CHLORINATION OF QUINOXALINO[2,3-*c*]CINNOLINES:

MECHANISTIC STUDIES

A thesis presented to the University of St. Andrews

for the degree of Master of Philosophy

by

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November 1995

University of St Andrews

CONTENTS

Declaration

I, Charles Richard White, hereby certify that this thesis has been composed by me, that is an accurate representation of the work undertaken by me in the University of St. Andrews since my admission as a Research Student on 1st October 1994, and that it has not been accepted in any previous application for any Higher Degree or professional qualification.

November 1995

Signed

I hereby certify that Charles Richard White has fulfilled the Regulations appropriate to the Degree.

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ACKNOWLEDGEMENTS

I am deeply indebted to Dr. David Smith for his excellent supervision, continual encouragement and enthusiasm during my tenure of this studentship and during the writing of this thesis.

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A note of thanks also goes to Dr. T. Shepherd for permission to reproduce Figure 2 from his Ph.D. thesis (1983)

My gratitude is unbounded for my parents who sponsored me throughout my research and without whom this thesis could not have been attempted.

Finally I would like to thank my friends in the School of Chemistry and especially Dr. Smith's research group; Neil, Mike, Colin, Brodyck and Karen, and also to all the staff in the Central Bar and Phil Gauld in the Students' Union.

ABSTRACT

Section 1 (Introduction) gives a brief outline of some cyanide-induced cyclisation reactions of *ortho*-substituted nitrobenzene derivatives, and the proposed mechanism for the cyclisation of *N*-(*o*-nitrobenzylidene)-*o*-phenylenediamines to quinoxalino[2,3-*c*]cinnolines. An overview of the mechanism for the chlorination of the quinoxalinocinnoline ring and the reasoning behind the hypothesis is also given, as are the aims of the project.

Section 2 (Results and Discussion) develops the mechanistic ideas outlined in Section 1 relating to the chlorination reaction, and attempts to divert the course of this reaction by hindering the protonation of the quinoxalinocinnoline at the preferred location. Chlorination of 1-methylquinoxalino-[2,3-*c*]cinnoline, however, still follows the usual pathway, although the reaction is both slow and incomplete. These results therefore support the previous proposal that protonation occurs preferentially at N-12.

Attempts to synthesise the analogous ring system in which N-12 is lacking have so far met with no success.

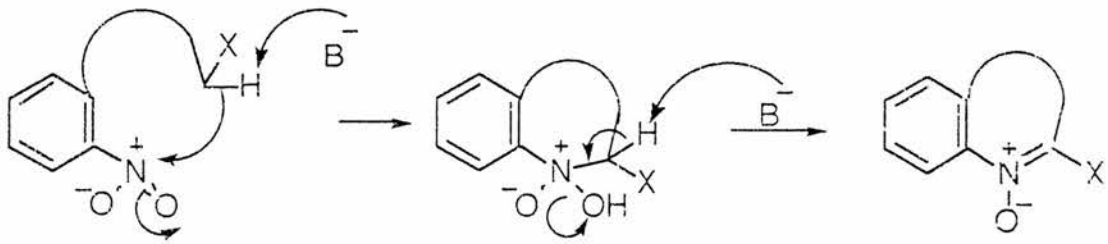
Section 3 (Experimental) details the synthetic procedures used and this is followed by the **Bibliography**.

SECTION 1

INTRODUCTION

The formation of heterocyclic compounds from the reaction of aromatic nitro-groups and *ortho*-substituents has been well known for many years, and has been the subject of two major reviews.[1,2] Most of these reactions appear to involve attack by a nucleophilic centre in the *ortho*- side-chain upon the electron-deficient nitro group. In the generally-accepted mechanism for these reactions, this attack occurs at the nitrogen (Scheme 1), although there are examples where intramolecular redox processes appear to be involved, and it is possible that these may proceed by initial nucleophilic attack on the oxygen.

SCHEME 1

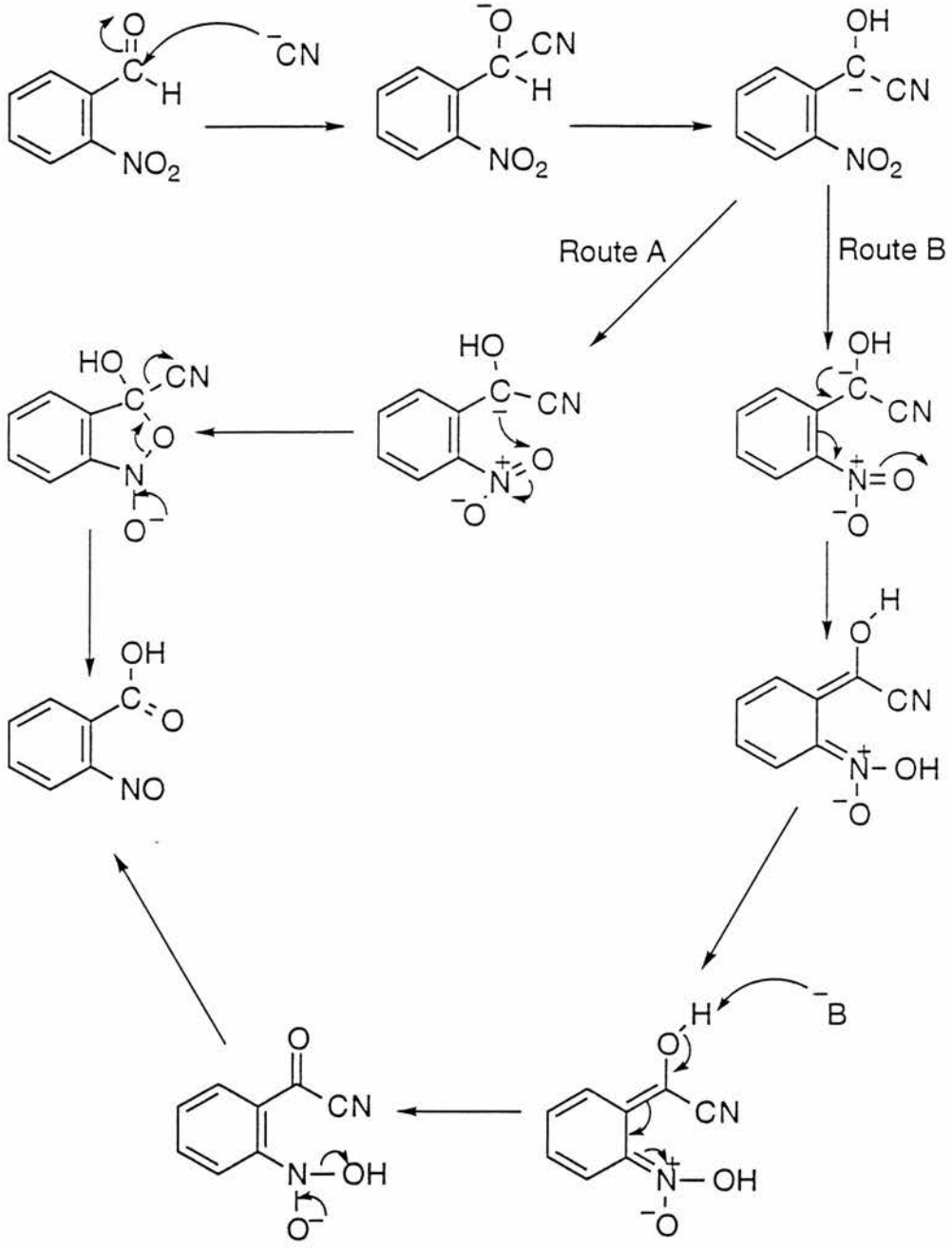


X = Electron Withdrawing Group.

The most common way of generating the nucleophilic centre in the *ortho*-side chain is by deprotonation of an 'activated' methylene group. However, an alternative method is by addition of an external nucleophile to an electrophilic double bond: for example, by addition of cyanide ion to a carbonyl compound or Schiff base. An interesting example of the former is the conversion of *o*-nitrobenzaldehyde into *o*-nitrosobenzoic acid initiated by cyanide ion.[3] The mechanism for this conversion is not yet fully understood, but it is possible that the initial addition of cyanide ion is followed by proton transfer from carbon to oxygen, as in the benzoin

reaction; the resulting stabilised carbanion may then undergo further possible transformations as shown in Scheme 2.*

