)	-	8.72(dd)	-	(9,11),2;(8,9),9.2; (8,11),0.6.
42(l)‡	9-Br	9.48-9.35(m)	8.12-8.32(m)		9.02-9.15(m)	8.75(dd)	-	8.22(dd)	8.44(dd)	-	(10,11),9.2;(8,10),2; (8,11),0.6.
42(h)‡	8,10-Cl_2	9.35-9.5(m)	8.22-8.4(m)		9.05-9.22(m)	-	8.26(d)	-	8.53(d)	-	(9,11),2.6.
42(m)‡	9-Cl-10-MeO	9.15-9.3(m)	8.06-8.21 (m)		8.87-9.00(m)	8.57	-	-	7.67	4.27 (-OCH_3)	-
42(n)‡	9,10-Cl_2	9.32-9.41(m)	8.18-8.31(m)		8.96-9.11(m)	8.80	-	-	8.67	-	(8.11),0.6.
42(o)‡	10-Br-9-Cl	a) 9.2-9.37(m) b) 9.26-9.41(m)	8.1-8.25(m) 8.19-8.34(m)		8.91-9.05(m) 9-9.12(m)	8.81 8.9	- -	- -	8.68 8.77	- -	- -
42(q)‡	9,10-$(MeO)_2$	9.25-9.4(m)	8.08-8.26(m)		8.92-9.1(m)	7.78	-	-	7.65	4.22, 4.26 (-OCH_3)	-
42(p)‡	9-Br-10-Cl-	9.19-9.35(m)	8.08-8.23(m)		8.9-9.07(m)	8.92	-	-	8.6	-	(8,11),0.6

Table 13 'H n.m.r. spectra of quinoxalino [2,3-c] cinnolines

‡V. dilute solution in $CDCl_3$ a) From (42 k) with HCl b) From (42 c) with HBr

(42 l) proton 8 is shifted downfield by δ0.2; in the 10-bromo- derivative (42 k) proton 11 is shifted downfield by about δ0.3; while in the 10-methoxy- derivative (42 f), proton 11 is shifted upfield by about δ0.75 and proton 9 is shifted upfield by about δ0.2-0.25 (figure 35(b)).

A substituent can affect the chemical shift of ortho-protons in a number of ways. There are diamagnetic anisotropy, electric field, inductive and mesomeric effects. To a first approximation these effects are constant for a given substituent, except for mesomeric interactions which are dependent on the distance between, and configurations of, the substituent and ortho-protons. Mesomeric effects are directly related to the bond orders within the compound.

$$(\Delta\delta)_a X_b = n_x J_{ab} + t_x$$

The change in chemical shift $\Delta\delta$ of aromatic ring protons at ring position a due to substituent X at the ortho position b, is linearly proportional to the ortho-coupling constant J_{ab} between the protons in these positions in the corresponding unsubstituted compounds.

Here n_x and t_x are constants for each substituent x; n_x is a measure of the mesomeric effect of substituents, while t_x is a measure of inductive, direct field and magnetic anisotropy effects. J_{ab} is related to the bond order of the bonds in question.[70]

Chemical shift changes of ortho-protons for a variety of

substituents in quinoxaline derivatives are known.[71] For 6-methoxyquinoxaline the changes are - 0.71 for H-5 and - 0.41 for H-7. The deviation in H-11 in 10-methoxyquinoxalinocinnoline is - 0.75, and for H-9 between - 0.2 and - 0.25, which compare favourably with the shifts in the methoxyquinoxaline.

In the case of bromo-compounds a very slight downfield shift might be expected, but not of the magnitude observed in 9- and 10-bromoquinoxalino[2,3-c]cinnolines.

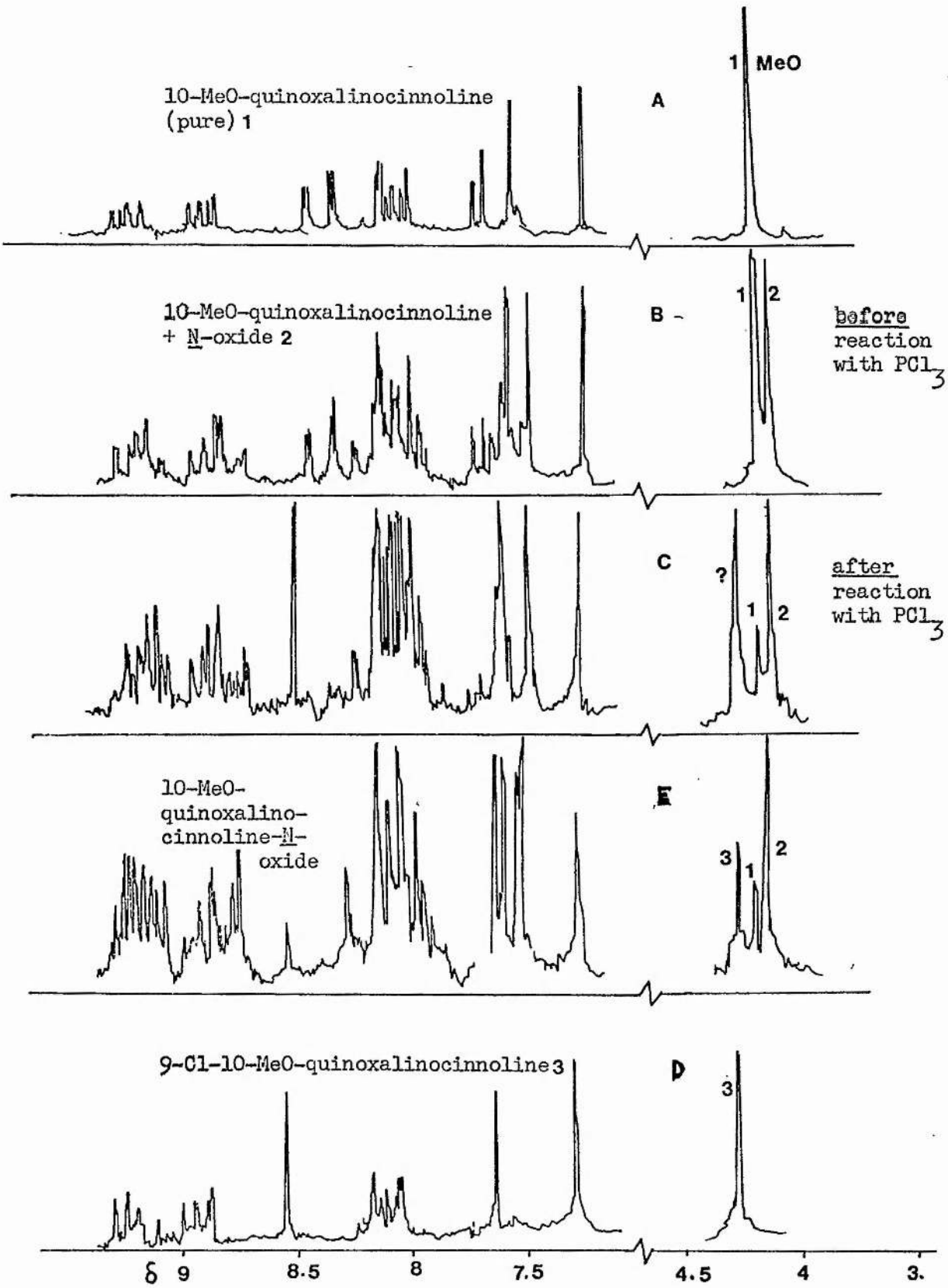
9,10-Disubstituted quinoxalino[2,3-c]cinnolines

The effects observed in the mono substituted derivatives with respect to chemical shift changes are also observed in the disubstituted derivatives. Introduction of an extra chlorine atom in the 9,10-dichloro derivative (42 n) is not considered to alter the relative order of the chemical shifts of protons 8 and 11, but both are shifted downfield by about 0.25. In the 9,10-dimethoxy derivative (42 q), an upfield shift due to the adjacent methoxy groups is observed for both protons 8 and 11. Again it is thought that the order of the protons is unaltered.

In the 9-chloro-10-methoxy derivative (42 m), proton 8 is unaffected, proton 11 being shifted upfield due to the adjacent methoxy group. In the 10-bromo-9-chloro derivative (42 o) a reversal in the order of the protons is observed. Proton 8 is shifted downfield by about 0.15, and proton 10 is shifted downfield by about 0.4 due to the adjacent bromine atom. In the 9-bromo-10-chloro

derivative (42 p) proton 11 is shifted downfield by about 0.2, and proton 8 is shifted downfield by about 0.35. The 9,10-disubstituted compounds are represented in figure 35(c).

The observed shielding of ortho-protons in the bromo-derivatives would appear to be somewhat unusual, since standard texts on n.m.r. spectroscopy give the substituent effect of bromine on ortho-protons in substituted benzenes, as being zero[72] or up to +0.2[73,74], while some of the shifts observed in the bromoquinoxalinocinnolines between +0.35 and +0.4. The cause of the shifts is perhaps due to the steric interaction of the relatively bulky bromine atom pushing the adjacent ortho-protons out of the plane of the molecule, and into a more deshielded region of the magnetic anisotropic zones created by the ring current in the ring system.



80 MHz ^{1}H n.m.r. spectra of 10-MeO-quinoxalinocinnoline its 5-oxide, and 9-Cl-10-MeO-quinoxalinocinnoline, along with mixtures of all three.

Figure 11

The ^{1}H n.m.r. spectrum of 10-methoxyquinoxalino-[2,3-c]cinnoline-5-oxide

It will be recalled from the end of chapter 3, that the ^{1}H n.m.r. spectrum of a mixture of 10-methoxyquinoxalinocinnoline (42 k) and its 5-oxide (60 k) obtained from the cyanide-induced cyclisation of the 5-methoxy-acetamido-anil (55 k) clearly shows the presence of two different methoxy-groups [figure 11(B)]. When the mixture was treated with phosphorus trichloride, the ^{1}H n.m.r. of the product showed three methoxy signals [figure 11(C)], the signal due to the 10-methoxyquinoxalinocinnoline being reduced in intensity, along with the concurrent appearance of a signal due to the 10-methoxy-9-chloro-derivative, while that due to the 5-oxide remained unchanged. In chapter 4, a method was described whereby a mixture of a quinoxalinocinnoline and its N-oxide could be separated, involving the reaction of the quinoxalinocinnoline with gaseous hydrogen chloride, leaving the N-oxide unchanged. In particular, this method was used to separate the mixture of methoxy compounds, with the result that the ^{1}H n.m.r. spectrum of the N-oxide was obtained. This is shown in the accompanying figure 11(D), along with the previously mentioned spectra. Also included is a spectrum of 10-methoxyquinoxalinocinnoline (figure 11(A)), and the 10-methoxy-9-chloro derivative (figure 11(D)). The spectrum of the N-oxide shows small amounts of both the above mentioned compounds but these are present in insufficient concentration to mask the spectrum of the N-oxide.

The general appearence of the spectrum is similar to that of 10-methoxyquinoxalinocinnoline. This would tend to indicate that there is a strong structural resemblance between the two compounds. The order of protons arising from the quinoxaline portion of the molecule appears to be unchanged, though upfield shifts are apparent, being greatest for proton 8 at about 0.2 p.p.m., while protons 9 and 11 are shifted by about 0.1 p.p.m. Similarly, there is a spreading out of the multiplet due to protons 2 and 3, indicating a possible slight upfield shift for at least one of them. The positions of the low-field protons 1 and 4 appear to be relatively unchanged, though it is possible that the order of the protons has been reversed, with an upfield shift for proton 1 and a downfield shift for proton 4. Anisotropic deshielding of the protons at position 8 peri to the nitrogen-oxygen bond in cinnoline-1-oxides has been observed in their spectra, though the magnitude of such shifts is variable (0.35 p.p.m. for 4-methylcinnoline-1-oxide in $CDCl_3$, and 0.06 p.p.m. for cinnoline-1-oxide in $CDCl_3$).[43,44,45] Therefore, it is possible that such an effect might occur with respect to the proton peri to the nitrogen-oxygen bond in quinoxalino[2,3-c]cinnoline-5-oxides, namely proton 4.

CHAPTER 7

The mass spectra of quinoxalino[2,3-c]cinnoline and its derivatives

The mass spectra of quinoxalino[2,3-c]cinnoline and its derivatives

The mass spectra of quinoxalino[2,3-c]cinnoline and its derivatives show a number of features that appear to be common to all, and these will be discussed in terms of a generalised fragmentation pathway, with specific examples used to illustrate particular features observed in the spectra. Meta-stable peaks were not observed in any of the spectra, and accurate masses were not recorded. Therefore, while certain processes were observed, the exact nature of the fragments produced, and mechanism of the fragmentation processes themselves, are open to conjecture. Where a fragment is represented as having a particular structure, this is shown only as a possibility, and no claim is made towards the exact identity of the fragment in question. Despite these limitations, a distinctive fragmentation process is observed which is considered to be characteristic of quinoxalino[2,3-c]cinnolines in general.

The major fragmentation process observed in virtually all spectra is the loss of 28 mass units from the molecular ions, corresponding to the loss of nitrogen. This fragmentation is a common feature in the mass spectra of many heterocyclic diaza compounds, such as cinnoline[75] and benzo[c]cinnoline.[76] In compounds such as these (including quinoxalinocinnolines), the diaza group is either 'sandwiched' between two aromatic ring systems, or as in the case of cinnoline, one end of the diaza group is directly bonded to an aromatic ring. In heterocyclic compounds such as phthalazine,[77] neither side is directly

bonded to a ring system, and loss of hydrogen cyanide, another common feature in the mass spectra of heterocyclic nitrogen compounds is the primary fragmentation process. Loss of nitrogen from quinoxalinocinnolines is represented in figure 36.

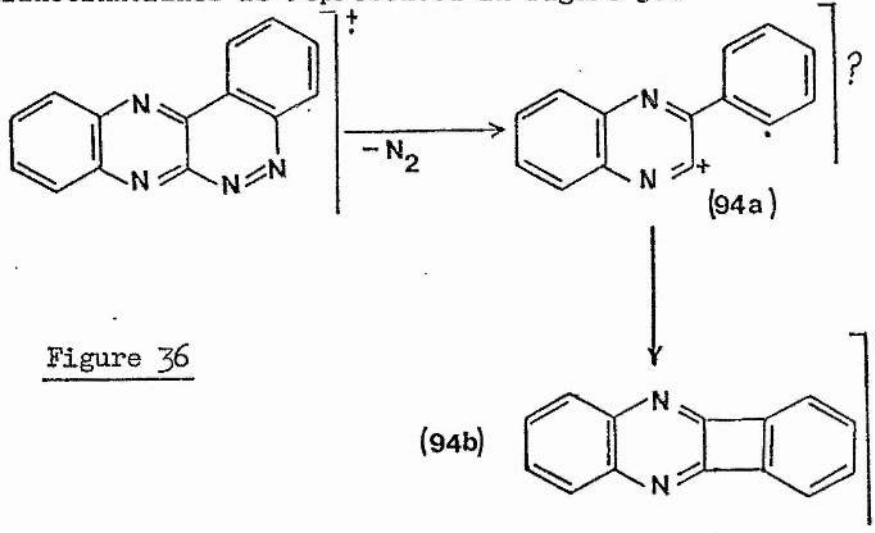
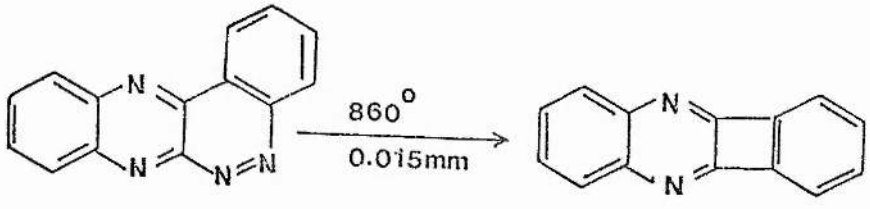


Figure 36

The structure of the fragment corresponding to loss of nitrogen (at m/e 204 in the spectrum of (42 a)) is represented either by the open form (94 a), or the closed form (94 b). Thermal extrusion of nitrogen from a number of structurally related heterocycles, including quinoxalinocinnoline (42 a) itself, has been found to result in the formation of compounds with biphenylene structures similar to (94 b).[78,32]