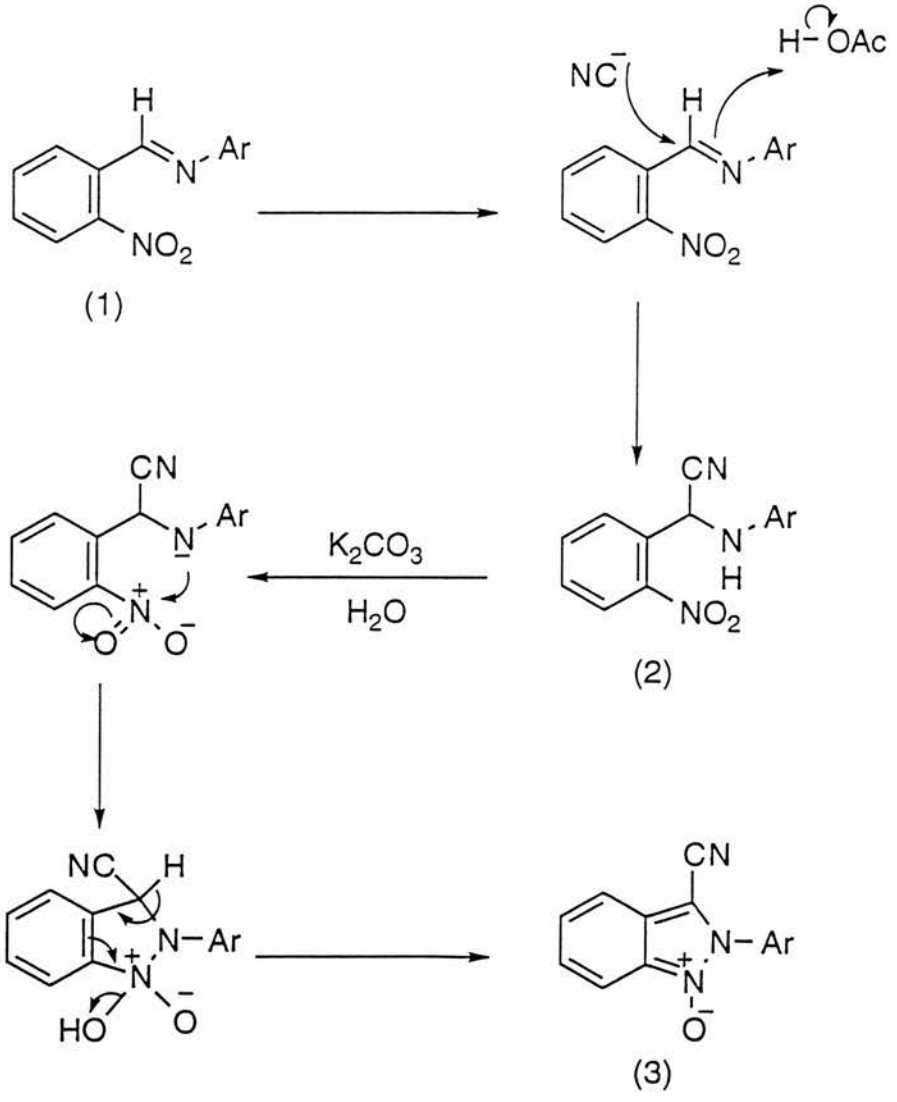
SCHEME 2



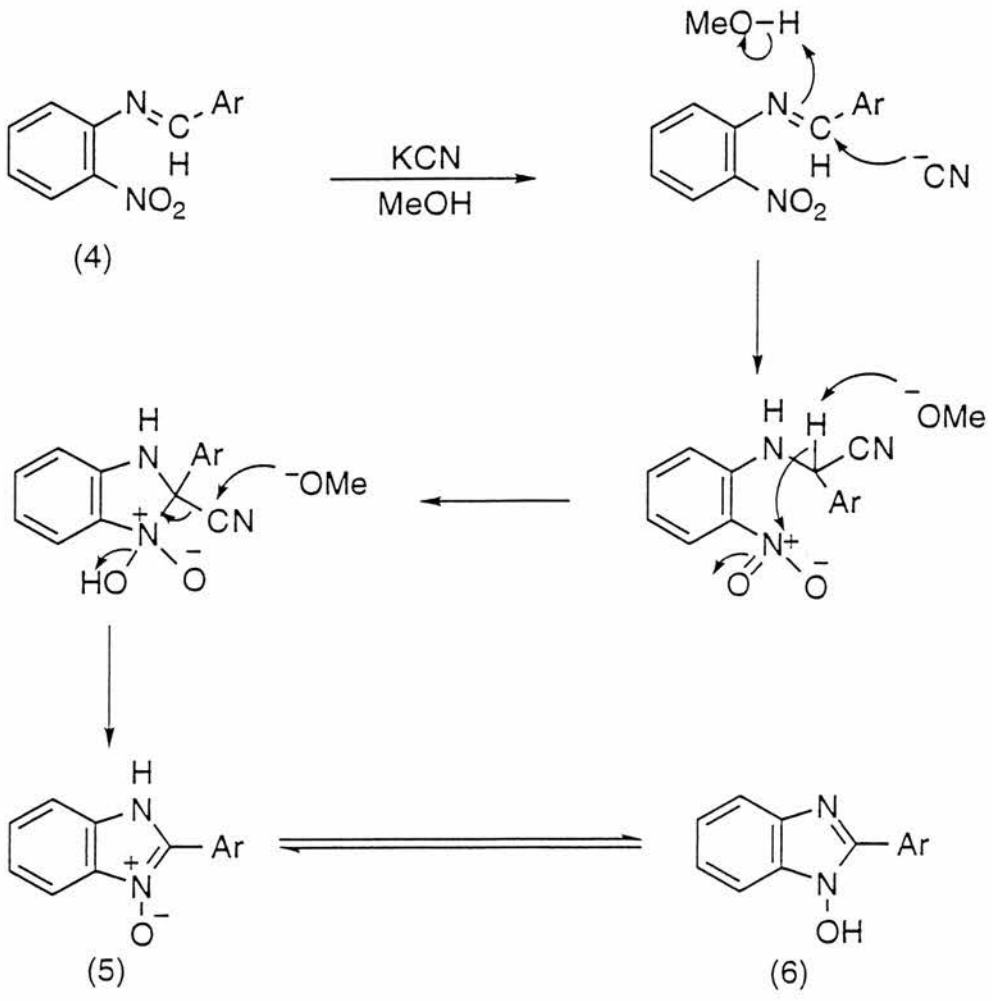
* Formation of a five membered ring by attack of a nucleophile on a doubly-bonded *carbon* constitutes a 5-*Endo-Trig* process which is disfavoured according to Baldwin's Rules.[4] Literature searches have shown no precedent for these rules to apply to systems where the electrophilic centre is a doubly-bonded *oxygen*.

N-*o*-Nitrobenzylideneanilines (**1**) react with potassium cyanide in acetic acid to give initially the HCN adducts (**2**), and these undergo base-catalysed cyclisation, under very mild conditions (aqueous potassium carbonate) to 2-aryl-3-cyano-2*H*-indazole 1-oxides (**3**) (Scheme 3).[5] *N*-Benzylidene-*o*-nitroanilines (**4**), with the *o*-nitro group in the other ring, are cyclised in methanolic potassium cyanide to give 2-aryl-1*H*-benzimidazole 3-oxides (**5**) [which are tautomeric with 2-aryl-1-hydroxybenzimidazoles (**6**)] (Scheme 4).[6]