Though direct comparison of mass spectral processes with thermal processes is not always valid, if the neutral molecule corresponding to an intense fragment ion in the mass spectrum is stable at pyrolytic

Substituents	1	2	3	4	5	6	7	
none	$C_{14}H_8N_4]^{\ddagger}$ 232(100)	$C_{14}H_8N_2]^{\ddagger}$ 204(98)	$C_{13}H_7N]^{\ddagger}$ 177(26)	$C_8H_4N_2]^{\ddagger}$ 128(12)	$C_6H_4]^{\ddagger}$ 76(100)	$C_8H_6]^{\ddagger}$ 102(31)	$C_6H_4]^{\ddagger}$ 76(100)	$C_4H_2]^{\ddagger}$ 50(74)
10-Cl	$C_{14}H_7N_4Cl]^{\ddagger}$ 266/268(100/33)	$C_{14}H_7N_2Cl]^{\ddagger}$ 238/240(98/33) $C_{14}H_7N_2]^{+}$ 203(44)	$C_{13}H_6NCl]^{\ddagger}$ 211/213(9/3) $C_{13}H_6N]^{+}$ 176(17)	-	$C_6H_3Cl]^{\ddagger}$ 110/112(99/33) $C_6H_3]^{+}$ 75(30)	$C_8H_6]^{\ddagger}$ 102(50)	$C_6H_4]^{\ddagger}$ 76(44) $C_6H_3]^{+}$ 75 (88)	$C_4H_2]^{\ddagger}$ 50(44)
9-Cl	266/268(100/33)	238/240 (83/27) 203(98)	211/213(17/15) 176(23)	128(13)	110/112(98/33) 75(95)	102(32)	76(47) 75(95)	-
10-Br	$C_{14}H_7N_4Br]^{\ddagger}$ 310/312(70/72)	$C_{14}H_7N_2Br]^{\ddagger}$ 282/284(65/65) 203(30)	176(20)	128(12)	$C_6H_3Br]^{\ddagger}$ 154/156(3/3) $C_6H_2Br]^{+}$ 75(30) $C_6H_2]^{\ddagger}$ 74(8)	102(60)	76(10) 75(30)	-
9-Br	310/312(20/20)	282/284(60/60)	$C_{13}H_6NBr]^{\ddagger}$ 255/257(5/5) 176(40)	128(60)	153/155(60/60) 75(98)	102(70) $C_8H_5]^{+}$ 101(96)	76(98)	50(100) 51(100)
2,10-Cl_2	$C_{14}H_6N_4Cl_2]^{\ddagger}$ 300/302/304(63/44/7)	$C_{14}H_6N_2Cl_2]^{\ddagger}$ 272/274/276(63/44/7) $C_{14}H_6N_2Cl]^{+}$ 237/239(18/6) $C_{14}H_6N_2]^{\ddagger}$ 202(18)	$C_{13}H_5N]^{\ddagger}$ 175(2)	$C_8H_3N_2Cl]^{\ddagger}$ 162/164(37/12)	110/112(100/33)	$C_8H_5Cl]^{\ddagger}$ 136/138(18/8) $C_8H_5]^{+}$ 101(20) $C_8H_4]^{\ddagger}$ 100(13)	$C_6H_3Cl]^{\ddagger}$ 110/112(100/33)	
8,10-Cl_2	300/302/304(31/18/4)	272/274/276(73/40/4) 202(36)	-	-	$C_6H_2Cl_2]^{\ddagger}$ 144/146/148(73/42/5)	102(18) 101(18)	-	
9-Br-10-Cl	$C_{14}H_6N_4ClBr^{+}$ 344/346/348(24/34/6)	$C_{14}H_6N_2ClBr]^{\ddagger}$ 316/318/320(28/39/7) $C_{14}H_6N_2Cl]^{+}$ 237/239(12/3) $C_{14}H_6N_2]^{\ddagger}$ 202(26)	-	128(16)	$C_6H_2ClBr]^{\ddagger}$ 188/190/192(36/44/8)	102(16) 101(18)	-	
10-Br-9-Cl	344/346/348(35/50/17)	316/318/320(33/49/12) 237/239(18/7) 202(18)			188/190/192(29/36/9) 109/111(60/30)			

Mass spectral fragmentation of quinoxalino [2,3-c] cinnoline and some of its derivatives

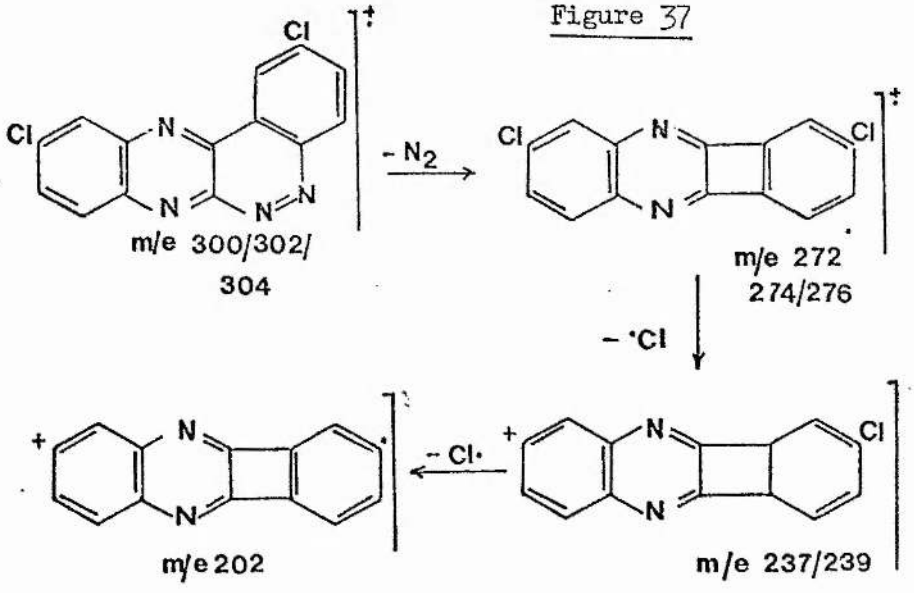
Table 14

temperatures, then the fragment is likely to have the same structure,[79] otherwise further reaction would occur.[80,81] Therefore, it is quite possible that the fragment observed at m/e 204 in the spectum of (42 a), and the corresponding fragments of its derivatives, actually has the structure (94 b) (table 14 , column 2)

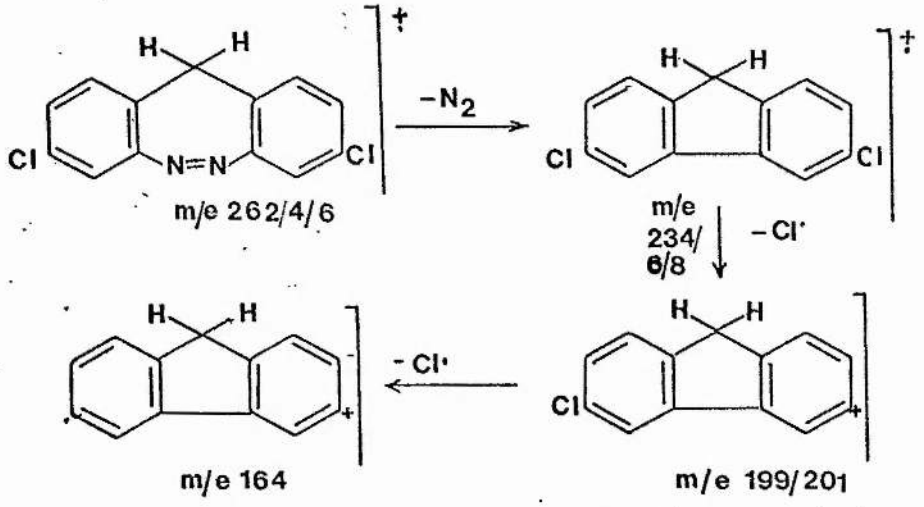
The remaining fragmentation processes observed in the spectra appear to derive from further breakdown of fragments (94 b). The fragmentation of (94 b) produces three groups of fragmentation products:

i) A group of fragments probably having a similar structure to (94 b) is formed by processes involving loss of all, or part of, the substituents in substituted derivatives of (42). In particular, in the spectra of the halogenated derivatives, loss of halogen atoms is observed in mono halogeno compounds, while in di-halogeno derivatives, successive loss of two halogen atoms is observed. These processes produce fragments of m/e 203 or 202 (table 14 , column 2). For example, the mass spectrum of the 2,10-dichloro-derivative (42 d) shows loss of two chlorine atoms following the loss of nitrogen. (figure 37).

Figure 37



The successive loss of two atoms from molecular ions or fragment ions is not an energetically favoured process. However, successive loss of halogen atoms (especially chlorine) is fairly common. For example, successive loss of chlorine atoms has been seen in the mass spectrum of 11H-dibenzo[c,f][1,2]-diazepines.[82]



The other fragmentation processes of (94 b) result in the formation of a group of breakdown products derived from the quinoxaline portion of the structure of the quinoxalinocinnoline(group (ii)), and a group derived from the cinnoline portion of the quinoxalinocinnoline (group (iii)):

ii) This group is characterised by the appearance of C_6 fragments that show the presence of the substituents in the quinoxaline portion of the molecule. Loss of the substituents is observed (for example loss of halogen atoms), resulting in formation of other C_6 fragments at m/e 76,75 and 74, which in turn can give rise to smaller fragments (table 14, columns 5 and 7).

iii) This group is characterised by the the appearance of fragments at m/e 102, thought to have the general formula $C_8H_6^{+\cdot}$ (or in the case of 2,10-dichloroquinoxalinocinnoline (42 d), $C_8H_5Cl^{+\cdot}$ at m/e 136/138 and $C_8H_5^+$ at m/e 101) (table 14, column 6).

A fragment at m/e 102 is observed in the mass spectrum of cinnoline,[75] shown in figure 38.

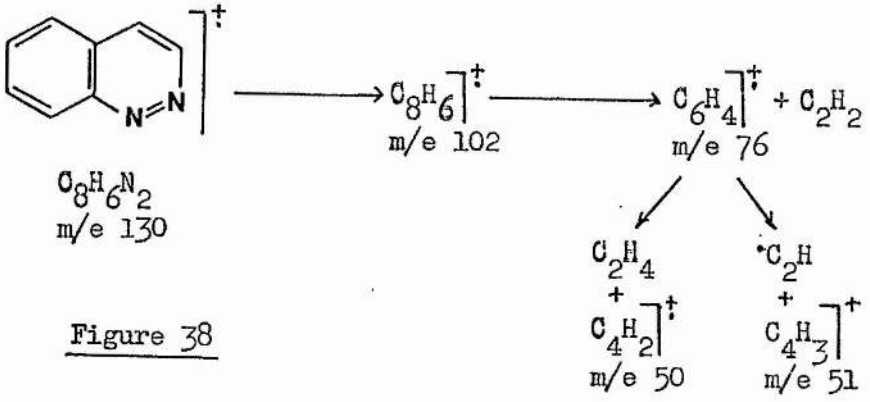
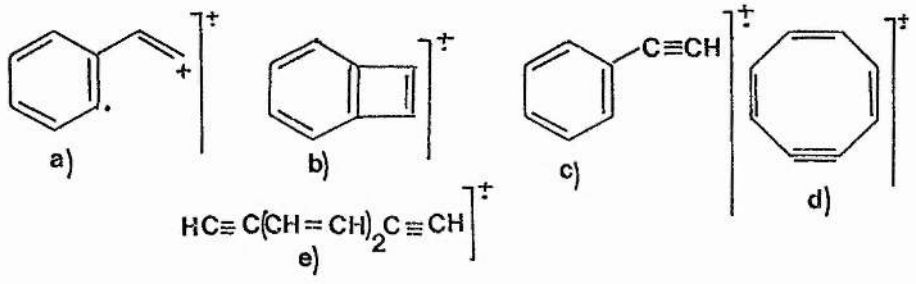


Figure 38

A number of structures have been proposed for the fragment at m/e 102 in the mass spectrum of cinnoline, the most likely being d) shown below.[75]

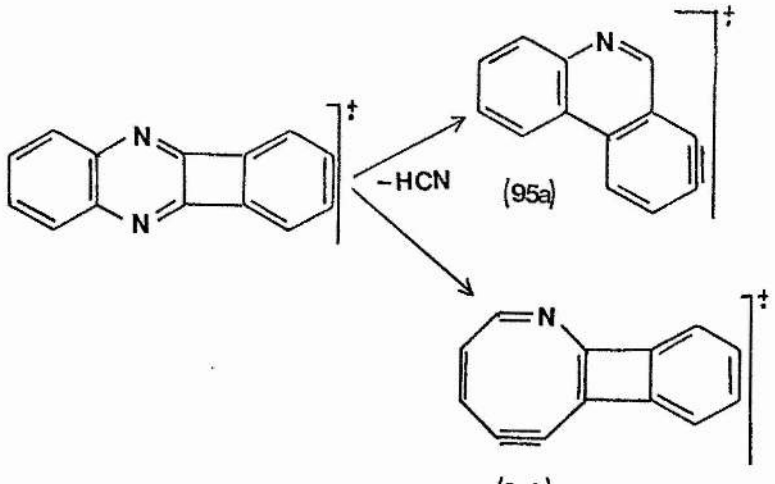


It is likely that the fragments observed at m/e 102 in the spectra of the quinoxalinocinnolines have similar structures to that proposed for the fragment at m/e 102 in cinnoline. Indeed, the

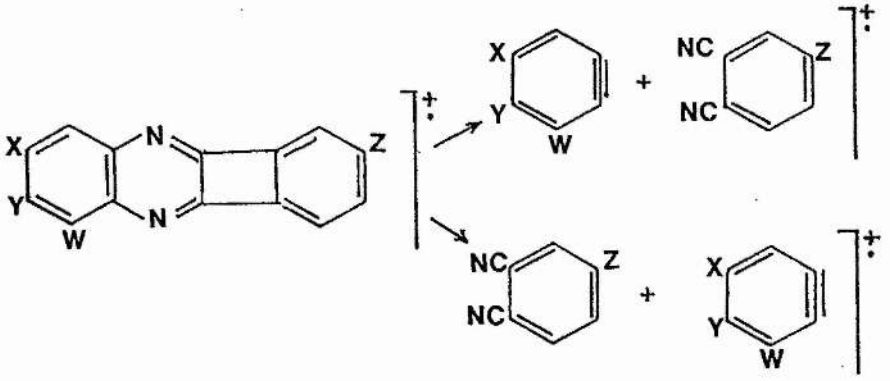
fragmentation of m/e 102 to give C_6 and C_4 fragments as shown above for cinnoline is also seen in the spectra of some of the quinoxalinocinnolines (table 14, column 7).

The exact route by which (94 b) breaks down to give the above products is not exactly clear. However, the appearance in the mass spectra of a number of other fragments gives some indication to the processes occurring.

Fragments are observed corresponding to loss of hydrogen cyanide from (94 b). In the parent compound this is observed at m/e 177, while in the case of the mono-halogeno compounds, the halogeno-fragment is often seen, along with the corresponding fragment due to loss of a halogen atom (m/e 176). The dihalogeno-compounds show no fragments of this type with substituents, but do show the fragments at m/e 175 in a few cases, probably corresponding to loss of hydrogen cyanide <u>after</u> loss of the halogen atoms from (94 b) (table 14, column 3). The nature of these fragments is unclear, but possibilities are shown below. Of the two structures shown, (95 a) is perhaps the most likely, and could also be a possible source of fragments at m/e 102.



The appearance of fragments at m/e 128 in a number of quinoxalinocinnolines implies the splitting of (94 b) into a C_6 fragment and a C_8N_2 fragment. This is represented below.



This type of fragmentation would give the C_6 fragments previously mentioned (table 14, column 5), and also the fragments at m/e 128. In addition, a fragment at m/e 162/164 is seen in the spectrum of 2,10-dichloroquinoxalinocinnoline, which corresponds to the mono-halogenated C_8N_2 fragment derived from the cinnoline portion of the quinoxalinocinnoline.

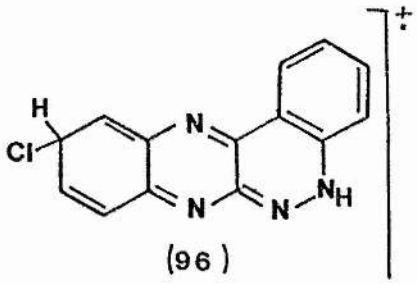
Finally, there are a few exceptions to the general fragmentation patten mentioned. These involve methoxy- and piperidino-quinoxalinocinnolines. The mass spectrum of the latter compound, the 10-piperidinoquinoxalinocinnoline is very similar, with the exception that loss of piperidine or a piperidino radical is observed to occur before as well as after loss of nitrogen. The rest of the fragmentation is as described.

The greatest difference is seen in the spectra of the methoxyquinoxalinocinnolines. In the spectra of these compounds, the first fragmentation process observed is loss of nitrogen as before. However, subsequent fragmentation is different, in that the processes observed involve the methoxy substituent directly. Rather than being lost in total as a radical species (as in the case of halogeno-compounds), the methoxy substituent fragments with loss of a methyl radical, followed by loss of carbon monoxide. This latter process involves formation of a C_{13} fragment, rather than the C_{14} fragments seen in the spectra of the other derivatives. Subsequent fragmentation is similar to that observed in the rest of the series, except where methoxide is again involved. In the 9-chloro-10-methoxy derivative, fragmentation involving the methoxy substituent appears to occur before loss of the chlorine. In the dimethoxy derivative, only one of the methoxy substituents is itself involved in the fragmentation process; the other appears to remain, even in smaller fragments.

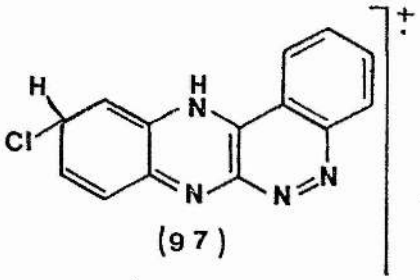
Mass spectra of the adducts formed between quinoxalino[2,3-c]cinnolines and hydrogen halides

The mass spectra of all adducts show molecular ions corresponding to a 1:1 adduct of the respective quinoxalino[2,3-c]cinnoline and hydrogen halide. The molecular ion of the adduct of quinoxalinocinnoline (42a) and hydrogen chloride shows a major fragmentation involving the loss of 30 mass units. The resultant fragment at m/e 238/240 then undergoes loss of a chlorine atom to give a fragment at m/e 203. The latter fragment appears to undergo further fragmentation similar to that of the fragment at m/e 203 observed in the mass spectum of the chloroquinoxalinocinnolines. Therefore, it is likely that fragments at m/e 238/240 and 203 have a similar structure to the biphenylene form (94 b), mentioned earlier in this chapter. Therefore, it would appear that the initial fragmentation (i.e. loss of 30 mass units) corresponds to loss of N_2H_2. In the absence of accurate mass data, or meta-stable ions corresponding to this process, it is not possible to say for certainty that N_2H_2 is lost, though it is considered likely.

Since the adducts are thought of as having one molecule of hydrogen halide covalently bound, and others in ionic association (but only show one hydrogen halide molecule in the mass spectrum), then the structure of the molecular ion of the adduct (42 a)+HCl can be represented by either of the two structures below (96) and (97).

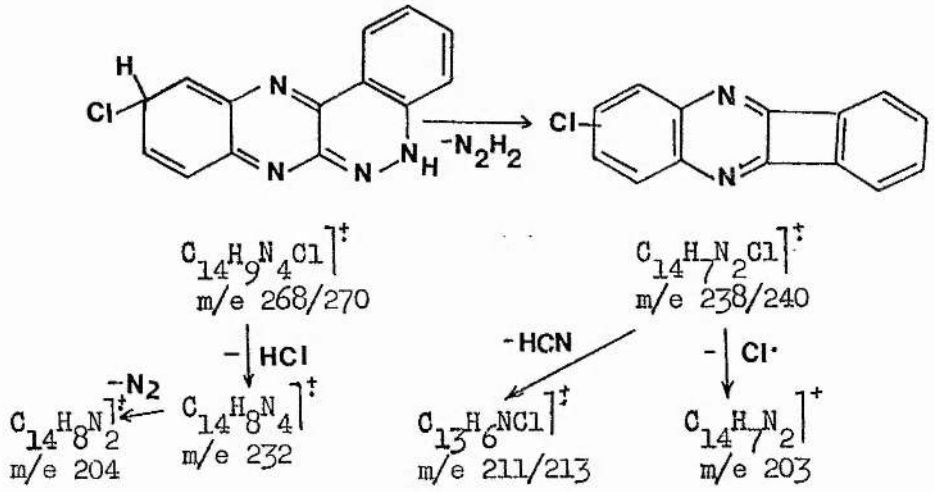


(96)



(97)

Also observed in the mass spectrum of the adduct (42 a)+HCl is the loss of hydrogen chloride from the molecular ion, to give a fragment at m/e 232 which then loses 28 mass units (presumably nitrogen) to give a fragment at m/e 204 which undergoes further fragmentation similar to that observed for the fragment at m/e 204 in the mass spectrum of (42 a). These processes are represented below.



The mass spectra of the remaining adducts appear to fall into two categories:

i) Those adducts formed between quinoxalinocinnolines unsubstituted at position 10, and hydrogen halides, show mass spectra with similar features to those of the adduct (42 a)+HCl. The loss of 30 mass units from $M^{+\cdot}$ is seen, along with loss of hydrogen halide (though the latter

appears to be a less prominent process). Further fragmentation appears to be similar to those observed in the mass spectra of the quinoxalinocinnolines, for fragments of the same m/e values.

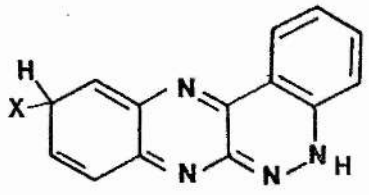
ii) Those adducts formed between quinoxalinocinnolines with halogeno-substituents at position 10, and hydrogen halides, (i.e. those considered to have geminal halogen substituents at positon 10), no longer show loss of 30 mass units as being the major initial fragmentation process. Loss of hydrogen halide appears to have become the initial primary process. Within this group of adducts, differences are seen between the spectra of the mixed halogen adducts. The adduct formed between 10-bromoquinoxalinocinnoline and hydrogen chloride shows two molecular ions, one containing a bromine atom and a chlorine atom, the other two chlorine atoms and a bromine atom. The major fragmentation process observed for both molecular ions are loss of hydrogen bromide or a bromine atom, followed by loss of hydrogen chloride or a chlorine atom. The reverse process is not observed.

The mass spectrum of the adduct formed between the 10-chloro-quinoxalinocinnoline and hydrogen bromide shows a molecular ion with a chlorine atom and a bromine atom. The major fragmentation process observed here is loss of hydrogen chloride or a chlorine atom, followed by loss of hydrogen bromide or a bromine atom. The reverse process is not seen. There is a fragment in the mass spectrum of this adduct that may be a fragmentation product of a dibromo-mono-chloro adduct (at m/e 312/314), possibly by loss of a bromine and chlorine atom.

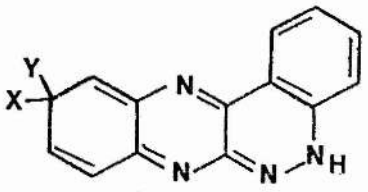
The difference between the mass spectra of the two above mentioned adducts is thought to be due to the presence of different adduct mixtures in each case (see chapter 4, p. 58-60).

In the mass spectrum of the adduct formed between 10-methoxy-quinoxalinocinnoline and hydrogen chloride, the major fragmentation process appears to be loss of 30 mass units followed by loss of hydrogen chloride or a chlorine atom, and fragmentation of the methoxy group.

The difference seen between the initial primary process in groups (i) and (ii) mentioned above, is considered to be connected with the difference between the general structure of the adducts in each case. These are represented by (98) and (99).



(98)



(99)

Assuming the loss of 30 mass units corresponds to loss of N_2H_2, then loss of N_2H_2 from (98) proceeds with formation of a relatively stable species (probably similar to the biphenylene species (94 b)). It is envisaged that loss of N_2H_2 from (99) is less favourable due to the structural difference (i.e. no hydrogen on C-10), and therefore, loss of hydrogen halide occurs.

Experimental

Materials and apparatus

^1H n.m.r. spectra were recorded on a Bruker WP 80 Fourier Transform instrument, operating at 80MHz, for 10% solutions in the appropriate solvent. For quinoxalino[2,3-c]cinnolines, weaker solutions were used (due to their relative insolubility). Tetramethylsilane was used as internal reference. Tables of ^1H n.m.r. for 2-acetamido-N-(o-nitrobenzylidene)anilines are to be found in chapter 1, and for quinoxalino[2,3-c]cinnolines in chapter 7.

Mass spectra were obtained on an AEI MS-902 spectrometer, operating at 70eV with a source temperature of about 200°C. Underlined numbers in the mass spectra recorded in this section represent molecular ions.

Abbreviations used: s: singlet, d: doublet, dd: double doublet, bs: broad singlet, m: multiplet, DMSO: dimethylsulphoxide, DMF: dimethylformamide.

Ultraviolet/visible spectra were recorded for solutions in ethanol, acetone, or acetone/water.

Initial starting materials were commercially available compounds, and unless otherwise stated, were not purified before use.

EXPERIMENTAL

STARTING MATERIALS

o-Nitroacetanilide[83]

To a solution of o-nitroaniline (15g, 0.11mol) in warm dry benzene (20ml), acetic anhydride (16.13ml) was carefully added along with 1-2 drops of concentrated sulphuric acid. The mixture was heated under reflux on a steam bath for 30 minutes, the solvent evaporated, and the residue cooled . A light yellow solid was obtained, which on recrystallisation from the minimum amount of aqueous ethanol, gave 16.9g (86%) of o-nitroacetanilide as pale yellow crystals of m.p. 92-93°C (lit.,[83] 92-93°C).

o-Aminoacetanilide[84]

o-Nitroacetanilide (9.0g, 0.05mol) was dissolved in methanol (180ml) (the bulk dissolved at room temperature, the remainder required gentle heating. On subsequent cooling no reprecipitation occurred). To the solution, 10% palladium on charcoal (1.0g) in a little methanol was added. The solution was then submitted to catalytic hydrogenation at approximately atmospheric pressure. On completion of hydrogen uptake (3.77 litres; theoretical value 3.36 litres), the solution was carefully filtered to remove the catalyst, and evaporated to yield 6g (80%) of o-aminoacetanilide of m.p. 130°C (lit.,[84] 132°C).

4-Chloro-2-nitroacetanilide[85]

To a solution of of 4-chloro-2-nitroaniline (10g, 0.0058mol) in

acetic acid (15ml), acetic anhydride (15ml) was carefully added. The mixture was heated on a steam bath for one hour, allowed to cool, and then poured on to crushed ice. A yellow solid precipitated out and was collected and recrystallised from ethanol to give 4-chloro-2-nitroacetanilide (11.8g, 95%), m.p. 100-102°C (lit.,[85] 103°C).

m-Chloroacetanilide[86]

To m-chloroaniline (29.9g, 0.21mol), acetic anhydride (50ml) was added. The mixture was heated under reflux for two hours, cooled and poured on to crushed ice. The resultant precipitate was collected and dissolved in ethanol (200ml) containing a little activated charcoal. The resulting mixture was boiled for a few minutes, and then filtered through celite to remove the charcoal. The solution on cooling and concentration yielded 30g (75%) of m-chloroacetanilide as white prisms of m.p. 79°C (lit.,[86] 79°C).

5-Chloro-2-nitroacetanilide[87]

A mixture of m-chloroacetanilide (17g, 0.1mol) in acetic anhydride (20g) and acetic acid (9g) was cooled to 0°C. The temperature was maintained between 0°C and 5°C while a mixture of acetic acid (9g) and fuming nitric acid (d1.52: 10g) was slowly added. After being allowed to stand overnight at room temperature, the clear liquid was poured on to crushed ice (400g). The resulting precipitate was collected, washed with water and dried under vacuum. The dry solid was triturated with two 100ml portions of dry benzene, leaving 3.5g (19%) of insoluble 3-chloro-4-nitroacetanilide of m.p. 141-143°C (lit.,[87] 145°C). Evaporation of the benzene washings

yielded a pale brown solid, which on recrystallisation from 95% ethanol gave 11.0g (60%) of 5-chloro-2-nitroacetanilide as straw coloured fibres of m.p. 118-120°C (lit.,[87] 117-118°C).

2-Amino-4-chloroacetanilide[88]

4-Chloro-2-nitroacetanilide (15.7g, 0.073mol) was gradually added, with stirring, to iron powder (13.3g) in water (42.3ml) and acetic acid (1.5ml). As the solid was added, the temperature of the reaction mixture was held in the range 65-80°C. When addition of all solid was complete, the temperature was held at 80°C for a few minutes, after which calcium carbonate (3.62g) was added to neutralise the excess of acid. After 10 minutes the hot mixture was filtered through a celite bed. The product was extracted from the filter cake by repeated washing with boiling ethanol. On evaporation of the washings, 8.4g (66%) of 2-amino-4-chloroacetanilide was obtained as white needles of m.p. 144-145°C (lit.,[88] 144°C).

2-Amino-5-chloroacetanilide

Using the above described method for 4-chloro-2-nitroacetanilide, 5-chloro-2-nitroacetanilide (10.6g, 0.05mol) was reduced with iron and acetic acid to yield 6g (70%) of 2-amino-5-chloroacetanilide as white needles of m.p. 144-145°C (lit.,[89] 130-132°C).

Found: C,51.8; H,4.9; N,15.2. $C_8H_9ClN_2O$ requires C, 52.0; H, 4.9; N, 15.2%. ^{1}H n.m.r. spectrum: δ(DMSO-d_6) 3.82 (2 H, s, NH_2); 6.75 (1 H, d, H-3); 6.96 (1 H, dd, H-4); 7.42 (1 H, d. H-6); 9.22 (1 H, bs, NH); $J_{4,6}$ 8.2Hz, $J_{3,4}$ was not observed.

4-Methoxy-2-nitroacetanilide[90]

4-Methoxy-2-nitroacetanilide (10g, 0.06mol) was dissolved in acetic acid (15ml), and acetic anhydride (15ml) was carefully added. The mixture was heated on a steam bath for one hour, then poured on to crushed ice. The resulting yellow precipitate was collected and recrystallised from ethanol to give of 4-methoxy-2-nitroacetanilide (11.45g, 91%) as bright yellow needles of m.p. 114-115°C (lit.,[90] 115°C).

2-Amino-4-methoxyacetanilide[91]

4-Methoxy-2-nitroacetanilide (4.23g, 0.02mol) in ethanol (120ml) was catalytically hydrogenated as previously described, using 0.6g of catalyst. On completion of hydrogen uptake (1.47 litres, theoretical value 1.34 litres), removal of the catalyst and evaporation of 90% of the solvent, 2-amino-4-methoxyacetanilide (3.3g, 91%) was obtained as

colourless needles of m.p. 147-148°C (lit.,[91] 146-148°C).

4-Methyl-2-nitroacetanilide[92]

A solution of 4-methyl-2-nitroaniline (14.3g, 0.094mol) in acetic anhydride (16ml) was heated under reflux for 2.5 hours. On cooling, the solution was poured on to crushed and the resulting solid was recrystallised from 30% ethanol to give 15.1g (85%) of 4-methyl-2-nitroacetanilide as orange needles of m.p. 91-92°C (lit.,[92] 91-92°C).

2-Amino-4-methylacetanilide

A solution of 4-methyl-2-nitroacetanilide (5.9g, 0.03mol) in methanol (150ml) was catalytically reduced as previously described, using 0.8g of catalyst. On completion of hydrogen uptake (2.3 litres, theoretical value 2.1 litres), removal of catalyst, and evaporation of the bulk of the solvent, 4.8g (90%) of 2-amino-4-methylacetanilide was obtained as white crystals of m.p. 133-134°C (lit.,[93] 131-132°C).

p-Bromoacetanilide[94]

p-Bromoaniline (25g, 0.14mol) was partially dissolved in acetic acid (20ml), to which acetic anhydride (20ml) was carefully added. During this process all the remaining solid dissolved. The solution was gently heated on a water bath for a few minutes, during which time a white precipitate formed. This precipitate was collected, washed with water and dried, 27g (89%) of p-bromoacetanilide being obtained as white crystals of m.p. 167°C (lit.,[94] 168°C).