SCHEME 3

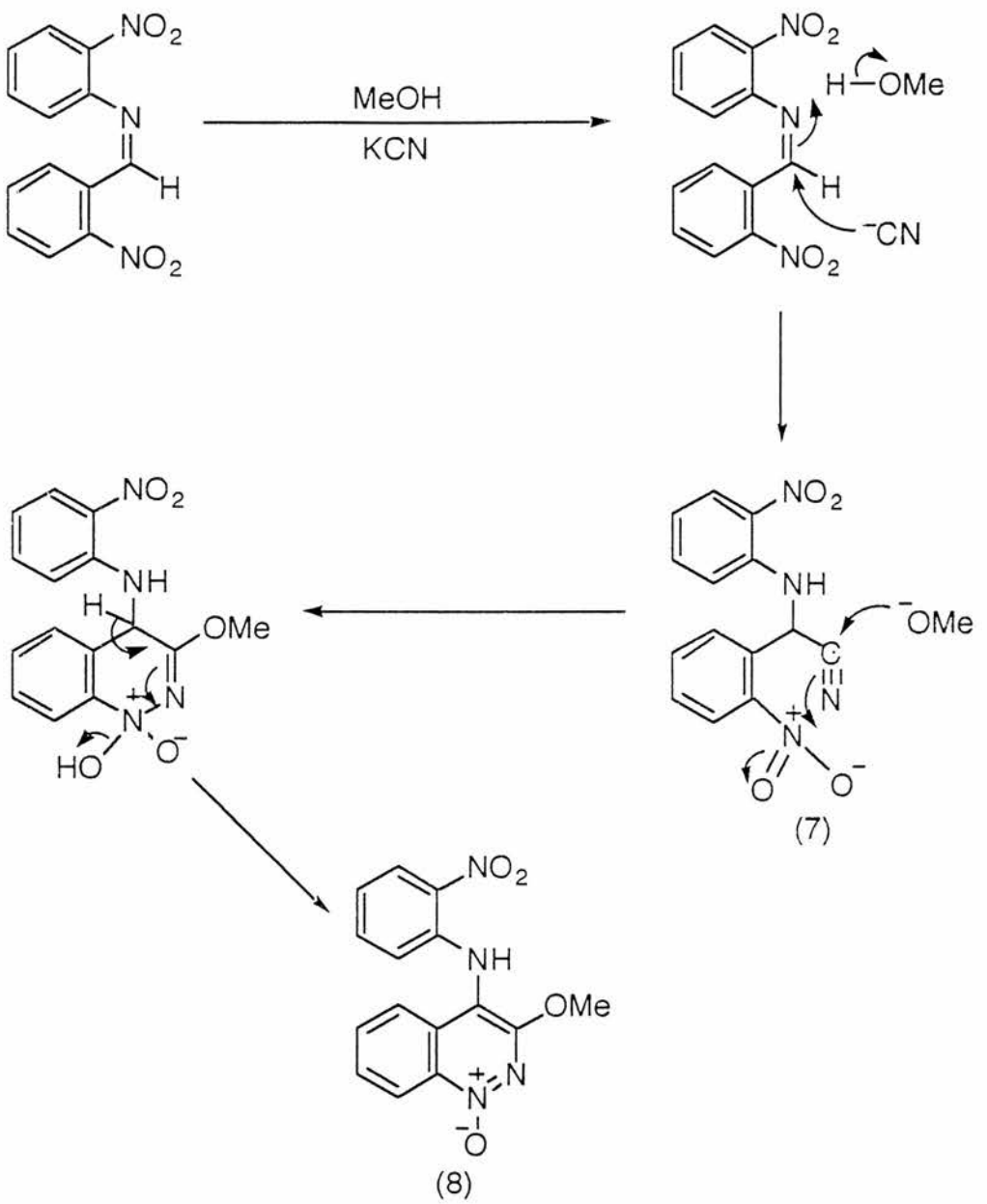


SCHEME 4



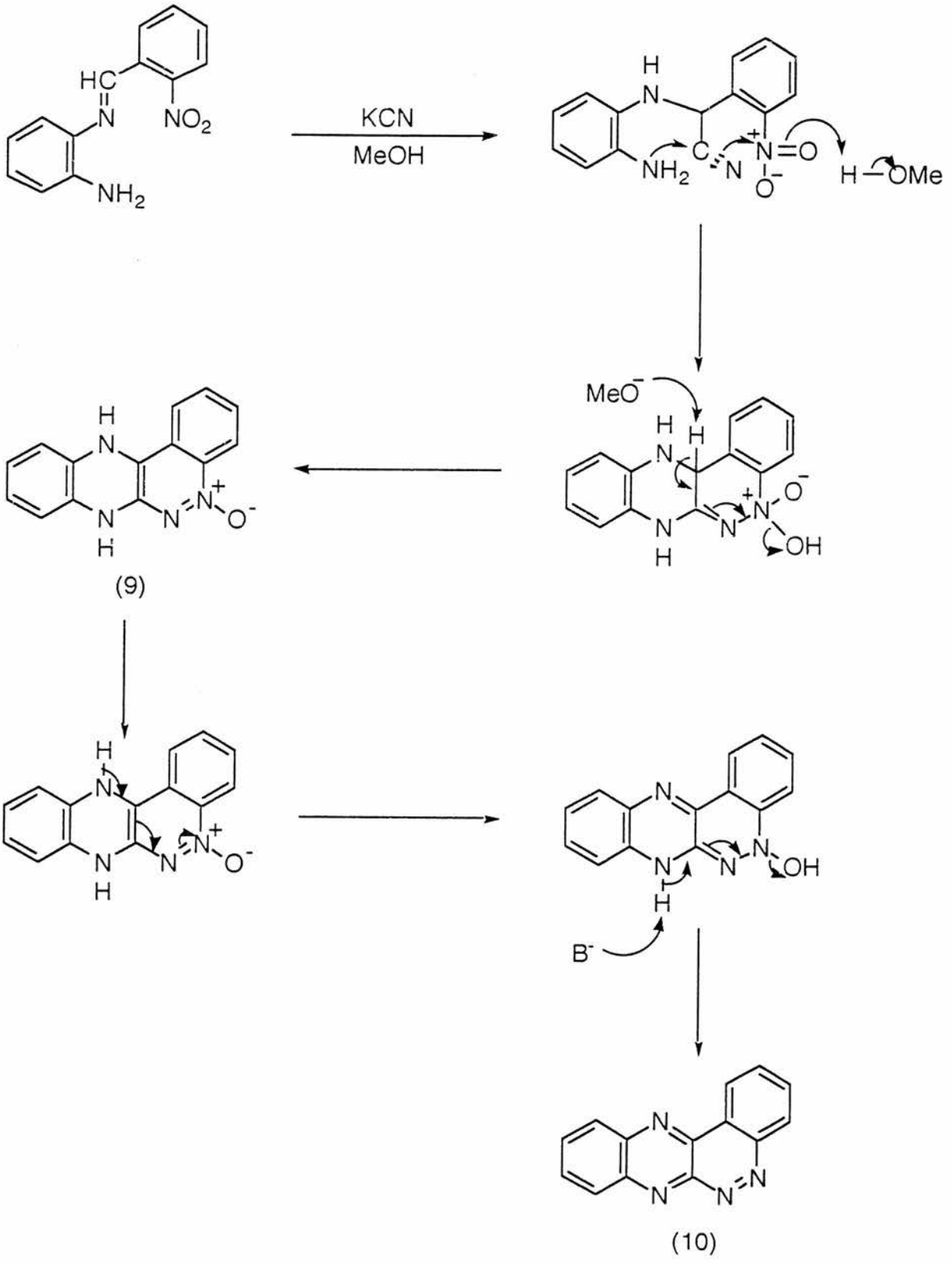
When there is an *o*-nitro group in both rings, reaction with potassium cyanide in methanol results in neither of the above reactions being observed. The product which crystallises out from the refluxing methanolic cyanide solution is neither an indazole oxide nor a benzimidazole oxide, but an orange/red compound identified as 3-methoxy-4-(*o*-nitroanilino)-cinnoline 1-oxide (**8**) (Scheme 5).[6] The formation of (**8**) is most simply explained by the addition to the C=N group of cyanide ion and a solvent derived proton. The methoxide ion thus generated then attacks the cyano-group in the intermediate (**7**), and this initiates attack by the cyano-nitrogen upon the nitro group to yield, after dehydration, the final product (**8**).

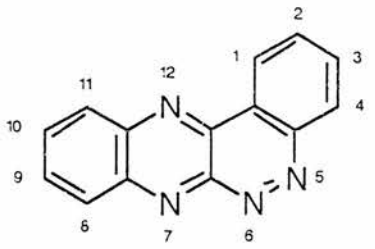
SCHEME 5



Introduction of an internal nucleophile into the amine-derived ring of the Schiff base permits intramolecular attack upon the cyano group in competition with the attack of the external nucleophile (methoxide ion). When the internal nucleophile used is an *o*-amino-group, the expected final structure becomes (**9**) (Scheme 6). However the product is in fact the dehydrated, fully conjugated molecule, quinoxalino[2,3-*c*]cinnoline (**10**).[7]

SCHEME 6





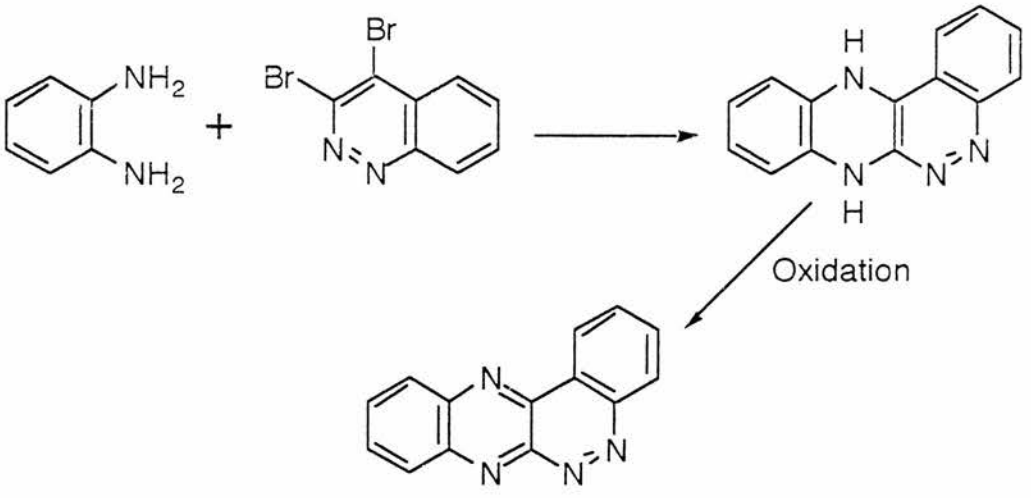
(10)

QUINOXALINO[2,3-*c*]CINNOLINE

The structure (**10**) has been supported by mass spectral data showing an especially large peak at $(M-28)^{+\cdot}$ due to the loss of the azo-nitrogens N-5 and N-6. This loss of dinitrogen has also been observed during flash vacuum pyrolysis of compound (**10**).[8]

The final confirmation of the structure was the independent synthesis of (**10**) *via* the reaction of 3,4-dibromocinnoline and *o*-phenylenediamine followed by oxidation (Scheme 7).[8]