4-Bromo-2-nitroacetanilide[95]

Concentrated nitric acid (7ml, d 1.42) was added dropwise with shaking to a solution of p-bromoacetanilide (20.0g, 0.093mol) in concentrated sulphuric acid (150ml) cooled to 3°C. The solution was poured on to crushed ice, a bright yellow precipitate being formed. On isolation the precipitate was washed with sodium bicarbonate solution, and recrystallised from 95% ethanol to give 10.1g (42%) of 4-bromo-2-nitroacetanilide as yellow needles of m.p. 102-103°C (lit.,[95] 103-104°C).

2-Amino-4-bromoacetanilide

4-Bromo-2-nitroacetanilide (9g, 0.035mol) was reduced with iron powder (3.9g) in water (29ml) and acetic acid (1.0ml) in the same manner as for 4-chloro-2-nitroacetanilide. The yield was 3.5g (44%) of 2-amino-4-bromoacetanilide as white needles of m.p. 161-162°C. Found C, 41.6; H, 3.9; N, 12.1. $C_8H_9BrN_2O$ requires C, 41.95; H, 4.0; N, 12.2%. δ(acetone-d_6) 4.8 (2 H, s, NH_2), 6.78 (1 H, dd, H-5), 7.04 (1 H, d, H-3), 7.3 (1 H, d, H-6), 8.65 (1 H, bs, NH); $J_{5,6}$ 8.2Hz, $J_{3,5}$ 2.2Hz.

m-Bromoacetanilide

m-Bromoaniline (25g, 0.14mol) was acetylated in the same manner as p-bromoaniline to give 29g (95%) of m-bromoacetanilide as white crystals of m.p. 87°C (lit.,[96] 87.5°C).

5-Bromo-2-nitroacetanilide[87,97,98]

A solution of m-bromoacetanilide (29g, 0.135mol) in acetic acid (26ml), and of concentrated sulphuric acid (48ml), was maintained at 10°C while fuming nitric acid (d1.52: 17.6ml) was slowly added. The

solution was allowed to stand for 30 minutes after which it was poured on to crushed ice. The resulting precipitate was left overnight to solidify fully, and was then filtered and dried. The precipitate was triturated with three 100ml portions of dry benzene, the undissolved material filtered off, and the filtrate evaporated to dryness. The resulting solid was recrystallised from 95% ethanol and yielded 6.7g (20%) of 5-bromo-2-nitroacetanilide as straw coloured crystals of m.p. 140°C (lit.,[98] 144°C). The residue from trituration was treated with 200ml of aqueous ethanolic potassium hydroxide solution (75g of potassium hydroxide in 475ml of water and 100ml of ethanol) to remove any remaining o-nitro compound, and an insololuble residue was fitered off, washed with water and recrystallised from 95% ethanol to give 14.05g (42%) of 3-bromo-4-nitroacetanilide as straw coloured crystals of m.p. 145-148°C (lit.,[98] 150-151°C). The filtrate from the above was acidified with acetic acid and the precipitate was filtered off and recrystallised from 96% ethanol, yielding a further 0.31g (1%) of 5-bromo-2-nitroacetanilide of m.p. 140°C.

2-Amino-5-bromoacetanilide

5-Bromo-2-nitroacetanilide (7g, 0.027mol) was reduced with iron and acetic acid as described for 4-chloro-2-nitroacetanilide, yielding on recrystallisation from ethanol, 3.6g (46%) of 2-amino-5-bromoacetanilide as white crystals of m.p. 173-175°C.

Found: C, 42.0; H,4.0; N,12.2. $C_8H_9BrN_2O$ requires C, 41.95; H, 4.0; N, 12.2%.

o-Chloroacetanilide

o-Chloroaniline (30g, 0.235mol) in acetic acid (50ml) was

acetylated with acetic anhydride (50ml) using the same method as described for p-bromoaniline. The yield was 33.6g (84%) of o-chloroacetanilide as white crystals of m.p. 87-89°C (lit.,[86] 87-88°C).

6-Chloro-2-nitroacetanilide[40a]

A solution of o-chloroacetanilide (27g, 0.16mol) in acetic anhydride (32ml) and acetic acid (14.7ml) was maintained at 0-5°C, while a mixture of fuming nitric acid (10.5ml, d: 1.52) and acetic acid (14.5ml) was carefully added. On completion of addition, the solution was poured on to crushed ice, and the resultant precipitate filtered off and washed with water. The nitration product was shaken and stirred with 150ml of ice cold ethanolic aqueous potassium hydroxide solution (75g of potassium hydroxide in 475ml of water and 100ml of ethanol), any residue being filtered off and discarded. The dark red filtrate was allowed to stand for 18 hours at 5-15°C, during which time a solid precipitated out. On filtration this solid was found to be almost pure 2-chloro-4-nitroaniline of m.p. 102°C (lit.,[40a] 102-104°C). Upon treatment of the filtrate with acetic acid, the colour changed to yellow, and a solid precipitated out. This was filtered off, washed with water, and recrystallised from 95% ethanol to give 5.26g (18%) of 6-chloro-2-nitroacetanilide as straw coloured needles of m.p. 190-191°C (lit.,[40a] 194°C).

2-Amino-6-chloroacetanilide

6-Chloro-2-nitroacetanilide (10g, 0.047mol) was reduced with iron and acetic acid as described for 4-chloro-2-nitroacetanilide, giving 2.4g (30%) of 2-amino-6-chloroacetanilide as white needles of m.p.

138-140°C on recrystallisation from ethanol.

Found: C, 51.6; H, 4.8; N, 15.0. $C_8H_9N_2OCl$ requires C, 52.0; H, 4.9; N, 15.2%.

2,4-Dichloroacetanilide[99]

2,4-Dichloroaniline (40g, 0.247mol) was dissolved in acetic anhydride and the solution heated on a steam bath for 0.5 h. The product which recrystallised on cooling was filtered off, dissolved in ethanol and decolourised with charcoal. The resultant solution, on removal of the charcoal, and subsequent concentration, gave 31.24g (62%) of 2,4-dichloroacetanilide as white crystals of m.p. 143-145°C (lit.,[99] 147°C).

4,6-Dichloro-2-nitroacetanilide[100]

To each of four securely clamped beakers cooled on ice, 30ml of fuming nitric acid (d: 1.52) was carefully added. When the temperature of each was below 5°C, 7g (0.034mol) of 2,4-dichloroacetanilide was added in small portions with constant stirring to each beaker, while the temperature was held at 5-15°C. On completion of addition, the content of each beaker was poured on to crushed ice, and a yellow solid was precipitated out. On filtration and recrystallisation from methanol, a total of 31.5g (92%) of 4,6-dichloro-2-nitroacetanilide was obtained as pale straw coloured needles of m.p. 187-188°C (lit.,[100] 188°C).

2-Amino-4,6-dichloroacetanilide

4,6-Dichloro-2-nitroacetanilide (16.8g, 0.067mol) was reduced

with iron and acetic acid as for 4-chloro-2-nitroacetanilide to give on recrystallisation from ethanol, 10.42g (70%) of 2-amino-4,6-dichloroacetanilide as white needles of m.p. 170-172°C. Found: C, 43.9; H, 3.7; N, 12.9. $C_8H_8Cl_2N_2O$ requires C, 43.9; H, 3.7; N, 12.8%. δ(DMSO-d_6) 5.12 (2 H, s, NH_2), 6.75 (1 H, d, H-5 or H-3), 6.86 (1 H, d, H-5 or H-3), 8.05 (1 H, bs, NH); $J_{3,5}$ 2.1Hz.

4-Bromo-2-nitroaniline[101]

A suspension of 4-bromo-2-nitroacetanilide (12.8g, 0.05mol) in 70% (by volume) sulphuric acid (120ml) was heated under reflux for 30 minutes. The deep red solution was poured on to crushed ice, an orange solid precipitating out which was collected and washed with water. On recrystallisation from ethanol, 8.7g (81%) of 4-bromo-2-nitroaniline was obtained as bright yellow needles of m.p. 109-110°C (lit.,[101] 110°C).

4-Bromo-o-phenylenediamine[101]

To a thoroughly stirred hot solution of ethanol (40ml), water (80ml) and 20% sodium hydroxide (40%), 4-bromo-2-nitroaniline (8g, 0.037mol) in an intimate mixture with of sodium dithionite (26g) was carefully added over a period of 80 minutes. The solution darkened during this process, and on completion of addition of solid, a further 40ml of 25% sodium hydroxide and 26g of sodium dithionite was carefully added in small portions over a period of 15-20 minutes. On completion of the addition of solid, a precipitate was filtered off and washed with ether. The filtrate was poured on to crushed ice, yielding a second precipitate which was also filtered off and extracted with ether. The ether washings and extracts were combined, dried over anhydrous sodium sulphate, and evaporated to yield a brown oil, which solidified on cooling. The resultant soild was recrystallised from ethanol to give 3.1g (45%) of 4-bromo-o-phenylenediamine as pale brown plates of m.p. 61°C (lit.,[101] 63°C).

Formation of 2-acetamido-N-(o-nitrobenzylidene)anilines

General Procedure

Method A: Equimolar quantities of the appropriate o-aminoacetanilide and o-nitrobenzaldehyde were ground together to form an intimate mixture. Ethanol was added to this mixture, and the solution gently heated on a water bath for 5-10 minutes, during which time the product anil often precipitated out. The product was filtered off and recrystallised from the appropriate solvent (usually ethanol). Method B: The two reactants were individually predissolved in ethanol, and the solutions mixed. The solutions were heated and the products isolated as above (method A).

On occasion a few crystals of toluene-p-sulphonic acid were used to assist condensation.

2-Acetamido-N-(o-nitrobenzylidene)aniline (55 a)

o-Aminoacetanilide (4.5g, 0.03mol) and o-nitrobenzaldehyde (4.9g, 0.03mol) in ethanol (20ml) were condensed using method A, to give on recrystallisation from ethanol, 7g (82%) of the unsubstituted anil (55 a) as brilliant yellow needles of m.p. 124-126°C.
Found: C, 63.5; H, 4.6; N, 14.9. $C_{15}H_{13}N_3O_3$ requires C, 63.6; H, 4.6; N, 14.8%.

5-Chloro-2-acetamido-N-(o-nitrobenzylidene)aniline (55 b)

2-Amino-4-chloroacetanilide (3.1g, 0.017mol) and o-nitro-

benzaldehyde (2.54g, 0.017mol) in ethanol (20ml) yielded by method A, 4.31g (82%) of the 5-chloro anil (55 b) as fibrous yellow needles of m.p. 152-153°C (from ethanol).

Found: C, 56.4; H, 3.7; N, 13.1. $C_{15}H_{12}ClN_3O_3$ requires C, 56.7; H, 3.8; N, 13.2%.

4-Chloro-2-acetamido-N-(o-nitrobenzylidene)aniline (55 c)

2-Amino-5-chloroacetanilide (3.1g, 0.017mol) and o-nitrobenzaldehyde (2.54g, 0.017mol) in ethanol (20ml) were condensed using method A, yielding 4.04g (78%) of the 4-chloro-anil (55 c) as bright yellow prisms of m.p. 162-164°C (from ethanol).

Found: C, 56.5; H, 3.7; N, 13.2. $C_{15}H_{12}ClN_3O_3$ requires C, 56.7; H, 3.8; N, 13.2%.

5-Chloro-2-acetamido-N-(5 -chloro-2-nitrobenzylidene)aniline (55 d)

2-Amino-4-chloroacetanilide (3.0g, 0.016mol) and 5-chloro-2-nitrobenzaldehyde (3.0g, 0.016mol) in ethanol (20ml) yielded by method A, 4.89g of the 5,5'-dichloro-anil (55 d) as fibrous yellow needles of m.p. 208-210°C (from ethanol).

Found: C, 51.2; H, 3.1; N, 11.8. $C_{15}H_{11}Cl_2N_3O_3$ requires C, 51.2; 3.1; 11.9%.

5-Methyl-2-acetamido-N-(o-nitrobenzylidene)aniline (55 e)

2-Amino-4-methylacetanilide (2.8g, 0.017mol) and o-nitrobenzaldehyde (2.54g, 0.017mol) in ethanol (20ml) yielded by method A, 3.4g (68%) of the 5-methyl-anil (55 e) as fibrous yellow needles of m.p. 133-134°C (from ethanol).

Found: C, 64.8; H, 5.05; N, 14.15. $C_{16}H_{15}N_3O_3$ requires C, 64.6; H, 5.1; N, 14.1%.

5-Methoxy-2-acetamido-N-(o-nitrobenzylidene)aniline (55 f)

2-Amino-4-methoxyacetanilide (0.9g, 0.005mol) and o-nitrobenzaldehyde (0.8g, 0.005mol), each in ethanol (15ml), yielded by method B, 1.31g (77%) of the 5-methoxy-anil (55 f) as fibrous yellow needles of m.p. 137-138°C (from ethanol).

Found: C, 61.2; H, 4.9; N, 13.25. $C_{16}H_{15}N_3O_4$ requires C, 61.3; H, 4.8; N, 13.4%.

2-Acetamido-N-(5-chloro-2-nitrobenzylidene)aniline (55 g)

o-Aminoacetanilide (1.5g, 0.01mol) and 5-chloro-2-nitrobenzaldehyde (1.85g, 0.01mol), each in ethanol (10ml), yielded by method B, 2.8g (91%) of the 5'-chloro-anil (55 g) as lemon coloured fibrous needles of m.p. 200°C (from ethanol).

Found: C, 56.7; H, 3.7; N, 13.0. $C_{15}H_{12}ClN_3O_3$ requires C, 56.7; H, 3.8; N, 13.2%.

3,5-Dichloro-2-acetamido-N-(o-nitrobenzylidene)aniline (55 h)

2-Amino-4,6-dichloroacetanilide (2.18g, 0.01mol) and o-nitrobenzaldehyde (1.51g, 0.01mol), each in ethanol (15ml), with a few crystals of toluene-p-sulphonic acid, yielded by method B, 2.8g (83%) of the 3,5-dichloro-anil (55 h) as very pale yellow needles of m.p. 216-217°C (from butanone).

Found C, 50.7; H, 3.1; N, 11.8. $C_{15}H_{11}N_3Cl_2O_3$ requires C, 51.2; H, 3.15; N, 11.9%.

3,5-Dichloro-2-acetamido-N-(5-chloro-2-nitrobenzylidene) aniline (55 i)

2-Amino-4,6-dichloroacetanilide (2.18g, 0.01mol) and 1.85g of 5-chloro-2-nitrobenzaldehyde, each in 15ml of ethanol, gave by method B, 2.0g (54%) of the 3',5',5-trichloro-anil (55 i) as very pale straw coloured fibrous needles of m.p. 226-228°C (from butanone).

3-Chloro-2-acetamido-N-(o-nitrobenzylidene)aniline (55 j)

2-Amino-6-chloroacetanilide (1.5g, 0.008mol) and o-nitrobenzaldehyde (1.27g, 0.008mol), each in ethanol (15ml), gave by method B, 1.78g (68%) of the 3-chloro-anil (55 j) as very pale straw coloured fibrous needles of m.p. 186-188°C (from butanone).

Found C, 56.3; H, 3.9; N, 13.1. $C_{15}H_{12}N_3ClO_3$ requires C, 56.7; H, 3.8; N, 13.2%.

5-Bromo-2-acetamido-N-(o-nitrobenzylidene)aniline (55 k)

2-Amino-4-bromoacetanilide (2.3g, 0.01mol) and o-nitrobenzaldehyde (1.51g, 0.01mol), each in ethanol (15ml), gave by method

B, 3.05g (87%) of the 5-bromo-anil (55 k) as bright yellow fibrous needles of m.p. 160-161°C (from ethanol).

Found: C, 50.1; H, 3.3; N, 11.65. $C_{15}H_{12}BrN_3O_3$ requires C, 49.7; H, 3.3; N, 11.6%.

4-Bromo-2-acetamido-N-(o-nitrobenzylidene)aniline (55 l)

2-Amino-5-bromoacetanilide (2.3g, 0.01mol) and o-nitrobenzaldehyde (1.51g, 0.01 mol), each in ethanol (15ml), gave by method B, 2.6g (74%) of the 4-bromo-anil (55 l) as bright yellow prisms of m.p. 165-167°C (from ethanol).

Found: C, 49.6; H, 3.3; N, 11.5. $C_{15}H_{12}BrN_3O_3$ requires requires C, 49.7; H, 3.3; N, 11.6%.

4-(or 5-)*Chloro-N-(o-nitrobenzylidene)-o-phenylenediamine[30]

4-Chloro-o-phenylenediamine (1.42g, 0.01mol) and o-nitrobenzaldehyde (1.51, 0.01mol) were each predissolved in ethanol (10ml), and the solutions were mixed. The mixture was heated gently on a water bath for 5-10 minutes, and on cooling an orange precipitate formed, which was filtered off. 4- (or 5-)Chloro-N-(o-nitrobenzylidene)-o-phenylenediamine (2.54g, 92%) was obtained as orange needles of m.p. 90-91°C (lit.,[30] 92-94°C). Further purification was not carried out.

*Ref. 30 does not specify the position of the substituent.

4-(or 5-)Bromo-N-(o-nitrobenzylidene)-o-phenylenediamine

4-Bromo-o-phenylenediamine (1.87g, 0.01mol) and o-nitrobenzaldehyde (1.51g, 0.01mol), each dissolved in ethanol (10ml), were mixed and gently heated on a water bath for 5-10 minutes. On cooling an orange precipitate formed, which was was filtered off and dried. A mixture of 4- (or 5-)bromo-N-(o-nitrobenzylidene)-o-phenylenediamine with a small amount of a colourless contaminant was obtained as 2.7g (84%) of orange solid of melting point 78-82°C. No further purification was attempted.

Cyanide induced cyclisation of N'-acetyl-N-o-nitrobenzylidene-o-phenylenediamines

General Procedure

Suspensions or solutions of the appropriate anil in methanol, together with two mole equivalents of potassium cyanide, were heated under reflux for varying lengths of time, then cooled on ice. The resulting crystalline products (if any) were filtered off, and in some cases the filtrates were diluted with water to yield further products. Some cyclisations were carried out in air (method A);[30] while the majority were carried out in degassed methanol under nitrogen (method B). Solvent was degassed by boiling, while being infused with a stream of nitrogen gas. The solvent was allowed to cool before addition of reactants.

Quinoxalino[2,3-c]cinnoline (42 a)

i) N'-Acetyl-N-o-nitrobenzylidene-o-phenylenediamine (1.41g, 0.005mol) and (0.651g, 0.01mol) of potassium cyanide in methanol (100ml) was heated under reflux for 3 hours, yielding 0.45g (39%) of quinoxalino-[2,3-c]cinnoline as orange needles of m.p. 224-226°C (lit.[30] 228-230°C) (from DMF).

ii) The above procedure was repeated, but after 45 minutes, solid present in the reaction mixture was filtered off, and the filtrate was heated under reflux for the remainder of the 3 hours. An initial crop of orange crystals (0.26g), m.p. 224-226°C, was obtained, while

further product obtained after three hours gave a total yield of 0.46g (40%) of quinoxalino[2,3-c]cinnoline as orange needles of m.p. 224-226°C (from DMF).

iii) (1.41g, 0.005mol) of The anil and (0.651g, 0.01mol) of potassium cyanide were reacted for 1 hour using method B, yielding an initial crop of bright orange needles (0.5g) of m.p. 223-225°C. On dilution of the filtrate a further crop (0.18g, m.p. 214-216°C) was obtained. Recrystallisation of both crops from DMF gave 0.6g (52%) of quinoxalinocinnoline as fibrous orange needles of m.p. 223-225°C.
Mass spectrum of quinoxalino[2,3-c]cinnoline:
249(4),248(26),233(21),232(100),229(1),228(7),205(16),204(98),
203(21),202(3),201(1),200(10),178(9),177(26),176(4),175(1),153(6),
154(12),142(9),141(31),129(10),128(12),115(9),103(4),102(31),90(30),
78(2),77(16),76(100),75(30),74(10),61(7),62(11),63(10),51(29),50(74),

10-Chloroquinoxalino[2,3-c]cinnoline (42 b)

i) (1.59g, 0.005mol) of the anil (55 b) and (0.651g, 0.01mol) of potassium cyanide in methanol (100ml), yielded by method A after 2.5 hours, 10-chloroquinoxalinocinnoline (0.1g, 7.5%) as orange needles or m.p. 240-242°C (from DMF).
Mass spectrum: 268(33),266(100),262(20),241(6),240(33),239(17),
238(98),234(22),219(10),213(3),211(9),203(44),191(6),176(17)
119(22),112(33),110(99),102(50),76(44),75(88),74(22),63(50),50(44)....

ii) The above procedure was repeated, but the reaction was terminated after 25 minutes. A yield of 0.6g (45%) of the 10-chloroquinoxalinocinnoline was obtained as orange needles of m.p. 238-240°C (from

DMF). Further recrystallisation of a small sample from chloroform yielded bright red needles of m.p. 251-252°C.

iii) The above reaction was repeated using the anil (0.77g, 0.0025mol) and potassium cyanide (0.325g, 0.05mol), the reaction being terminated after 1 hour. The yield was 0.17g (25%) of orange needles of m.p. 239-241°C (from DMF). Dilution of the filtrate on removal of initial product gave a yellow/brown solid of m.p. about 130°C. A mass spectrum of this material revealed the presence of 4 compounds, the 10-chloroquinoxalinocinnoline (mass ion M^+), and compounds of mass ion $(M+16)^+$, $(M+34)^+$ and $(M-4/6)^+$.

Mass spectrum of mixture:

302(21),300(63),284(16),282(50),268(22),266(66),262(75),256(16),
254(50),240(37),238(75),234(50),219(25),203(37),168(8),166(31)
126(37),124(75),110(63),106(100).....

iv) The anil (1.59g, 0.005mol) and potassium cyanide (0.651g) were reacted using method B for 35 minutes in methanol (100ml). An initial crop of 0.43g (32%) of orange needles of m.p. 246-247°C (from DMF) was obtained. The filtrate was diluted with water, and 0.3g of a pale brown solid of m.p. 180°C (with decomposition) was collected. The filtrate was finally extracted with chloroform, the chloroform dried over anhydrous sodium sulphate, and then evaporated to yield 0.04g of a bright yellow solid of m.p. 300-304°C.

v) The above reaction was repeated, the reaction being terminated after 50 minutes. The resulting precipitate was filtered off to yield 0.47g (35%) of orange needles of m.p. 242-244°C (from DMF). The

filtrate was diluted with water, yielding 0.37g of a brownish-yellow solid which partially melted at 130°C, and was totally molten at 240°C. Mass spectra of the main product and dilution products were obtained.

Mass spectrum of main product:

284(3.5),282(10),269(5),268(33),267(15),266(100),263(2),262(10),
241(3),240(27),239(14),238(80),235(>1),234(3),204(3),203(30),
202(4),177(2),176(8),175(1),120(16),119(5),112(30),110(60),
77(40),76(70),75(20),51(10),50(30).....

Mass spectrum of dilution product:

302(27),300(87),282(2),268(33),266(100),262(27),240(27),232(80),
234(7),303(33),178(9),176(27).....

The mass spectrum of the main product from reaction v) shows a substantial reduction in the relative proportions of the peaks at $(M+16)^+$, $(M+34)^+$ and $(M-4/6)^+$, compared to M^+.

For 10-chloroquinoxalino[2,3-c]cinnoline, found:

C, 62.85; H, 2.6; N, 20.8%. $C_{14}H_7N_4Cl$ requires

C, 63.05; H, 2.6; N, 21.0%.

9-Chloroquinoxalino[2,3-c]cinnoline (42 c)

i) The 4-chloro-acetamido-anil (55 c) (1.5g, 0.005mol) and potassium cyanide (0.651g) were reacted together in methanol (100ml) for 1 hour using method A. 9-Chloroquinoxalinocinnoline was obtained as 0.72g (54%) of orange needles of m.p. 278°C (lit.,[30] 274-276°C).

ii) The reaction was repeated using method B, for 25 minutes. An initial yield of 0.64g of orange needles of m.p. 278°C was

obtained. On dilution of the filtrate, a further 0.225g of brown solid was obtained, which on recrystallisation from DMF gave 0.18g of the 9-chloro compound, of m.p. 277°C. The total yield was 0.82g (62%).

Mass spectrum of 9-chloroquinoxalino[2,3-c]cinnoline:

268(33),266(100),240(27),238(83),213(5),211(17),203(98),189(1), 187(3),177(5),176(23),175(3),165(1),163(3),128(13),126(3),124(3), 112(33),110(98),102(32),101(13),76(47),75(95).....

2,10-Dichloroquinoxalino[2,3-c]cinnoline (42 d)

i) The 5,5'-dichloro-acetamido-anil (55 d) (1.76g, 0.005mol) was reacted with potassium cyanide (0.651g) in methanol (100ml) for 40 minutes using method A. On cooling an orange solid settled out, which on filtration and recrystallisation from DMF gave 0.17g (11%) of 2,10-dichloroquinoxalinocinnoline as orange needles of m.p. 288-290°C. On dilution of the filtrate with water, 0.1g of a brown solid (m.p. 250°C) was obtained. On being left to stand for a few hours the filtrate yielded a further 0.07g of a bright yellow solid of m.p. 300°C.

Mass spectrum of 2,10-dichloroquinoxalino[2,3-c]cinnoline:

304(7),302(44),300(63),296(4),276(7),274(44),272(63),268(2),239(6), 237(18),202(18),175(2),164(12),162(37),138(8),136(20),112(33),110(100), 101(20),100(10),75(98).....

Mass spectrum of yellow solid:

338(8),337(4),336(64),335(28),334(98),333(16),308(12),307(16),306(8), 305(12),304(48),306(24),302(100),301(16),300(40),298(28),292(12), 290(40),288(44),287(32),279(8).....

ii) The previous experiment was repeated with the addition of DMF (45ml) as cosolvent. An initial crop of 0.12g (8%) of the 2,10-dichloroquinoxalinocinnoline, m.p. 287°C was obtained, followed by a further 0.13g of yellow solid of m.p. 300°C.

For 2,10-dichloroquinoxalino[2,3-c]cinnoline,
found: C, 55.8; H, 1.7; N, 18.8%. $C_{14}H_6N_4Cl_2$ requires
C, 55.8; H, 2.0; N, 18.6%.

Attempted formation of 10-methylquinoxalino[2,3-c]cinnoline (42 e)

i) The 5-methyl-acetamido-anil (55 e) (1.48g, 0.005mol) and potassium cyanide (0.651g) were reacted together in methanol (100ml) using method A, for 3 hours. On cooling 0.6g of brownish solid was collected. A t.l.c. using methanol as developing solvent (the sample being applied in chloroform solution to a plate with a silica-gel coating), indicated the presence of up to 5 or 6 compounds. A mass spectrum of the mixture was obtained.
280(10),264(80),246(100),218(4).....

ii) The above experiment was repeated using method B, 0.57g of brown solid being obtained. Again t.l.c. showed the presence of 5 or 6 compounds.

10-Methoxyquinoxalino[2,3-c]cinnoline (42 f)

i) The 5-methoxy-acetamido-anil (55 f) (1.56g, 0.005mol) and potassium cyanide (0.651g) were reacted together in methanol (100ml) for 45 minutes, using method B. On cooling an orange solid separated out, which on isolation and recrystallisation from DMF gave 0.92g (m.p.

266-268°C) of a mixture of 10-methoxyquinoxalinocinnoline and a by-product of molecular mass M+16, where M is the molecular mass of the methoxyquinoxalinocinnoline. This is thought to be the 5-oxide of the methoxyquinoxalinocinnoline. A ^{1}H n.m.r. spectrum of the product revealed that both compounds were present in approximately equal quantities.

Mass spectrum of product mixture:

279(3),278(14),263(17),262(70),235(6),234(26),220(4),219(16),
181(4),180(25),152(10),139(3),138(8),137(7),135(6),125(6),124(16),
117(10),111(10),110(22),109(26),107(6),106(64),97(22),96(50),95(66),
83(30),82(80),81(98),71(40),70(100),69(80).....

ii) The previous experiment was repeated, but the solution was heated under reflux for 2 hours. The final yield of product obtained was 0.8g (60%) of 10-methoxyquinoxalinocinnoline, of m.p. 266-268°C

For 10-methoxyquinoxalino[2,3-c]cinnoline,

found: C, 69.0; H, 3.85; N, 21.6%. $C_{15}H_{10}N_4O$ requires

C, 68.7; H, 3.8; N, 21.4%.

2-Chloroquinoxalino[2,3-c]cinnoline (42 g)

i) The 5'-chloro-acetamido-anil (55 g) (1.59g, 0.005mol) and potassium cyanide (0.651g) in methanol (100ml) were reacted for 50 minutes using method B. On cooling and filtration, 0.56g (m.p. 255-257°C) of a pale yellow solid was collected. Mass spectral analysis revealed this to be a mixture of approximately equal proportions of the 2-chloroquinoxalinocinnoline (mass M), and a by-product of mass M+16. The approximate yield of each component was 20%.

Mass spectrum of product mixture:

285(6),284(29),283(15),282(83),269(6),268(33),267(17),266(100)
255(1),254(3),253(2),241(6),240(29),239(15),238(84),203(33)....

ii) The above experiment was repeated with a reaction time of 2 hours. A yield of 0.57g (43%) of 2-chloroquinoxalinocinnoline was obtained as pale orange needles of m.p. 259-262°C.(lit.,[31] 260-261°C).

Attempted formation of 8,10-dichloroquinoxalino[2,3-c]-cinnoline (42 h)

The 3,5-dichloro-acetamido-anil (55 h) (1.1g, 0.0031mol) and potassium cyanide (0.41g) in methanol (150ml) were reacted for 45 minutes using method B. On cooling a dark brown solid was collected, and after standing for a few hours, a second crop of brown solid was obtained. Both materials had a m.p. of 240-242°, and identical mass spectra, which revealed them to be a mixture of the required 8,10-dichloroquinoxalinocinnoline (mass M), and a by-product of mass M+16 (from the mass spectrum). The total yield of solid was 0.4g
Mass spectrum of product mixture:
320(2),319(2),318(15),317(5),316(25),304(6),303(6),302(35),301(9),
300(53),298(3),296(11),276(12),275(11),274(64),273(14),272(100),
270(2),268(7),238(9),237(7),236(28),235(8),200(41),162(2),160(18),
158(27).....

Attempted formation of 8-chloroquinoxalino[2,3-c]cinnoline (42 j)

The 3-chloro-acetamido-anil (55 j) (1.0g, 0.0031mol) and potassium cyanide (0.41g) in methanol (100ml) were reacted usingmethod B for 1 hour. On cooling a yellow solid precipitated out, which was

collected and recrystallised from DMF. A yield of 0.48g of yellow needles of m.p. 300-301°C (with decomposition) was obtained. The mass spectrum of this substance shows it to be a mixture of the required product (mass M), and a by-product of mass M+16.

Mass spectrum of product mixture:

285(6),284(36),283(24),282(100),269(6),268(30),267(18),266(90),234(3), 253(3),252(24),241(3),239(15),248(24),238(72),126(6),124(60),112(24), 110(72),76(42),75(96).....

Attempted formation of 2,8,10-trichloroquinoxalino[2,3-c]-cinnoline (42 i)

The 3,5,5'-trichloro-acetamido-anil (1.25g, 0.0032mol) and potassium cyanide (0.41g) in methanol (150ml) were reacted for one and a half hours using method B. On cooling, no precipitate was present, and the solution was then diluted with water, yielding a dark brown solid. This solid was found to be insoluble in both DMF and an ethanol/DMF mixture. Decolourisation with charcoal yielded a brownish-orange solid of m.p. 285-287°C. The mass spectrum of the solid showed the presence of a compound of mass M+34, where M is the mass of the required trichloroquinoxalinocinnoline. No other compounds (i.e. of mass M or M+16) were seen.

10-Bromoquinoxalino[2,3-c]cinnoline (42 k)

The 5-bromo-acetamido-anil (55 k) (1.81g, 0.005mol) and potassium cyanide (0.651g) in methanol (100ml) were reacted for 1 hour using method B. A yield of 0.78g (50%) of the 10-bromoquinoxalinocinnoline was obtained as copper coloured needles of m.p. 263-265°C (from DMF).