SCHEME 7

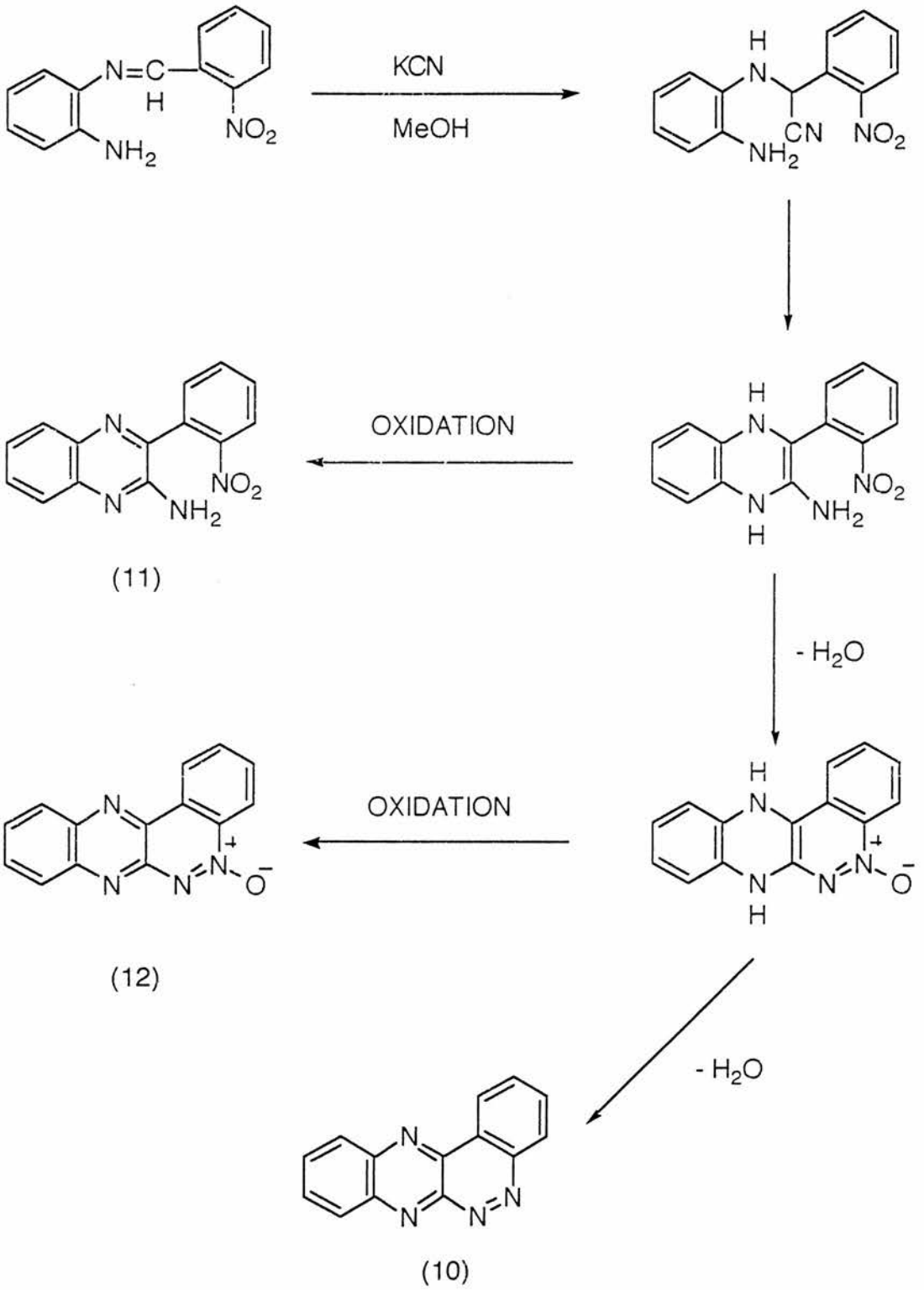


(10)

In the synthesis of the quinoxalinocinnoline ring system by the Schiff base/ cyanide route, a potential problem can be the formation of by-products (**11**) and (**12**). These probably

arise by oxidation of one or other of the intermediates shown in Scheme 8, but the problem can be eliminated (or at least minimised) by maintaining an inert atmosphere and degassing all solvents.

SCHEME 8



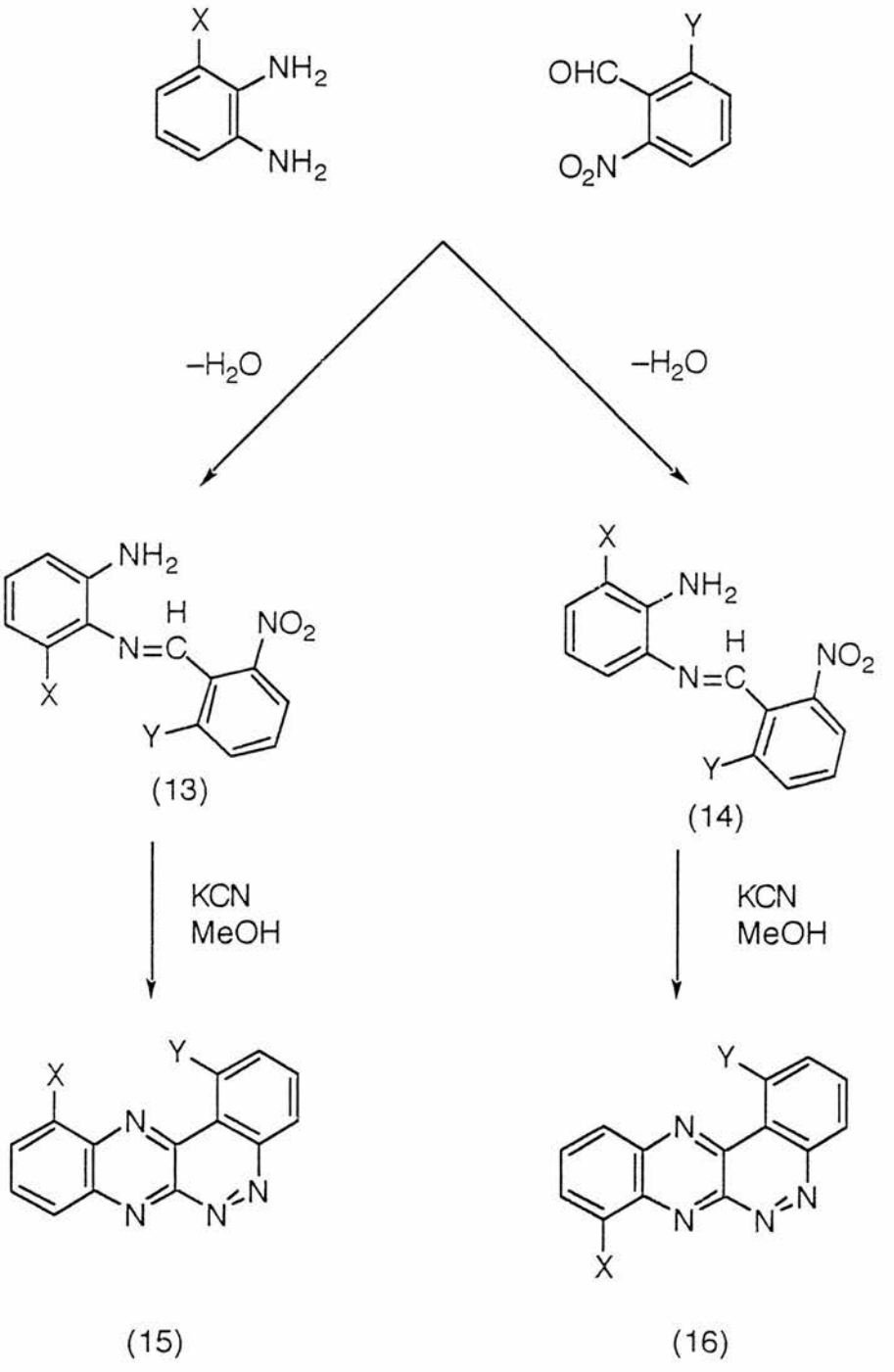
(11)

(12)

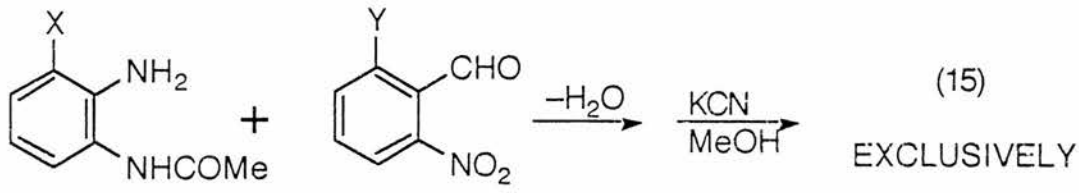
(10)

Extension of the synthesis to substituted quinoxalino[2,3-*c*]cinnolines is subject to two major limitations. The first is the availability of a suitably substituted *o* -nitrobenzaldehyde. The second is that the use of an unsymetrically substituted diamine for the formation of the anil (Schiff base) might give two isomers (**13** and **14**), and these isomers (or the resulting quinoxalinocinnolines [**15** and **16**]) might be very difficult to separate and distinguish from each other (Scheme 9).

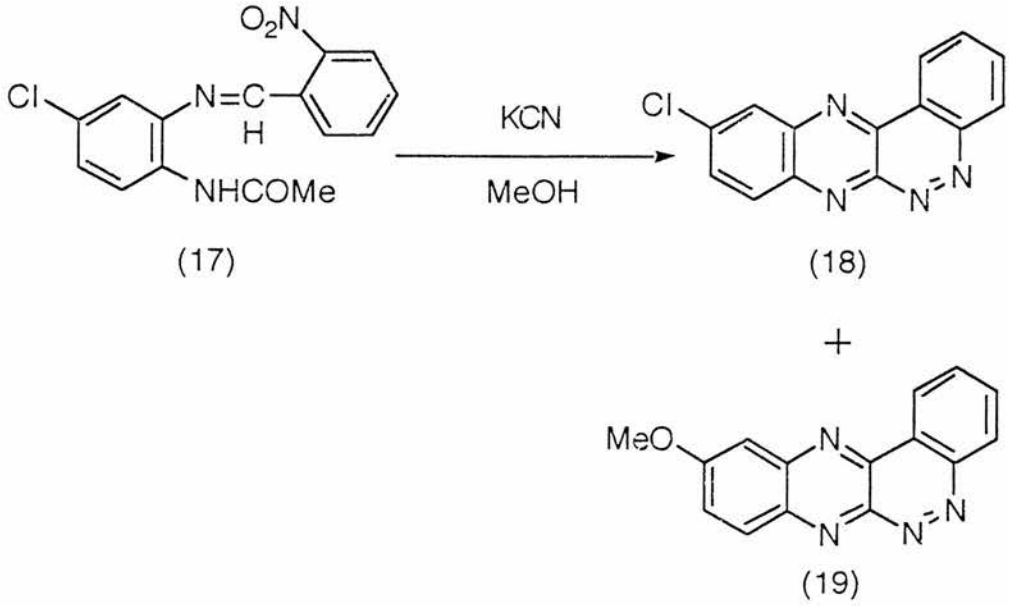
SCHEME 9



This second problem was overcome by the use of an *o*-aminoacetanilide for the formation of the Schiff base. Cyclisation of this was accompanied by deacetylation and the required quinoxalino[2,3-*c*]cinnoline was formed directly with no need for a separate deprotection step. This enabled the individual substituted quinoxalino[2,3-*c*]cinnolines to be obtained unambiguously,[9] i.e.:



During the work to make and examine quinoxalino[2,3-*c*]cinnoline analogues it was found that the cyclisation of 4'-chloro-2'-(2-nitrobenzylideneamino)acetanilide (**17**) to obtain the 10-chloroquinoxalino[2,3-*c*]cinnoline (**18**) was strongly time dependent with the yield of (**18**) dropping off markedly as time progressed. Both ^{1}H NMR and mass spectra showed the presence in the product of a methoxy-group, which suggested displacement of the chlorine with methoxide to give 10-methoxyquinoxalino[2,3-*c*]cinnoline (**19**)[3].