Mass spectrum of 10-bromoquinoxalino[2,3-c]cinnoline

313(12),312(72),311(12),310(70),285(10),284(65),283(10),282(65),204(7)
203(30),202(4),183(3),182(15),181(4),180(4),179(2),178(2),177(12),
176(20),175(5),168(6),167(5),166(20),165(5),163(3),156(3),155(25),
154(3),153(25),152(3),151(3),142(10),141(10),136(4),135(20),131(8),
130(6),129(15),128(12),127(3),120(5),119(25),118(4),117(8),116(7),
115(12),111(4),110(2),109(4),105(10),102(60),93(5),92(8),91(24),
90(3),89(5),88(3),87(2),86(20),85(2),84(2),83(4),82(18),80(18),79(8),
78(3),77(9),76(10),75(30),74(8),73(4).....44(80),40(100),.

Found: C, 54.2; H, 2.25; N, 18.1%. $C_{14}H_7N_4Br$ requires
C, 54.0; H, 2.3; N,18.0%.

9-Bromoquinoxalino[2,3-c]cinnoline (42 1)

The 4-bromo-acetamido-anil (55 1) (1.81g, 0.005mol) and potassium cyanide (0.651g) in methanol (100ml) were reacted for 1 hour using method B. An initial yield of 0.81g (52%) of the 9-bromo-quinoxalinocinnoline was obtained as orange needles of m.p. 252-254°C (from DMF). Dilution of the filtrate on removal of the initial product yielded 0.38g of a brick-red solid of m.p. 267-270°C.

Mass spectrum of 9-bromoquinoxalino[2,3-c]cinnoline:

328(1),326(1),312(20),310(20),284(60),282(60),257(5),255(5),,
205(8),303(70),202(10),182(8),180(8),177(10),176(40),175(12),155(60),
154(30),153(60),152(30),129(95),128(60),127(20),119(7),117(7),114(15),
113(6),112(7),111(7),102(70),101(96),100(96),88(55),87(30),76(98),
75(98),74(96),73(5),64(20),63(40),62(30),61(5),52(20),51(100),
50(100).....

Mass spectrum of the brick-red solid:

321(8),319(8),302(10),300(10),284(2),282(2),275(4),273(3),261(3),

359(3),238(5),219(4),212(5),210(5),192(40),184(20),183(23),180(12), 179(13),170(28),168(26),166(28),165(20),164(35),140(7),139(8),138(7), 134(24),131(5),130(5),129(15),104(100),103(40).....

For 9-bromoquinoxalino[2,3-c]cinnoline

found: C, 53.4; H, 2.2; N, 17.9. $C_{14}H_7N_4Br$ requires

C, 54.0; H, 2.3; N, 18.0%.

The analytical result shown is low in carbon, and this was found to be the case each time analysis was carried out. The presence of small amounts (less than 2%) of the 5-oxide of the parent base is thought to be the cause of this problem.

Reaction of Schiff bases with cyanide in dimethylformamide[31]

Reaction of N-o-nitrobenzylidene-o-phenylenediamine

The anil (1.2g, 0.005mol) and potassium cyanide (0.48g) in DMF (20ml) and water (3ml), were stirred together at room temperature for 3 hours. The solution was poured on to crushed ice, a yellow precipitate being formed. This precipitate was filtered, washed with water and dried. On recrystallisation from an ethanol/DMF mixture, 2-amino-3-(o-nitrophenyl)quinoxaline (59 a) was obtained as 0.8g (60%) of fibrous yellow needles of melting point 260-261°C (lit.,[31] 260°C).

Reaction of 2-acetamido-N-(o-nitrobenzylidene)aniline (55 a)

The 2-acetamido-anil (55 a) (1.32g, 0.047mol) and potassium cyanide (0.48g) in DMF (50ml) and water (3ml) were reacted as described in the previous experiment. A yield of 0.96g (72%) of 2-amino-3-(o-nitrophenyl)quinoxaline (59 a) was obtained as fibrous yellow needles of m.p. 260-261°C (from 50:50 ethanol/DMF). The mass spectra and ^{1}H n.m.r. spectra were identical with those obtained from the previous experiment.

Reaction of 5,5'-dichloro-2-acetamido-N-(o-nitrobenzylidene)-aniline (55 d)

The 5,5'-dichloro-acetamido-anil (55 d) (1.76g, 0.005mol) and potassium cyanide (0.651g) in DMF (100ml) and water (20ml) were reacted as described in the previous experiment. A yield of 1.3g (68%) of 2-amino-6-chloro-3-(5-chloro-2-nitrophenyl)quinoxaline (55 d) was obtained as fibrous yellow needles, of m.p. 300-301°C (from

45:45:10 DMF/ethanol/water). The mass spectra and ^{1}H n.m.r. spectra of this compound are identical with those of the yellow solid (m.p. 300°C) obtained from the cyclisation of the same anil with cyanide in methanol.

Found: C, 49.9; H, 2.5; N.16.6. $C_{14}H_8N_4Cl_2O_2$ requires C, 50.1; H, 2.4; N, 16.8%.

Attempted cyclisation of 2-amino-3-(o-nitrophenyl)quinoxaline to quinoxalino[2,3-c]cinnoline-5-oxide (60 a)

Method A: 2-Amino-3-(o-nitrophenyl)quinoxaline (0.4g, 0.0015mol) was suspended in a solution of sodium hydroxide (0.1g, 0.0025 mol) in methanol (20ml), and the mixture was heated under reflux for 7 hours. The solution was poured on to crushed ice, and the solid product collected as a mixture of pale yellow and orange/brown solid which melted at approximately 200°C. A mass spectrum of the mixture indicated that no cyclisation had occured.

Method B:[102] The solid product from the previous reaction was suspended in N-benzyltrimethylammonium hydroxide (20ml of a 40% solution in methanol), and heated under reflux for 6 hours. The solution was extracted with chloroform (2 30ml), and the chloroform extracts (red in colour) were acidified with concentrated HCl until the solution was approximately neutral, the colour changing from red to yellow. The extracts were then washed with water, dried with anhydrous sodium sulphate, and concentrated until solid began to

form. The mixture was left until no more solid had appeared, and the latter was filtered off and dried. A yield of 0.21g of a brownish solid was obtained, the mass spectrum of which showed the presence of a low intensity peak at m/e 232, possibly indicating the presence of quinoxalinocinnoline (42 a) in low yield. No trace of the N-oxide (60 a) was detected.

The reaction of quinoxalino[2,3-c]cinnoline and some derivatives with phosphorus trichloride

The initial reason for carrying out these reactions was to try to deoxygenate a suspected N-oxide. The series was continued qualitatively.

Attempted deoxgenation of a mixture of 10-methoxyquinoxalino-[2,3-c]cinnoline and its suspected N-oxide

Phosphorus trichloride (0.3ml) was added to a mixture of the product of the cyanide induced cyclisation of the 5-methoxy-acetamido-anil (a supposed mixture of the 10-methoxy-quinoxalinocinnoline and its N-oxide) (0.15g), and chloroform (5ml). The mixture was heated under reflux for 1 hour. The solution, initially orange-red in colour, darkened, and a dark precipitate formed. The mixture was neutralised with base (4M NaOH), and the organic products extracted with chloroform. The chloroform extracts were dried with anhydrous sodium sulphate, evaporated, and the resulting solid recrystallised from DMF.

The product thus obtained was in the form of orange-red needles of m.p. 226-228°C. ^{1}H n.m.r. indicated that a third methoxy compound had been formed, with loss of the 10-methoxy-quinoxalinocinnoline, but little, if any, apparent loss of the suspected N-oxide (the n.m.r. spectra of reactant and product mixtures can be found facing p.38). Mass spectral evidence suggested that inclusion of one chlorine atom into the 10-methoxy-quinoxalinocinnoline had occurred, giving the 9-chloro-

10-methoxy-quinoxalinocinnoline. The yield (from n.m.r. integrals) was about 80% for conversion of the 10-methoxy derivative to the 9-chloro-10-methoxy derivative.

Reaction with quinoxalino[2,3-c]cinnoline

The previous reaction was repeated on a solution of quinoxalino[2,3-c]cinnoline (42 a) in chloroform (5ml), and phosphorus trichloride (0.3ml). A blue precipitate formed that was basified as described, giving the 10-chloroquinoxalinocinnoline (42 b) (0.16g, 92%) as orange needles of m.p. 248-249°C (from DMF).

Reaction with 10-chloroquinoxalino[2,3-c]cinnoline

The reaction was repeated using the 10-chloro derivative (42 b) (0.15g), giving 10-chloroquinoxalinocinnoline (42 b) (0.14g, 93%) as the final product. However, a blue precipitate was again obtained, indicating that a reaction of some form had occurred.

Reaction with 9-chloroquinoxalino[2,3-c]cinnoline

The reaction was repeated using the 9-chloro derivative (42 c) (0.15g), giving 9,10-dichloroquinoxalinocinnoline (42 n) as orange needles (0.14g, 83%) of m.p. 256-258°C (lit.,[31] 256-258°C).

Reaction of 10-methoxyquinoxalino[2,3-c]cinnoline

The reaction was repeated using 10-methoxyquinoxalinocinnoline (0.1g) in chloroform (3.5ml) and phosphorus trichloride (0.2ml). A yield of (0.19g, 79%) of 9-chloro-10-methoxyquinoxalinocinnoline was obtained as orange needles of m.p. 242-243° (lit.,[31] 230-234°C).

Reaction of quinoxalino[2,3-c]cinnoline with redistilled and dried phosphorus trichloride and chloroform

To quinoxalino[2,3-c]cinnoline (0.15g) in freshly redistilled and dried chloroform (15ml), freshly redistilled and dried phosphorus trichloride (0.5ml) was added dropwise with stirring. On addition of all phosphorus trichloride, the mixture was heated under reflux for one hour and then left to cool. The solution had darkened somewhat, and on filtration yielded a few milligrams of blue solid. Water was added to the filtrate, resulting in the formation of a deep blue precipitate. This was filtered off to give 0.18g of deep blue lustrous needles.

The above experiment was repeated, but the mixture was not heated. Again, little precipitate formed initially, but on dilution with water, 0.18g of blue crystals were obtained. The melting point of these crystals was found to be 245-247°C, and a mass spectrum was obtained of them:

270(33),268(100),240(30),238(90),232(60),204(45),203(45),178(6),
177(18),176(15),112(15),110(45),76(90),75(88).....

The reaction of quinoxalino[2,3-c]cinnoline and its derivatives with gaseous hydrogen halides

Reaction of quinoxalino[2,3-c]cinnoline with gaseous hydrogen chloride

Hydrogen chloride gas was passed through a solution of quinoxalinocinnoline (42 a) (0.16g, 0.00069mol) in chloroform (15ml), for about 30 seconds. The blue precipitate thus formed (m.p. 279-281°C) was filtered off, washed thoroughly with chloroform and dried. The filtrate and washings were combined, dried with anhydrous sodium sulphate, and evaporated to yield 0.01g of orange material of m.p. 214-216°C (presumably unreacted starting material).

The blue solid, once dried, gave 0.185g of tiny lustrous blue crystals. Starting from (0.16-0.01g) of quinoxalino[2,3-c]cinnoline, for quinoxalinocinnoline+nHCl, this is 107% for n=1, 94% for n=2 and 87% for n=3.

The blue compound (0.16g) was shaken with chloroform (40ml) and 6M sodium hydroxide (40ml), until the blue solid had dissolved, and the organic layer had become orange in colour. The blue solid was observed to dissolve at the interface between the aqueous and organic layers. On separation of the chloroform layer, it was dried with anhydrous sodium sulphate and evaporated, to give 10-chloroquinoxalino[2,3-c]cinnoline (42 b) as orange needles of melting point 248-250°C (from DMF). The yield was 0.095g (64% from quinoxalinocinnoline (42 a)).

The reaction was repeated using quinoxalinocinnoline (2g), giving

3.02g of blue crystals of m.p. 280°C. On treatment of all the solid with chloroform and sodium hydroxide, the 10-chloro quinoxalinocinnoline (1.75g, 75%), (m.p. 250-252°C) was obtained. For quinoxalinocinnoline+nHCl, this is 103% for n=3, and 93% for n=4.

Reaction of quinoxalino[2,3-c]cinnoline with gaseous hydrogen bromide

Quinoxalino[2,3-c]cinnoline (42 a) (0.185g, 0.00079mol) in chloroform (15ml) was treated with hydrogen bromide gas for 2 minutes. A dark blue-purple solid was precipitated, collected by filtration and dried. The filtrate was coloured pale blue, presumably due to partial solubility of the solid in chloroform. 0.3g of lustrous blue-purple needles were collected. For quinoxalinocinnoline+nHBr, this is 95% for n=2, and 79% for n=3.

The blue solid (0.15g) was treated with 6M NaOH and chloroform as previously described. The organic layer yielded 0.124g of the 10-bromoquinoxalinocinnoline (42 k) as lustrous bronze needles of m.p. 261-263°C (from DMF). The overall yield of unsubstituted compound to 10-bromo derivative is 70%

Mass spectrum of blue solid:

314(20),312(20),284(15),282(15),279(10),258(10),243(15),232(5),204(12), 203(15),167(20),163(10),149(100),123(15),111(15),109(15),97(20), 95(20),82(80),80(80).....

Reaction of quinoxalino[2,3-c]cinnoline with hydrogen bromide in the presence of a radical inhibitor

Quinoxalinocinnoline (0.1g) in chloroform (30ml), in the presence of 2,6-di-t-butyl-p-cresol (0.005g), was treated with hydrogen bromide gas for 30 minutes. The reaction was carried out in total darkness

under a nitrogen atmosphere. On completion of the reaction the apparatus was flushed out with nitrogen to remove dissolved hydrogen bromide. On examination, it was found that a blue precipitate was present. This was isolated, and found to have an identical mass spectrum to that of the blue solid prepared from the same reactants under 'normal' conditions (previous experiment). Basification of the blue solid yielded 10-bromoquinoxalinocinnoline as orange needles (0.09g, 68%) of m.p. 260-262°. This product was found to be identical to samples of 10-bromoquinoxalinocinnoline produced by alternative methods.

Reaction of 10-chloroquinoxalino[2,3-c]cinnoline with gaseous hydrogen chloride

10-Chloroquinoxalino[2,3-c]cinnoline (42 b) (0.1g, 0.00038mol) in chloroform (30ml) was treated with gaseous hydrogen chloride for 3 minutes, a blue precipitate being formed. The blue solid (m.p. 274-276°C) was collected as 0.14g of lustrous blue needles. For 10-chloroquinoxalinocinnoline+nHCl, this is 99% for n=3, and 90% for n=4.

The blue solid was treated with sodium hydroxide and chloroform as described previously, yielding 0.09g of the 10-chloroquinoxalinocinnoline (90% recovery from starting compound).

Mass spectrum of blue compound:

306(12),305(12),304(66),303(30),302(100),277(2),276(12),275(3),274(6), 272(14),270(10),269(14),268(40),267(24),266(14),265(12),242(2),241(6), 240(14),239(10),238(22),237(6),236(4),229(4),230(14),231(36),212(6), 211(2),210(8),206(2),205(4),204(14),203(22),202(20),201(6),154(6), 153(4),152(98),151(10),150(10),149(8),148(4),147(10),146(16),145(16),

144(24),129(38),128(20),127(12),126(12),125(8),124(9),112(12),111(30), 110(26),109(46),103(24),102(40),101(16),100(20),99(12),98(8),97(10), 79(10),78(14),77(28),76(56),75(74),74(36),73(8),69(8),67(16),65(12), 64(20),63(28),62(16),52(16),51(26),50(20),49(19),48(20).....

Reaction of 10-chloroquinoxalino[2,3-c]cinnoline with gaseous hydrogen bromide

10-Chloroquinoxalino[2,3-c]cinnoline (42 b) (0.1g, 0.00038mol) in chloroform (50ml) was treated with gaseous hydrogen bromide for 30 minutes, during which time a blue precipitate formed. A yield of 0.15g of lustrous blue needles of melting point greater than 360°C was obtained. For 10-chloroquinoxalinocinnoline+nHBr, this is 93% for n=2, 78% for n=3, and 68% for n=4.