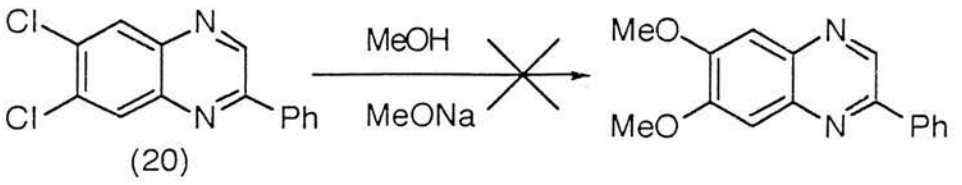
This is confirmed by heating to reflux a solution of 10-chloroquinoxalino[2,3-*c*]-cinnoline and sodium methoxide in methanol which gives 10-methoxyquinoxalino[2,3-*c*]-cinnoline in 82% yield.

Attempted displacement of a chlorine in the 9-position, even under more forceful conditions, is usually unsuccessful.[9] However when 9,10-dichloroquinoxalino-[2,3-*c*]cinnoline is heated with sodium methoxide in methanol, the 10-position is readily substituted - unsurprisingly - but after an extended period of time the chlorine at the 9-position also undergoes substitution.

The C-10 position is so prone to substitution that attempts to isolate 10-chloro-9-methoxyquinoxalino[2,3-*c*]cinnoline from the cyclisation of the corresponding Schiff base have proved impossible, due to the lability of the chlorine in the methoxide/methanol solution.

The reactions of other 10-halogenoquinoxalino[2,3-*c*]cinnolines also show this trend. However, overall bromo- is less labile than chloro-, and fluoro- is more labile to the extent that 10-fluoroquinoxalino[2,3-*c*]cinnoline has so far proved impossible to isolate, and the 9-fluoro isomer also undergoes nucleophilic substitution.[10]

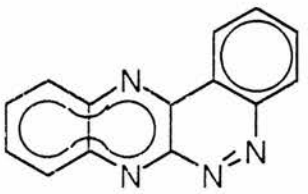
The corresponding simple quinoxalines, e.g. (**20**), do not make good models for the quinoxalino[2,3-*c*]cinnolines: these have proved to be resistant to any nucleophilic substitution of halogens, and even the corresponding fluoroquinoxalines undergo nucleophilic substitution only under forcing conditions.[11]



(20)

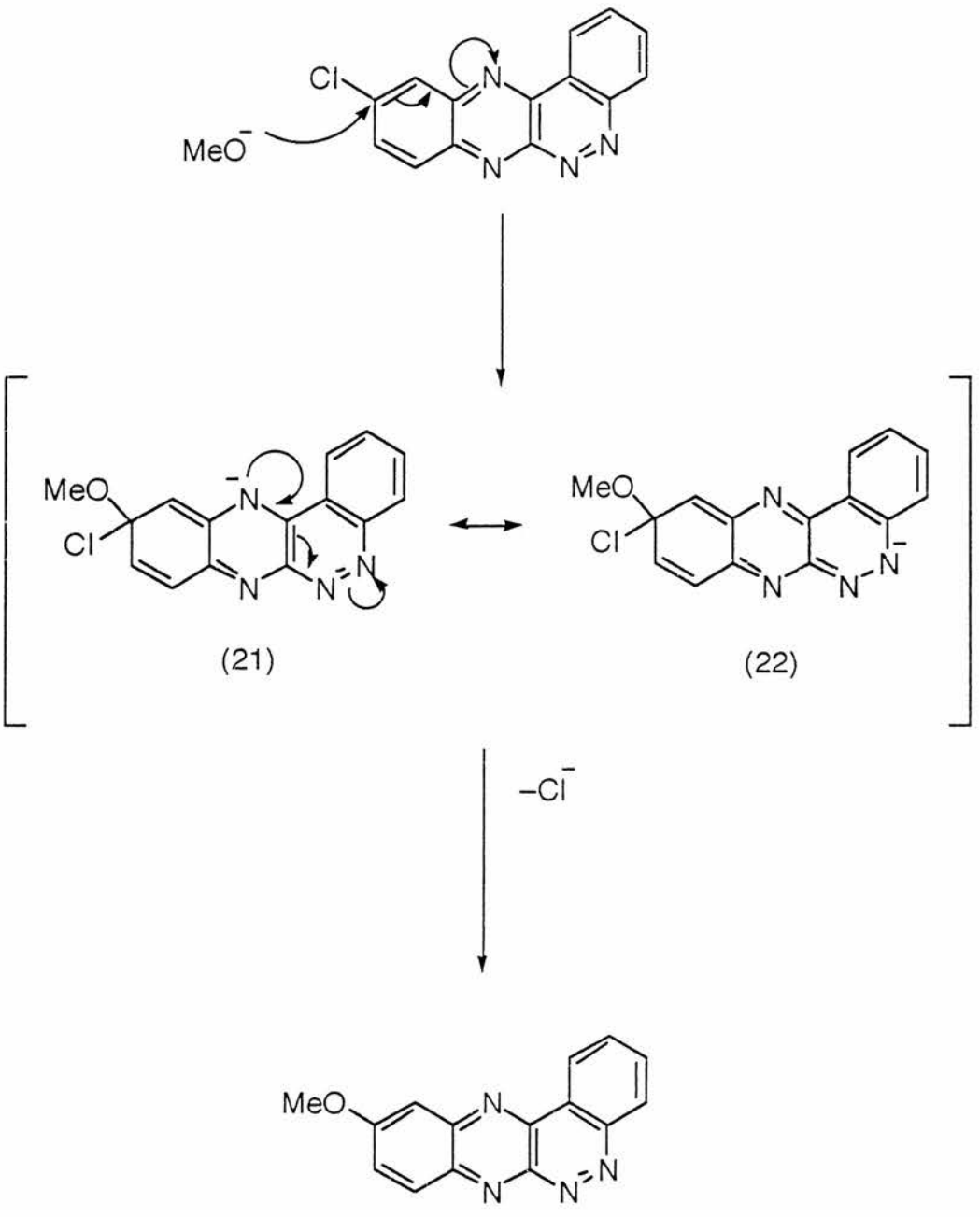
All of this makes halogenoquinoxalino[2,3-*c*]cinnolines quite remarkable compounds since they often react readily at C-10 (and occasionally at C-9) with nucleophiles. However, they are as resistant to nucleophilic substitution of chlorine at C-1, C-2, C-3 and C-4 as, say, chlorobenzene.

One aid in helping to explain these phenomena are MNDO calculations which propose that the most plausible delocalisation pattern is thus:[9]