On treatment of the blue solid with sodium hydroxide and chloroform, 0.094g of orange crystals were obtained of m.p. 243-245°C. The mass spectral and ^{1}H n.m.r. data show that this is predominantly the 10-chloro compound, with a trace of a mono-chloro-mono-bromo compound, probably the 9-bromo-10-chloro compound (42 p).

Mass spectrum of the blue solid:

350(8),349(6),348(29),347(8),346(22),314(4),312(4),305(4),304(10), 270(24),269(68),268(48),267(100),266(48),243(6),242(13),241(35), 240(44),239(57),238(60),237(5),234(10),233(57),232(33),231(37),206(36), 205(30),204(42),203(62),202(30).....

Mass spectrum of product quinoxalinocinnolines:

348(1),346(2),344(1),320(1),318(3),316(2),268(15),266(42),240(33), 238(100),213(11),211(35),204(18),203(93),202(50),176(70),120(10), 119(96),118(50),.....

Reaction of 10-bromoquinoxalino[2,3-c]cinnoline with gaseous hydrogen chloride

10-Bromoquinoxalino[2,3-c]cinnoline (42 k) (0.11g, 0.00035mol) in chloroform (35ml) was treated with hydrogen chloride for one hour, during which time a blue solid was formed. The yield of blue compound was 0.13g (m.p. 278-281°C). For 10-bromoquinoxalinocinnoline +nHCl, this is 97% for n=2, 87% for n=3, and 80% for n=4.

On basification, 0.073g of orange crystals were obtained, which were found to be, from the mass spectral and ^{1}H n.m.r. data, a mixture of the 10-bromo-9-chloro and 10-bromo quinoxalinocinnolines, (42 o) and (42 k) in approximately 40% and 20% yields respectively. The melting point of the mixture was 212-214°C.

Mass spectrum of blue solid:

388(1),386(8),385(4),384(22),383(5),382(19),350(15),349(9),348(51), 347(12),346(33),315(5),314(33),313(10),312(30),311(9),310(4),307(4), 306(17),305(9),304(21),303(7),269(6),268(12),267(30),266(9),265(21), 234(4),233(18),232(36),231(100).....

Reaction of 9-bromoquinoxalino[2,3-c]cinnoline with gaseous hydrogen chloride

9-Bromoquinoxalino[2,3-c]cinnoline (42 l) (0.1g, 0.00032mol) in chloroform (30ml) was treated with hydrogen chloride gas for 20 minutes. A blue precipitate formed, yielding 0.14g of blue crystals. For 9-bromoquinoxalinocinnoline+nHCl, this is 103% for n=3, and 95% for n=4. On basification of the blue compound, 9-bromo-10-chloroquinoxalino[2,3-c]cinnoline (42 p) was obtained as orange needles (0.078g, 70%) of m.p. 274-276°C (from chloroform).

Mass spectrum of 9-bromo-10-chloroquinoxalino[2,3-c]cinnoline:

348(6),346(34),344(24),320(7),318(39),316(28),312(4),310(4),284(4),
282(4),239(3),238(2),237(12),203(8),202(26),201(4),192(8),190(44),
188(36),138(5),136(9),134(9),132(5),129(19),128(16),127(4),126(4),
125(21),124(5),123(20),121(6),119(10),108(10),107(7),105(12),102(16),
101(18),100(40),99(32),98(13),97(84),96(24),95(60),93(13),91(11),
88(35),87(16),86(7),85(60),84(24),83(100),82(24),81(68).....

For 9-bromo-10-chloroquinoxalino[2,3-c]cinnoline

Found C, 49.0; H, 1.9; N, 15.8. $C_{14}H_6N_4BrCl$ requires
C, 48.7; H, 1.75; N, 16.2%.

Reaction of 9-chloroquinoxalino[2,3-c]cinnoline
with gaseous hydrogen chloride

9-Chloroquinoxalino[2,3-c]cinnoline (42 c) (0.1g, 0.00038mol) in chloroform (30ml) was treated with hydrogen chloride gas for 10 minutes. The resultant blue precipitate, on isolation, was obtained as 0.13g of lustrous blue needles of m.p. 283-286°C. For 9-chloroquinoxalinocinnoline+nHCl, this is 102% for n=2, 92% for n=3, and 84% for n=4. The blue solid was basified, and yielded 9,10-dichloroquinoxalino[2,3-c]cinnoline (42 n) as fibrous red needles (0.081g, 72%) of m.p. 257-258°(lit.,[31] 256-258°C) (from chloroform).

calculated for $C_{14}H_6N_4Cl_2$: C, 55.8; H, 2.0; N, 18.6%.
Found: C, 55.75; H, 2.0; N, 18.7%.

Reaction of 9-chloroquinoxalino[2,3-c]cinnoline
with gaseous hydrogen bromide

9-Chloroquinoxalino[2,3-c]cinnoline (42 c) (0.6g, 0.0023mol) in chloroform (150ml) was treated with hydrogen bromide gas for 30

minutes. The resulting blue solid, on isolation, was obtained as 0.79g of lustrous blue needles (m.p. 279-281°C). For 9-chloroquinoxalinocinnoline+nHBr, this is 101% for n=1, 82% for n=2. On basification of the blue solid, 0.5g of red/orange needles were obtained of m.p. 235-236°C. Investigation of the product by ^{1}H n.m.r. revealed it to be a mixture of the 10-bromo-9-chloro- and 9-chloroquinoxalinocinnolines (42 o) and (42 c) in the ratio 5:3, of overall yields 45% and 27% respectively. No attempt was made to separate the components of the mixture.

Reaction of 2-chloroquinoxalino[2,3-c]cinnoline with gaseous hydrogen chloride

2-Chloroquinoxalinocinnoline (42 g) (0.35g, 0.0013mol) in chloroform (100ml) was treated with hydrogen chloride gas for 15 minutes. The resulting blue precipitate on isolation, was obtained as lustrous blue needles of m.p. 290°C. For 2-chloro-quinoxalinocinnoline+nHCl, this is 98% for n=3, and 89% for n=4. On basification of the blue solid, 2,10-dichloro- quinoxalinocinnoline (42 d) was obtained as orange needles (0.28g, 70%) of m.p. 288-290° (from chloroform).

Mass spectrum of blue solid:

306(11),305(11),304(66),303(20),302(100),301(30), 276(4),275(4), 274(24),273(7),272(36).....

Reaction of a mixture of 2-chloroquinoxalino[2,3-c]cinnoline and its 5-oxide with gaseous hydrogen chloride

A mixture of 2-chloroquinoxalinocinnoline (42 g), and its 5-oxide (60 g) (0.3g), was treated with hydrogen chloride gas as described

above. On filtration of the blue solid 0.19g of blue crystals was obtained, which on basification yielded 2,10-dichloroquinoxalinocinnoline (0.075g, 22%) as orange needles of m.p. 228-290°C (from chloroform). Evaporation of the filtrate from above, yielded orange yellow crystals (0.165g) presumably the 5-oxide, of m.p. 304-306°C.

Reaction of 8-chloroquinoxalino[2,3-c]cinnoline and its 5-oxide with gaseous hydrogen chloride

A mixture of 8-chloroquinoxalinocinnoline and its 5-oxide (42 j) and (60 j) (0.15g) in chloroform (50ml), was treated with hydrogen chloride gas, yielding a purple/red solid. On isolation, 0.1g of a purple/red powder was obtained. The filtrate remaining when the purple/red solid was isolated, yielded on evaporation, the 5-oxide (0.079g) as a bright yellow powder. This material was recrystallised from ethanol, giving yellow needles of m.p. 319-321°C, but was found to be still contaminated with traces of the parent quinoxalinocinnoline, therefore a correct elemental analysis could not be obtained. On basification, the purple/red solid yielded 8,10-dichloroquinoxalinocinnoline (42 h) (0.075g, 93%) as bright red needles of m.p. 250-252°C (from chloroform).

Mass spectrum of blue/red solid:

306(13),305(11),304(60),302(100),276(3),275(4),274(10),273(4),
272(7),269(4),268(10),267(11),266(7),265(6),240(4),239(4),238(3),
237(3),231(60),201(4),202(17),203(10),204(7),181(21),177(11),
176(11),175(9),160(11),158(14),146(13),144(18),129(40),128(35),
109(84),110(20),111(35).....

Mass spectrum of 8-chloroquinoxalino[2,3-c]cinnoline-5-oxide:

285(2),284(10),283(5),282(30),268(1),266(2),255(17),254(3),253(6),
252(1),240(1),126(30),124(100).....

Mass spectrum of 8,10-dichloroquinoxalino[2,3-c]cinnoline:

304(4),303(2),302(18),300(31),276(4),275(5),274(40),273(13),
272(73),203(9),202(36),201(7),148(5),146(42),145(15),144(73),
143(13),112(9),111(31),110(27),109(100),108(20),102(18),101(18),
100(31),99(31),98(12),88(14),87(18),86(13),85(9),84(24),83(16),
81(13),64(14),63(16),62(18),61(14),60(10),57(35),56(12),55(40),
52(10),51(30),50(70),43(54),41(34),39(27).....

For 8,10-dichloroquinoxalino[2,3-c]cinnoline

Found: C, 55.75; H, 2.0; N, 18.6. $C_{14}H_6N_4Cl_2$ requires
C, 55.8; H, 2.0; N, 18.6%

Reaction of 8,10-dichloroquinoxalino[2,3-c]cinnoline and its 5-oxide with gaseous hydrogen chloride

A mixture of 8,10-dichloroquinoxalinocinnoline and its 5-oxide (42 h) and (60 h) (0.15g), in chloroform (50ml), was treated with hydrogen chloride gas for 15 minutes. A red/purple solid was formed, which on filtration yielded 0.12g of tiny red/purple crystals of melting point 315-317°C. For 8,10-dichloroquinoxalinocinnoline+nHCl, this is 98% for n=3, and 89% for n=4. The filtrate from above was evaporated and dried, yielding a very small quantity of yellowish material, which was not investigated further. Basification of the red/purple material yielded 8,10-dichloroquinoxalinocinnoline (0.08g, 89%) as red crystals m.p. 250-252°C (from chloroform). This material was found to have identical n.m.r. and mass spectra to the product of the previous experiment.

Mass spectrum of red/purple product:

342(5),341(5),340(30),339(20),338(90),336(100),312(1),311(3),
310(9),309(7),308(32),703(10),306(36),305(9),304(50),303(28),
302(94),301(26),300(30),276(6),275(9),274(35),273(17),272(45),
268(8),267(30),266(18),265(70),184(5),182(15),180(42),178(40)..

Reaction of 10-methoxyquinoxalino[2,3-c]cinnoline
with gaseous hydrogen chloride

10-Methoxyquinoxalino[2,3-c]cinnoline (42 f) (0.1g) in chloroform (20ml) was treated with hydrogen chloride gas for 10 minutes. The resulting blue precipitate was isolated, yielding 0.12g of deep blue lustrous needles of m.p. 275-277°C. For 10-methoxy-quinoxalinocinnoline+nHCl, this is 100% for n=2, and 94% for n=3. On treatment of the blue solid with base, 9-chloro-10-methoxyquinoxalino[2,3-c]cinnoline (42 m) was obtained as red needles (0.85g, 76%) of m.p. 242-243°c (lit.,[31] 230-234°C)(from chloroform).

Mass spectrum of 9-chloro-10-methoxyquinoxalino[2,3-c]cinnoline:
299(3),298(24),297(10),296(74),279(2),278(12),272(1),270(16),
268(52),267(10),262(50),256(1),255(12),254(3),253(39),235(8),
234(31),228(1),227(3),226(3),225(18),220(18),219(3),142(40),
141(9),140(100),129(4),128(4),127(5),125(20),107(5),106(68),
100(9),99(34),98(5),97(90),89(10),88(32),77(16),76(19),75(29),
74(15),64(9),63(83),62(39).....

Mass spectrum of the blue solid:
300(30),298(90),285(4),283(12),270(8),268(24),256(33),254(100),
221(16),220(20),142(16),140(48),103(15),102(35),98(35),97(80)...

Reaction of 10-methoxyquinoxalino[2,3-c]cinnoline and its 5-oxide with gaseous hydrogen chloride

A mixture of 10-methoxyquinoxalinocinnoline and its 5-oxide (60 f) (0.1g) in chloroform (20ml) was treated with hydrogen chloride as described in the previous experiment. From the filtrate, after removal of the blue solid, 10-methoxyquinoxalinocinnoline-5-oxide (60 f) was obtained as 0.04g of orange/yellow needles of m.p. 274-276°C. The sample was found to be slightly contaminated with both the 9-chloro-10-methoxy- and 10-methoxyquinoxalinocinnolines (42 m) and (42 f), therefore elemental analysis was not attempted. However, it was possible to obtain a ^{1}H n.m.r. spectrum of the compound (to be found in chapter 6).

Mass spectrum of 10-methoxyquinoxalinocinnoline-5-oxide:

298(2),296(6),279(7),278(42),263(2),262(8),235(6),234(25)

220(3),219(18),124(6),110(12),70(100).....

Reactions of 10-halogeno-quinoxalino[2,3-c]cinnolines with nucleophiles

A)Reactions with sodium methoxide

Reaction of 10-chloroquinoxalino[2,3-c]cinnoline with methanolic sodium methoxide

10-Chloroquinoxalino[2,3-c]cinnoline (0.226g, 0.00085mol) was dissolved by boiling in a solution of sodium methoxide (50mg of sodium in 25ml of methanol), and dimethylformamide (10ml, as cosolvent). The solution was heated under reflux for one hour, and then allowed to cool overnight. An orange precipitate was collected by filtration, and washed with water entil the washings were free of chloride ion (tested with silver nitrate solution). The solid was recrystallised from dimethylformamide, to give 10-methoxyquinoxalino[2,3-c]cinnoline (42 f) as bright orange needles (0.185g, 83%) of m.p. 262-264°C.

Reaction of 9-chloroquinoxalino[2,3-c]cinnoline with sodium methoxide in methanol

The previous reaction was repeated using 9-chloroquinoxalino-[2,3-c]cinnoline (0.226g, 0.00085mol), except that the solution was heated under reflux for eight hours. On isolation, the product was found to be starting material, in 92% recovery. Increased reaction time (up to 10 hours) had no effect on the outcome of the reaction.

Reaction of 9,10-dichloroquinoxalino[2,3-c]cinnoline with methanolic sodium methoxide

9,10-Dichloroquinoxalinocinnoline (42 n) (0.25g, 0.00083mol) was dissolved in methanolic sodium methoxide (100mg of sodium in 40ml of methanol), and the solution was heated under reflux for 1 hour. The solution was then diluted with water, and a precipitate obtained. A ^1H n.m.r. spectrum of the crude product revealed the presence of 9-chloro-10-methoxyquinoxalinocinnoline (42 m), while the mass spectrum revealed the presence of trace amounts of a dimethoxyderivative, presumably the 9,10-dimethoxyquinoxalinocinnoline (42 q). The yield of product was 0.22g (90%). The crude product was dissolved in a further 40ml of the above methoxide solution, and heated for a further 1.5 hours, after which product was again obtained by dilution. Examination of the product by ^1H n.m.r. spectroscopy revealed the presence of the previously mentioned two isomers, in the ratio of 6:4 in favour of the mono-chloro-mono-methoxy compound. A yield of 0.21g of product was obtained, being approximately 50% of (42 m), and 35% of (42 q). Mass spectral data also show the increase in the amount of the dimethoxy-derivative. The product was redissolved in methoxide solution (40ml), and heated for a further 7.5 hours. A product was obtained by dilution, and investigated by ^1H n.m.r. spectroscopy, revealing that the relative proportions of the two components had changed to about 5:1 in favour of the dimethoxy-compound (42 q). The yield was 0.20g, being 68% of (42 q), and 13% of (42 m). Again, the mass spectrum reflects the change in distribution of products.

Mass spectrum of product after 1 hour:

299(3),298(20),297(10),296(60),293(3),292(20),271(2),270(13),
269(8),268(40),265(1),264(8),.....97(100).....

Mass spectrum of product after 2.5 hours:

299(2),298(7),297(5),296(20),293(10),292(32),271(1),270(6),
269(4),268(18),265(2),264(13).....93(100).....

Mass spectrum of product after 10 hours:

299(3),298(5),297(4),296(16),293(12),292(60),270(3),269(2),
268(8),265(3),264(15),250(3),249(12),142(8),140(3),139(8),
136(75),99(16),97(100),97(42),.....

Reaction of 10-bromoquinoxalino[2,3-c]cinnoline
with methanolic sodium methoxide

10-Bromoquinoxalino[2,3-c]cinnoline (42 k) (0.155g, 0.0005mol) was treated with methoxide solution (40mg of sodium in 40ml of methanol)as previously described for 10 hours. On isolation of the product it was found to be mostly starting material, though a trace of a methoxy- derivative was detected in the mass spectrum. The recovery was 90%.

Mass spectrum of product:

312(100),310(100),284(30),282(30),262(15),234(6),219(3),203(20).

Reaction of 9-bromoquinoxalino[2,3-c]cinnoline
with methanolic sodium methoxide

The previous experiment was repeated using an equal quantity of 9-bromoquinoxalino[2,3-c]cinnoline (42 l). No reaction took place, and the starting material was recovered in 95% yield.

B)Reactions of 10-chloroquinoxalino[2,3-c]cinnoline with nitrogen nucleophiles

a)With piperidine

10-Chloroquinoxalinocinnoline (0.266g, 0.1mol) was added to piperidine (30ml). The mixture was heated on a steam bath for 1.5 hours, the solution becoming deep red in colour. After heating, the solution was filtered hot, and a colourless crystalline solid filtered off. This solid, which was found to be water soluble was thought to be piperidine hydrochloride. The filtrate was evaporated , but some piperidine remained. An attempt was made to extract the product into chloroform, but in isolation of the product from chloroform it was found to be still contaminated with piperidine. The product was then dissolved in a 50:50 ethanol/water solution, which was then evaporated until solid started to form. The resultant precipitate was filtered off, and dried in air. Residual piperidine was no longer present. The product was obtained as fine needles, possessing a bronze coloured metallic lustre . A yield of 0.25g (79%) was obtained. It was found that the compound was very insoluble in most solvents, and attempts at recrystallisation from ethanol/water were not successful. Although no analysis of this compound was attempted, its mass spectrum is consistent with the quinoxalinocinnoline structure, and it is considered to be 10-piperidinoquinoxalinocinnoline (42 s).

Mass spectrum of 10-piperidinoquinoxalinocinnoline:

316(2),315(5),314(2),287(3),260(1),231(2),230(4),229(1),204(1),
203(2),159(3),158(3),103(50),102(40),101(15),100(8),93(46),
92(100),91(95),90(55),89(70),74(40),75(50),76(60),77(55),57(45),
56(50),55(60),53(60),52(60),51(80),50(80)..

b)With diethylamine

10-Chloroquinoxalinocinnoline (0.266g, 0.001mol) was dissolved in diethylamine (65ml), and the mixture was heated under reflux for 3 hours. The starting maerial was recovered in 80% yield.

c)With benzylamine

10-Chloroquinoxalino[2,3-c]cinnoline (0.226g, 0.001mol) was dissolved in benzylamine (50ml) and heated on a steam bath for four hours. On cooling, the solution was diluted with water, and filtered through filter paper, a dark blue solid being obtained. The solid was found to be insoluble in most solvents, though in chloroform, a purple solution was formed, which on acidification with hydrochloric acid turns red in colour. The mass spectrum of the solid indicates it to be a 1:1 adduct of 10-chloroquinoxalinocinnoline and benzylamine. The melting point of the solid was 260-264°C. The reaction was repeated in boiling benzylamine (182-185°C), resulting in recovery of 10-chloroquinoxalinocinnoline in 70% yield.

Mass spectrum of blue solid:

376(3),375(33),374(12),373(100),372(6),337(1),297(6),296(4),
295(12),298(1),282(3),280(8),269(1),268(6),267(4),266(18),
232(4),231(28),204(5),303(7),202(6).....

References

1a) P.N. Preston and G. Tennant, Chem.Rev., 1972, 27, 627;

b) J.D. Loudon and G.Tennant, Quart.Rev., 1964, 18, 389.

2) A.R. Katritzky and J.M. Lagowski, "Chemistry of Heterocyclic N-Oxides", Academic Press, New York, 1971, pp 120-141.

3) M.A. Morrison in "The Chemistry of Nitro and Nitroso Groups", Part 1, H. Feuer, Ed., Interscience, New York, 1969, pp 165-215.

4) A. Reissert, Ber., 1896, 29, 639.

5) S. Gabriel, W. Gerhard, and R. Wolter, Ber., 1923, 56, 1024.

6) I.P. Sword, J.Chem.Soc.(C), 1970, 1916.

7) J.D. Loudon and I. Wellings, J.Chem.Soc., 1960, 3462.

8) J.D. Loudon and G. Tennant, J.Chem.Soc., 1960, 3466.

9) W. Wislicenus and M. Goldchmidt, Ber., 1900, 33, 1467.

10) T. Okamato and H. Takahashi, Chem.Pharm.Bull.(Japan), 1971, 19, 1809.

11) G.W. Stacy, B.V. Ettling, and A.J. Papa, J.Org.Chem., 1964, 29, 1537.

12) R. Marshall and D.M. Smith, J.Chem.Soc.(C), 1971, 3510.

13) D. Johnston and D.M. Smith, J.Chem.Soc. Perkin I, 1976, 399.

14) J.S. Walia, L. Guillot, J. Singh, M.S. Chattha and M. Satyanarayana, J.Org.Chem., 1972, 37, 153.

15) Y. Ogata and A. Kawasaki, J.Chem.Soc.(B), 1971, 325.

16) Y. Ogata and A. Kawasaki, J.Chem.Soc. Perkin II, 1972, 1792.

17) D.B. Livingstone and G. Tennant, J.C.S.Chem.Comm., 1973, 96.

18) c f. Ref. 2, p 340.

19) c f. Ref. 1a, p 640.

20) G. Heller and G. Spielmeyer, Ber., 1925, 58, 834.

21) A. Reissert and F. Lemmer, Ber., 1926, 59, 351.

22) K. Akashi, Bull.Inst.Phys.Chem.Res.(Tokyo), 1941, 20, 798. (Chem.Abs., 1949, 43, 7934); L.C. Behr, J.Am.Chem.Soc.,1954, 76, 3672; L.C. Behr, E.G. Alley, and M. Levand, J.Org.Chem., 1962, 27, 65.

23) D. Johnston and D.M. Smith, Tetrahedron Letters, 1975, 1121.

24) S. Secareanu and I. Lupas, Bull.Soc.Chim.France, 1934, 54, 373.

25) S. Secareanu and I. Lupas, Bull.Soc.Chim.France, 1935, 55, 69.

26) T.W.M. Spence and G. Tennant, J.Chem.Soc. Perkin I, 1972, 98; Chem.Comm., 1969, 194.

27) D.M. Smith, unpublished results.

28) F. Arndt, Ber., 1913, 46, c f. Ref. 1a, 1b.

29) G. Tennant, J.Chem.Soc.(C), 1967, 1279.

30) A. Ahmad, F.A. Brand, D. Johnston, and D.M. Smith, J.Chem.Res.(S), 1980, 208.

31) A. Ahmad, M.Sc. Thesis, St. Andrews, 1978.

32) S. Kanoktanaporn and J.A.H. MacBride, J.Chem.Res., 1980, (S) 206; (M) 2941.

33) A. Ahmad and D.M. Smith, unpublished results.

34) L. M. Jackman and S. Sternhell, "Applications of N.M.R. Spectroscopy in Organic Chemistry", 2nd Edition, Pergamon Press, 1969, p 88.

35) M. Zanger, W.W. Simons, and A.R. Gennaro, J.Org.Chem., 1968, 33, 3673.

36) J. M. Appleton, B.P. Andrews, I.D. Rae, and B.E. Reichert, Aust.J.Chem., 1970, 23, 1667.

37) E.R Inman, J.M. McCrae, and J.A. Stirling, British Patent 1,413,514 (Chem.Abs., 1976, 84, 123418j).

38) G. Henseke and R. Jacobi, Annalen, 1965, 684, 146.

39) P. Vetesnik, J. Bielavsky, J. Kavalek, and M. Vecera, Coll.Czech.Chem.Comm., 1968, 33, 2902.

40a) B.M. Wepster and P.E. Verkade, Rec.Trav.Chim., 1949, 68, 88; b) B.M. Wepster and P.E. Verkade, Rec.Trav.Chim., 1949, 67, 77; c) B.M. Wepster and P.E. Verkade, Rec.Trav.Chim., 1948, 67, 425.

41) T.J. Batterham, "N.M.R. Spectra of Simple Heterocycles", Wiley, 1973, p 334.

42) D.E. Burton, D. Hughes, G.T. Newbold, and J.A. Elvidge, J.Chem.Soc.(C), 1968,1274.

43) c.f. Ref. 41, pp 325-326.

44) K. Tori, M. Ogata, and H. Kano, Chem.Pharm.Bull.(Japan), 1963, 11, 681; P. Hamm and W.V. Philipsborn, Helv.Chim.Acta., 1971, 54, 2363.

45) M. Ogata, K. Tori, and H. Kano, Chem.Pharm.Bull.(Japan), 1963, 11, 1527; M.H. Palmer and E.R.R. Russell, Chem. and Ind., 1966, 157; J.Chem.Soc.(C), 1968, 2621.

46) C. Glidewell, unpublished work; c f. C. Glidewell, T. Shepherd, and D.M. Smith, Tetrahedron Letters, 1983, 24, 3151.

47) M.J.S. Dewar and W. Thiel, J.Am.Chem.Soc., 1977, 99, 4899; W. Thiel, P. Wiener, J. Stewart, and M.J.S. Dewar, QCPE no 428.

48) D.E. Ames, C.V. Boyd, R.F. Chapman, A.W. Ellis, A.C. Lovesey, and D. Waite, J.Chem.Soc.(B), 1967, 748.

49) G.A. Swan and D.G.I. Felton, "Phenazines", Interscience, New York, 1957, pp 237-252.

50) H. McIlwain, J.Chem.Soc., 1937, 1704.

51) F. Kehrmann, Helv.Chim.Acta., 1924, 7, 1924.

52) F. Kehrmann, Ber., 1898, 31, 977; 1900, 33, 395.

53) S.F. Jaubert, Ber., 1895, 28, 508, 1584.

54) O. Fischer and C. Gieson, Ber., 1897, 30, 2489.

55) N.A. Kudryavtseva, Z.V. Pushkareva, and E.P. Darienko, Materialy Ural'sk. Soveshch. po Spektroskopii, 4th, Sverdlovsk 1963, 205-209 (Chem.Abs., 1966, 64, 19367e).

56) A. Albert, "Heterocyclic Chemistry", University of London, The Athlone Press, London, 1959, p 312.

57) F. Kehrmann and M. Sandoz, Helv.Chim.Acta., 1918,1,270; F. Kehrmann, R. Spiekel, and E. Grandmougen, Ber., 1914, 47, 3205; F. Kehrmann and M. Sandoz, Helv.Chim.Acta., 1920, 3, 104.

58) J.A. Joule and G.F. Smith, "Heterocyclic Chemistry", Van Nostrand Reinhold, London, 2nd Edition, 1978, p 64.

59) T.C. Lee and G. Salemnick, J.Org.Chem., 1975, 40, 3608.

60) c f. Ref. 58, p 73.

61) E.C. Taylor and J.S. Driscoll, J.Org.Chem., 1960, 25, 1716.

62) D.M. Smith, in "The Chemistry of Heterocyclic Compounds", Vol. 40, Part 1, P.N. Preston Ed., Wiley, New York, 1981, pp 315-316.

63) M. Ogata, Chem.Pharm.Bull.(Japan), 1963, 11, 1511.

64) J. Miller, "Aromatic Nucleophilic Substitution", Elsevier, 1968, pp 187-142,283.

65) E. Lunt, K. Washbourne, and W.R. Wragg, J.Chem.Soc.(C), 1968, 687.

66) P.J. Black and M.L. Heffernan, Aust.J.Chem., 1965, 18, 707.

67) From a sample supplied by May and Baker Ltd; c.f. Ref. 31.

68) T. Bluhm, J. Heterocyclic Chem., 1981, 18,189.

69) E.V. Donkt, R.H. Martin, and F. Greerts-Evrard, Tetrahedron, 1964, 20, 1495.

70) A.R. Katritzky, B. Ternai, and G.N.T. Tiddy, Tetrahedron Letters, 1966, 1713.

71) P. Brignell, A.R. Katritzky, R.E. Reavill, G.W.H. Cheeseman and A.A. Scarsfield, J.Chem.Soc(B), 1967, 1241.

72) W. Kemp, "Organic Spectroscopy", Macmillan, London, 1978, p 129.

73) S.F. Dyke, A.J. Floyd, M. Sainsbury, and R.S. Theobald, "Organic Spectroscopy, an intoduction", 2nd Edition, Penguin, London, p 169.

74) D.H. Williams and I. Fleming, "Spectroscopic Methods in Organic Chemistry", 2nd Edition, McGraw-Hill Ltd., London, 1978, p 135.

75) J.R Elkins and B.V. Brown, J. Heterocyclic Chem., 1968, 5, 639.

76) J.H. Bowie, G.E. Lewis, and J.A. Reiss, Aust.J.Chem., 1968, 21, 1233.

77) J.H. Bowie, R.G. Cooks, R.G. Donaghue, P.F. Halleday, and H.J. Rodds, Aust.J.Chem., 1967, 20, 2677.

78) J.A.H. MacBride, J.C.S.Chem.Comm., 1972, 1217; J.A.H. MacBride, S. Kanoktanaporn, and T.J. King, J.Chem.Res.(S), 1980, 204; J.A.H. MacBride, J.C.S.Chem.Comm., 1974, 359.

79) E.K. Fields and S. Meyerson, J.Am.Chem.Soc., 1966, 88, 2836.

80) D.C. DeJongh, R.Y. Van Fossen, and C.F. Bougeois, Tetrahedron Letters, 1967, 3, 271.

81) R.F. Brown and R.K. Sally, Aust.J.Chem., 1966, 19, 1045.

82) F.D. Popp, R.J. Dubois, K.T. Potts, and E. Brugel, Org.Mass. Spectrom., 1970, 3, 1169.

83) L.F. Fieser and E.L. Martin, J.Am.Chem.Soc., 1935, 57, 1835.

84) F. Bell and J. Kenyon, J.Chem.Soc., 1926,954.

85) F.D. Chattaway and K.J.P. Orton, J.Chem.Soc., 79, 466.

86) Dictionary of Organic Compounds, 4th Edition, Eyre and Spottiswoode Ltd., 1965, Vol. 2, p 595.

87) R.C. Fuson, R.A. Baumann, E. Howard Jnr., and E. Marvell, J.Org.Chem., 1947, 12, 799.

88) J.K. Landquist, J.Chem.Soc., 1956, 2550.

89) K. Tanaka, M. Shimazaki, and Y. Murakami, Chem.Pharm.Bull.(Japan), 1982, 30, 2714.

90) W.C. Lothrop, J.Am.Chem.Soc., 1942, 64, 1698.

91) R.C. Elderfield, W.T. Gensler, T.H. Bembry, T.A. Williamson, and H. Weist, J.Am.Chem.Soc., 1946, 68, 1589.

92) H. Green and A.R. Day, J.Am.Chem.Soc., 64, 1167.

93) c f. Ref. 89.

94) Dictionary of Organic Compounds, 4th Edition, Eyre and Spottiswoode Ltd., London, 1965, Vol.1, p 418.

95) D. Britton and W.E. Noland, J.Org.Chem., 1962, 27, 3219.

96) Dictionary of Organic Compounds, 4th Edition, Eyre and Spottiswoode Ltd., London, 1965, Vol.1, p 417.

97) H.A. Mayes and E.E. Turner, J.Chem.Soc., 1928, 691.

98) B.M. Wepster and P.E. Verkade, Rec.Trav.Chim., 1946, 68, 77.

99) H. Herz and J. Wagner, Monatsh., 1946, 76, 32.

100) H.H. Hodgson and A. Kershaw, J.Chem.Soc., 1929, 2917.

101) H. Hubner, Annalen, 1881,209, 364.

102) W.H. Poeshe, J.Chem.Soc(C), 1966, 890.