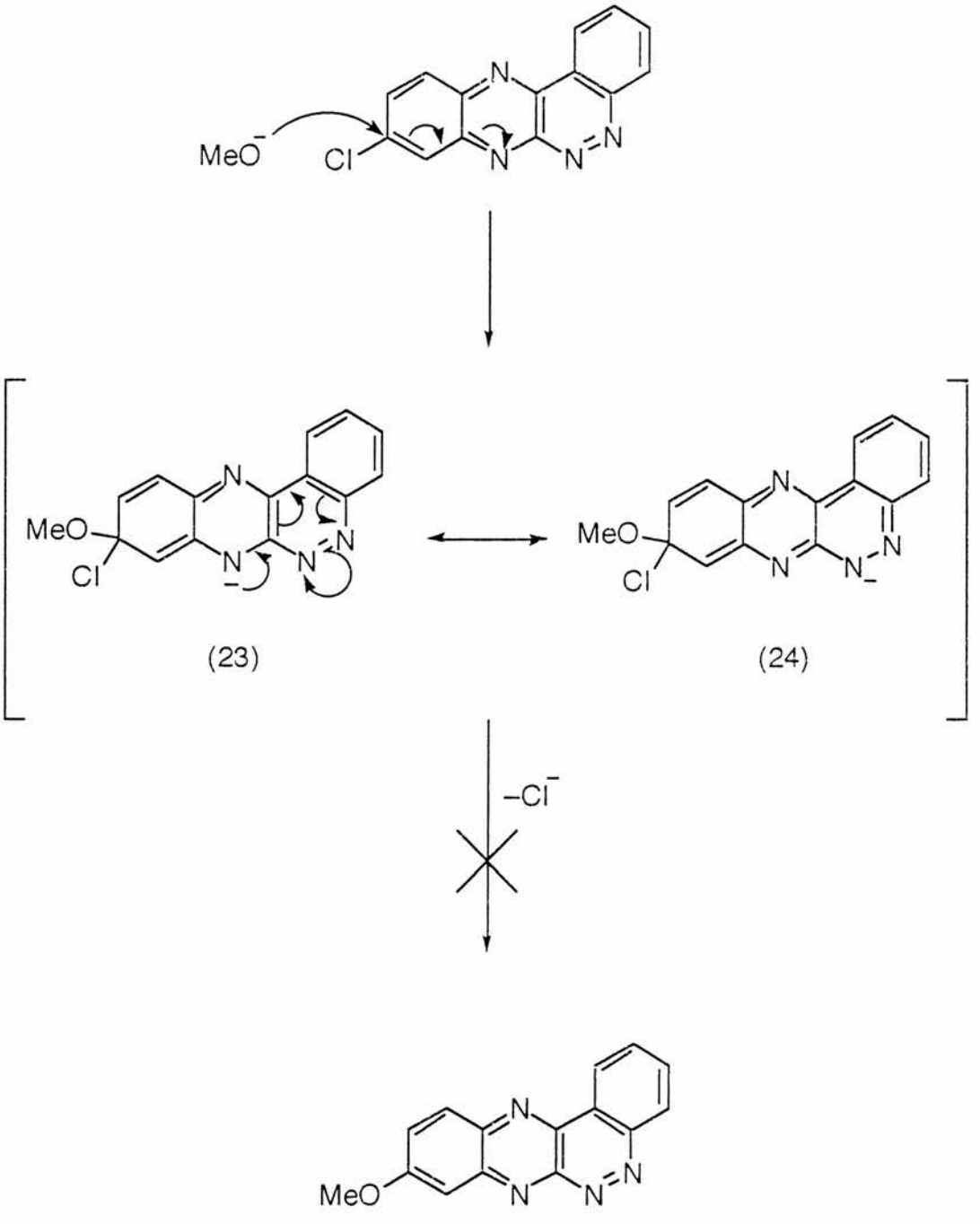


QUINOXALINO[2,3-*c*]CINNOLINE

What the calculations suggest is that the π-electrons are delocalised in three systems: firstly there is a 10π- system (quinoxalino), then a 6π- system (benzene) and finally a 2π-system (azo), and that these behave as if they are essentially independent of one another. This offers a possible explanation for the distinct lack of reactivity at C-1 - C-4, but does not explain the enhanced reactivity at C-10 relative to simple quinoxalines. So nucleophilic attack at C-10 must also involve the remainder of the ring system. The resultant negative charge may be delocalised as far as N-12 (**21**) while maintaining a 10π-system (at the cinnoline 'end' of the structure) and then through even to N-5 whilst maintaining an intact 6π-system (**22**).



Attack at C-9 still maintains the 10π (cinnoline) system if the charge is delocalised as far as N-7 (**23**) but then, if delocalisation extends to N-6 (**24**) the 6π- (benzene) system is also disrupted and therefore this is less favourable. Attack at C-10 therefore permits better stabilisation of the anionic intermediate and so is expected to be the more favoured reaction.



As mentioned previously (page 7) quinoxalinocinnoline 5-oxides are sometimes formed as by-products of the cyclisation reactions. One surprising and very interesting area of work has been opened up by the reaction of a mixture of the unsubstituted quinoxalino[2,3-*c*]cinnoline and its *N*-oxide (**12**) with phosphorus trichloride in an attempt to reduce the *N*-oxide function. It is the quinoxalinocinnoline ring which reacts, and not the *N*-oxide. The

product is a monochlorinated species with the chlorine covalently bonded to the quinoxalino[2,3-*c*]-cinnoline ring.[9]

It has been found that reaction of quinoxalino[2,3-*c*]cinnolines with chloride ions in acidic media will cause chlorination of the quinoxaline ring. Freshly redistilled phosphorus trichloride has no effect. Only when the reagent is 'aged' or the solvent is not dry will the chlorination take place, suggesting that the actual chlorinating agent is hydrogen chloride. This can be easily confirmed by bubbling dry hydrogen chloride gas through a solution of quinoxalino[2,3-*c*]-cinnoline in chloroform which gives a characteristic deep blue-coloured precipitate, and this, when subjected to a basic work-up, provides the monochloro-quinoxalino[2,3-*c*]cinnoline in excellent yield.

It has been shown that the reaction of a quinoxalino[2,3-*c*]cinnoline with dry hydrogen chloride gas will give the 10-chloroquinoxalino[2,3-*c*]cinnoline, exclusively and in very good yield. If C-10 is already substituted in the starting compound, no further chlorination is generally observed, although the 10-methoxy compound is chlorinated at C-9.

Experimentally, differentiation between the isomeric 9- and 10-substituted quinoxalino-[2,3-*c*]cinnolines proves, understandably, to be difficult, since the ^{1}H NMR spectra of, for example, the 9- and 10-chloro derivatives (and even their melting points) are very similar. It is only through independent synthesis of both isomers, and the assignments of all the aromatic signals in their ^{1}H NMR spectra, that these products have been unambiguously identified.

It is possible, thanks to MNDO calculations, to propose a likely mechanism for this novel chlorination reaction.

Initially the quinoxalinocinnoline becomes protonated at one of the four nitrogens: the calculations suggest N-7 an N-12 to be the most likely two. This enables the incoming halogen nucleophile to attack the quinoxalino 'end' of the molecule and have the nucleophile's negative charge delocalised as far as the protonated nitrogen. After oxidation of the adduct the fully conjugated halogenoquinoxalino[2,3-*c*]cinnoline is obtained.[9]

If N-7 was the preferred site for protonation then the resultant attack of the halogen would be at C-9, and if N-12 were the favoured site of protonation then the likely final product would be a 10-halogenoquinoxalino[2,3-*c*]cinnoline (Scheme 10).

From the calculations it is predicted that there should be very little difference between the probability of protonation at N-7 and N-12. N-12 would seem to be favoured due to its greater nucleophilicity (and hence basicity) over N-7 but protonation at N-7 leads to the more stable cation (with the lowest ΔH°_{f}).

From the experimental results the 10-chloroquinoxalino[2,3-*c*]cinnoline is the exclusive product from acidic chlorination of unsubstituted quinoxalino[2,3-*c*]cinnoline, which would seem to favour the mechanism proposing initial protonation at N-12.

It is hoped then that by inhibiting protonation at N-12 the chloride nucleophile could be diverted away from attack at C-10 to attack at C-9, or indeed could be prevented from attacking the protonated quinoxalino[2,3-*c*]cinnoline molecule at all.

There are two possible ways of preventing protonation at N-12 and these are:

1. Block approach to N-12 using the steric influence of another substituent bonded to the ring .

2. Remove N-12 altogether and instead attempt to halogenate a quino[2,3-*c*]cinnoline.

The former possibility has already been briefly touched upon in previous work. Of the two possible positions, C-1 and C-11, the better position to attach the bulky substituent would be at C-1 since attachment at C-11 would leave the substituent just too far removed from N-12 to ensure complete diversion of the incoming proton.

The synthesis of the starting 1-substituted quinoxalino[2,3-*c*]cinnoline molecules brought forth its own problems since the starting materials, namely 2-nitro-6-substituted benzaldehydes, can be difficult to obtain.

The first group used at the C-1 position was a halogen, since halogens have a relatively large atomic radius ; 2-chloro-6-nitrobenzaldehyde is expensive but available, and 2-bromo-6-nitrobenzaldehyde involves a drawn-out but relatively simple synthesis.

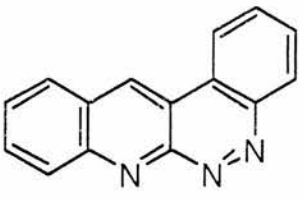
Upon chlorination of these 1-halogenoquinoxalino[2,3-*c*]cinnolines it was found that the yields of the chlorinated products dropped as the atomic radius of the C-1 halogen increased, such that chlorination of 1-chloroquinoxalino[2,3-*c*]cinnoline gave a 68% yield of dichloroquinoxalino[2,3-*c*]cinnoline (compared to 75% chlorination of unsubstituted quinoxalino[2,3-*c*]cinnoline). Chlorination of 1-bromoquinoxalino[2,3-*c*]cinnoline then only gave a 30% yield of bromochloroquinoxalino[2,3-*c*]cinnoline with a marked drop in rate of the chlorination showing some disruption of the mechanism. Unfortunately 1-iodoquinoxalino-[2,3-*c*]cinnoline proved impossible to synthesise.

Upon further consideration it was thought that although the halogen, due to its size, could interfere with the protonation, the very fact that the halogen is itself an electronegative atom may mean the approach of the proton is *assisted.* If this were the case calculations suggest the incoming proton must approach from out of the plane of the ring and the hence the larger the substituent on C-1 then the slower the protonation. This may well explain why a halogen at C-1 does not affect the overall yield of the chlorinated product but why the chlorination of 1-bromoquinoxalino[2,3-*c*]cinnoline is slower than chlorination of 1-chloroquinoxalino[2,3-*c*]-cinnoline.

An alternative group which has a similar effective radius to the chlorine atom is methyl. This has the advantage of not being electronegative and not being capable of forming hydrogen bonds. It should therefore be unable to attract the HCl-derived proton and thus aid the protonation at N-12.

Unfortunately synthesis of 1-methylquinoxalino[2,3-*c*]cinnoline requires 2-methyl-6-nitrobenzaldehyde as the starting aldehyde and this particular aldehyde is not readily synthesised. This is further discussed in Section 2.

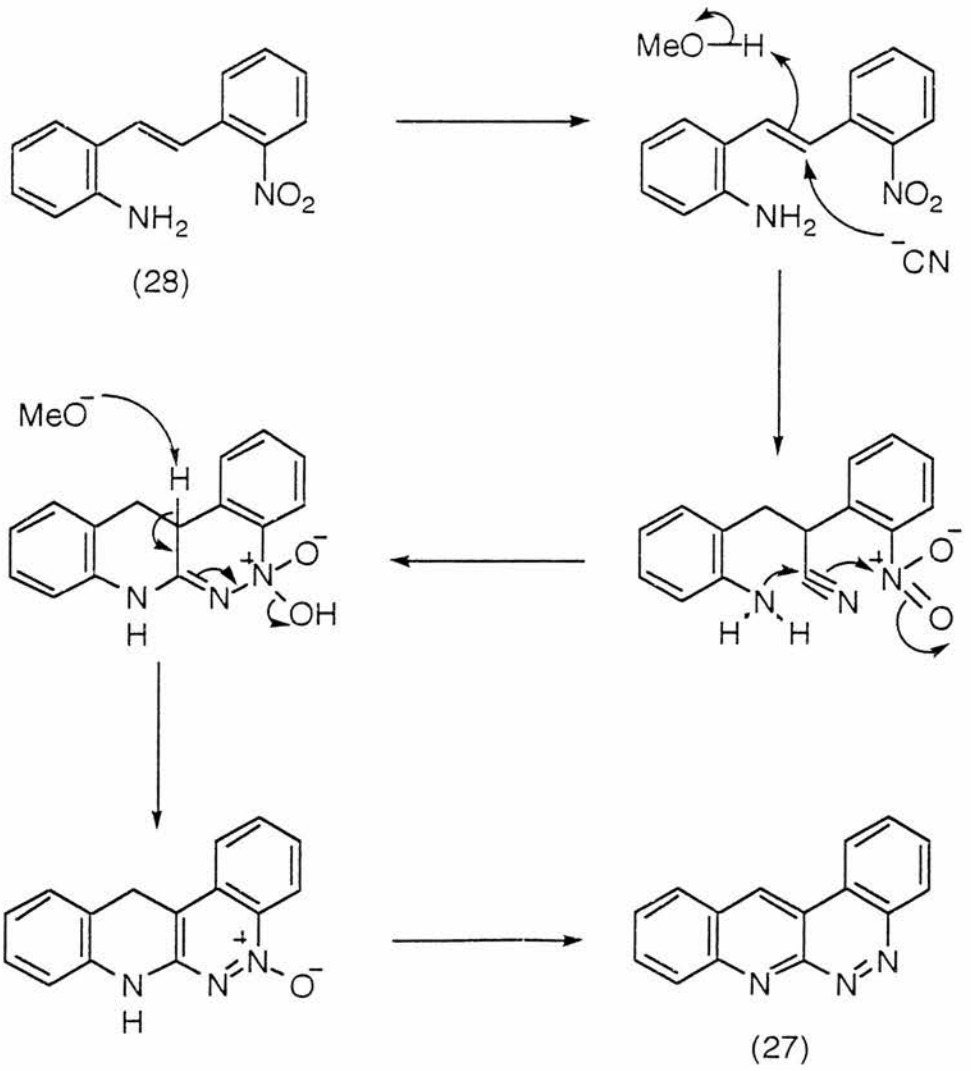
The second possibility for preventing N-12 protonation was to remove the nitrogen altogether from the 12- position to give a starting quino[2,3-*c*]cinnoline (**27**).



(27)

It was hoped that by using a stilbene instead of a Schiff base then hydrogen cyanide would add across the double bond in the same way as it does in the anil. In this way the

SCHEME 11

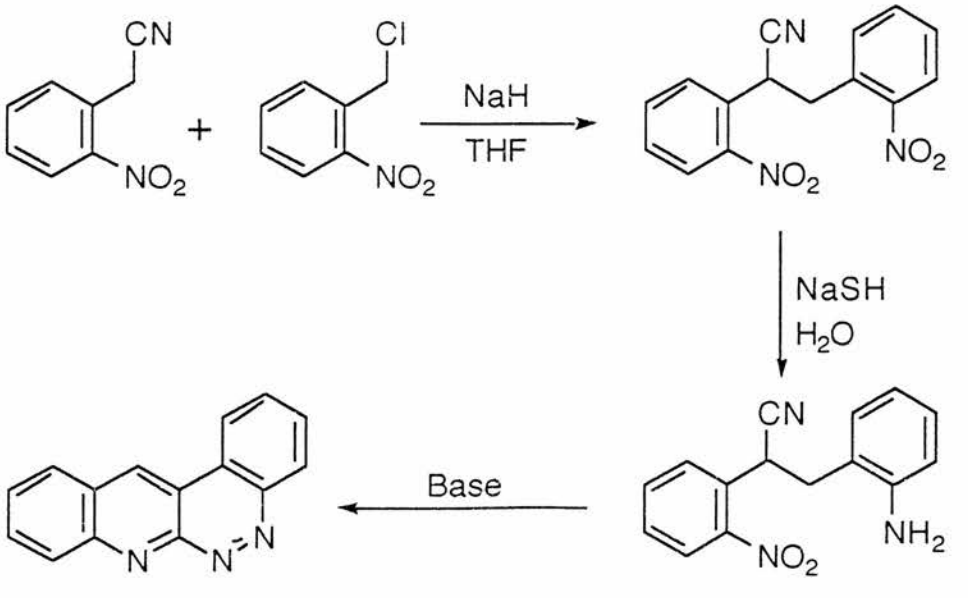


HCN/stilbene adduct could follow the same mechanism as that of the corresponding Schiff base/HCN adduct and thus furnish the quinocinnoline (Scheme 11).

During the initial cyanide induced cyclisation of a Schiff base the cyanide attacks the electrophilic carbon of the C=N bond. In the case of 2-amino-2'-nitrostilbene (**28**),if attack on the double bond occurs at all, it would be expected that the C in the double bond adjacent to the electron deficient *o*-nitrobenzene ring would be the more electrophilic of the two alkene carbons and therefore may be receptive to nucleophilic attack by the cyanide ion. It is also possible, of course, that attack on the other alkene carbon may result in a more stabilised carbanion (being delocalised by the nitro group). The required 2-amino-2'-nitrostilbene is obtained from base induced dimerisation of 2-nitrobenzyl chloride followed by selective reduction using aqueous sodium hydrogen sulphide.[12]

A second proposed route to the quinocinnoline is *via* the reaction of 2-nitrobenzyl chloride and 2-nitrobenzyl cyanide followed by selective reduction of one nitro- group and cyclisation (Scheme 12).

SCHEME 12



It was hoped that the precedent for the selective reduction of one nitro group in dinitrostilbenes by sodium hydrogen sulphide could be applied in these related molecules. If this were the case it was hoped that at reasonable proportion of the correct amino-nitro isomer would be obtained which would spontaneously cyclise in the basic media and hence become easily separable from the reaction mixture. This is also discussed in Section 2.

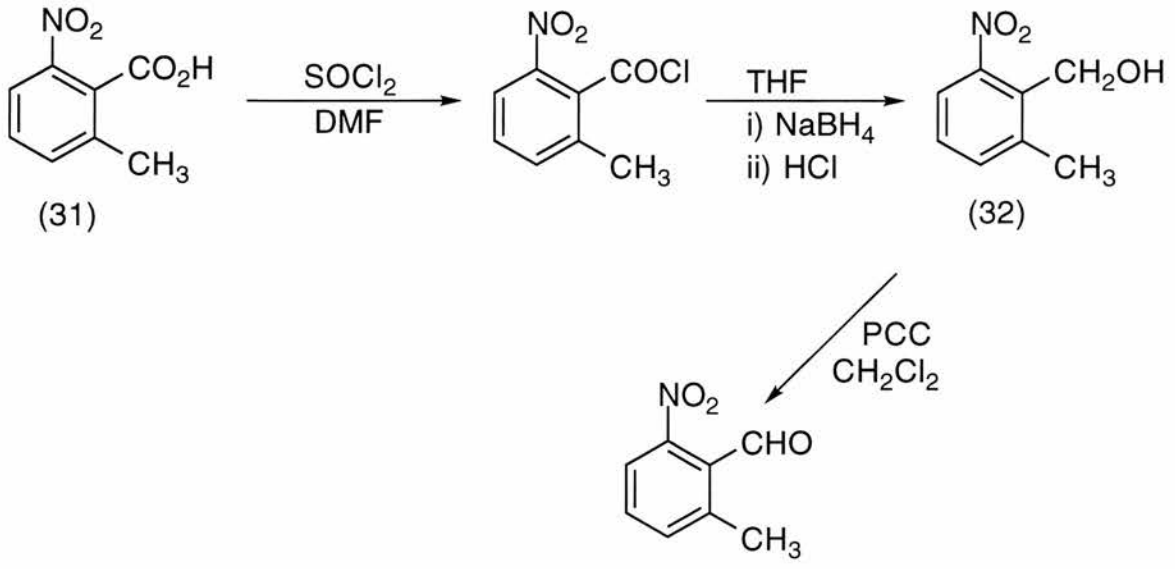
SECTION 2

RESULTS AND DISCUSSION

As indicated previously the first target molecule was 1-methylquinoxalino[2,3-*c*]-cinnoline. This requires the cyclisation of the anil formed between 2-methyl-6-nitrobenzaldehyde (**30**) and *o*-phenylenediamine (*cf.* Scheme 19, p.27).

2-Methyl-6-nitrobenzaldehyde has until recently been unknown. However Phillips and Hartman[13] reacted commercially available 2-methyl-6-nitrobenzoic acid (**31**) with thionyl chloride to form the acid chloride and reduction of this with sodium borohydride gave 2-methyl-6-nitrobenzyl alcohol (**32**). The alcohol formed was purified by column chromatography and then oxidised in excellent yield to the required aldehyde using pyridinium chlorochromate (Scheme 13).

SCHEME 13

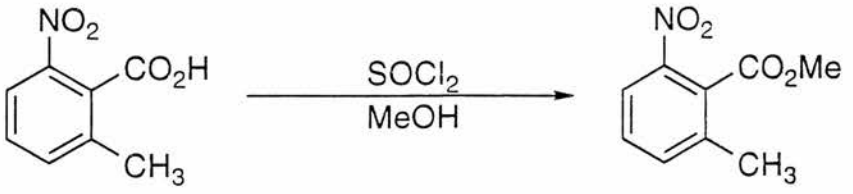


Attempts to follow Philips and Hartman's method proved problematic, however, since the procedure for the formation of the acid chloride requires *N,N*-dimethylformamide (DMF) both as a solvent and also as a catalyst. Due to the potentially explosive nature of some *o*-nitrobenzoyl chlorides[14] removal of the DMF by distillation was not considered advisable. 2-Methyl-6-nitrobenzoyl chloride is also moisture sensitive and so removal of the DMF by washing was also inadvisable. The problem was eased by using only a catalytic amount of DMF and an excess of thionyl chloride which meant less DMF to remove. The reduction of the crude acid chloride then proceeded very satisfactorily but unfortunately the yields of the intermediate alcohol proved to be very low and variable, usually towards the lower end of the range 30-65% over the two stages.

An alternative route to the alcohol was therefore examined. 2-Methyl-6-nitrobenzoic acid is commercially available but expensive and so it was hoped that activation of the acid moiety in a different way followed by reduction would furnish the required alcohol in better yield. Due to the susceptibility of the nitro-group to strong reducing agents, however, the reduction must be mild. It has been shown that the reduction of the ester groups of substituted methyl and ethyl benzoates to the corresponding alcohols can be achieved exclusively in the presence of nitro-groups by using lithium borohydride.[15] This route has the advantage that these simple esters of 2-methyl-6-nitrobenzoic acid ought to be isolatable, purifiable and characterisable.

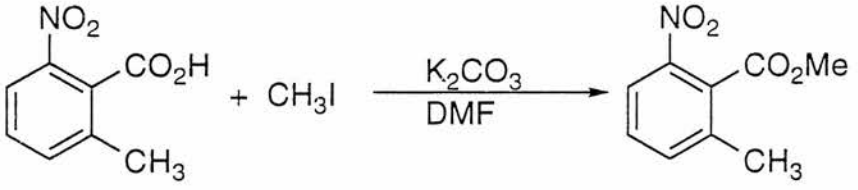
The first attempted esterification used thionyl chloride in methanol. After several hours at reflux the methanol and excess of thionyl chloride were evaporated off to give a cream solid which showed some ester present. After removal of acidic impurities (e.g. starting material) by washing with aqueous base there remained only a very small quantity of orange oil which appeared by ^{1}H NMR to consist of impure ester giving approximately 5% overall yield. The starting acid was then recovered by acidification of the basic extract to give a recovery of 82% (Scheme 14).

SCHEME 14



This esterification method was then abandoned and an alternative procedure was attempted which involved dissolving the acid in *N,N*-dimethylformamide and stirring the solution with potassium carbonate and methyl iodide for several days.[16] This then gave good quality material in 59% yield for the reduction (Scheme 15).

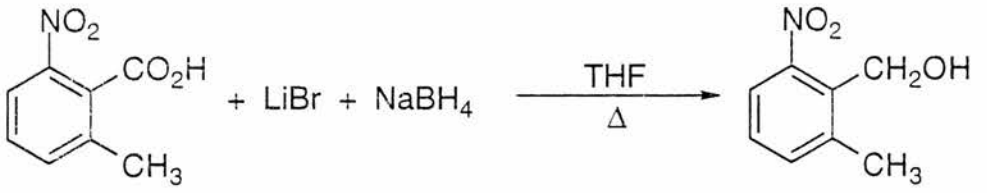
SCHEME 15



Lithium borohydride was then prepared by the literature procedure[17] in which sodium borohydride and lithium bromide are stirred in tetrahydrofuran (THF) ; the more soluble lithium borohydride is produced and the equilibrium is driven in the required direction by precipitation of the insoluble sodium bromide. The reagents were heated to reflux with vigorous stirring since the grinding action of the stirrer is thought to be of importance in forming the lithium borohydride.

A solution of lithium borohydride prepared in advance showed signs of deterioration upon standing (a precipitate formed) and so the lithium borohydride solution was formed *in situ* and used without delay (Scheme 16).

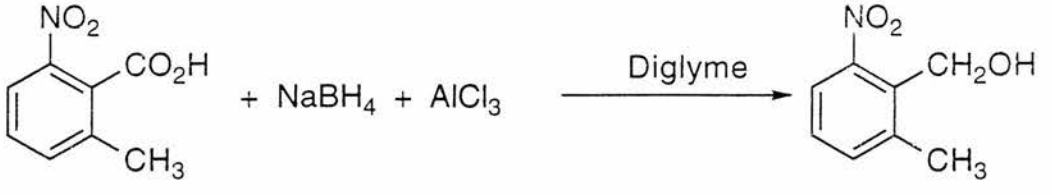
SCHEME 16



The first attempt on a small scale gave ca. 75% 2-methyl-6-nitrobenzyl alcohol (by ^1H NMR) and so the reaction was repeated on a larger scale which gave only 50% conversion to the alcohol after 12 hours. This approach to the alcohol was therefore abandoned since the yields of the alcohol obtained *via* the reduction of the ester proved to be much lower even than those obtained *via* the acid chloride.

One final attempt to find an alternative route to the nitrobenzyl alcohol was made. This synthesis involves using sodium borohydride and aluminium chloride in diglyme (2-methoxyethyl ether)[18] to reduce the acid to the alcohol directly without the need to derivatise the acid (Scheme 17).

SCHEME 17



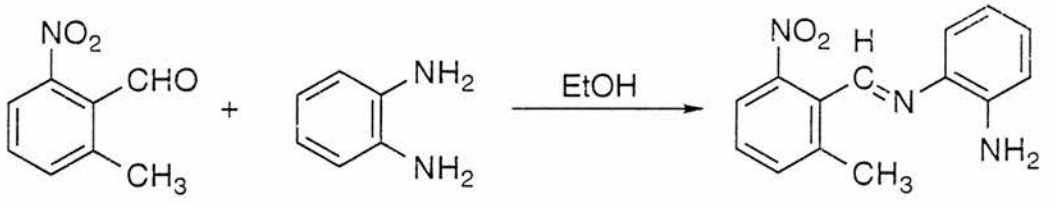
The mechanism for the reduction is unknown but it may be due to one of two things (or possibly both). The first explanation is that aluminium borohydride[18], formed *in situ* , is the reducing agent, but another suggestion is that the aluminium chloride acts as a Lewis acid which activates the acid group to allow reduction by the sodium borohydride.

Under these conditions 2-methyl-6-nitrobenzoic acid was unreactive. The analytical evidence showed no sign of any 2-methyl-6-nitrobenzyl alcohol so again this route was abandoned.

The best synthesis of the alcohol was in fact the acid chloride/sodium borohydride route and this was then used thereafter. The oxidation of the benzyl alcohol to the benzaldehyde was done in the standard way using pyridinium chlorochromate in dichloromethane which affords 2-methyl-6-nitrobenzaldehyde in almost quantitative yield.

The product obtained was a brown waxy solid of >98% purity by ^{1}H NMR and with a melting point 5°C below the literature value, and so was thought to be sufficiently pure to be used without any further purification steps. Purer (>99·5%) material was obtained by column chromatography on a small silica gel column and eluting with ether to give a white crystalline solid. The nitrobenzaldehyde was then dissolved in hot ethanol along with *o*-phenylenediamine to form the Schiff base (Scheme 18). After 2 minutes the solution was cooled and the Schiff base (**33**) crystallised out as orange crystals in reasonable purity. Unfortunately when the reaction was repeated on a larger scale the anil did not immediately precipitate out of the cold solution but when finally persuaded to do so (by ice-cooling and scratching to induce crystallisation) the yield was only 30% but the purity was high.

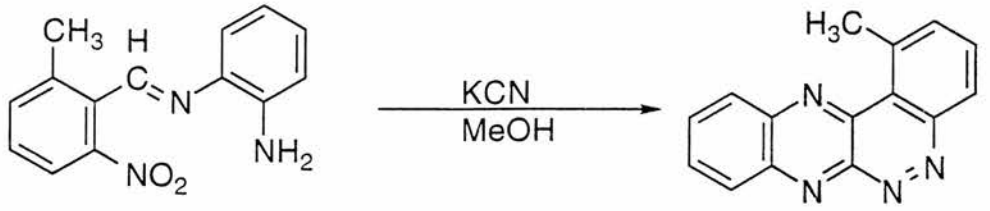
SCHEME 18



(33)

The recrystallised *N*-(2-methyl-6-nitrobenzylidene)-*o*-phenylenediamine (**33**) was then cyclised by heating it to reflux with a suspension of 2 equivalents of potassium cyanide in methanol for several hours and allowing the mixture to cool (Scheme 19).

SCHEME 19

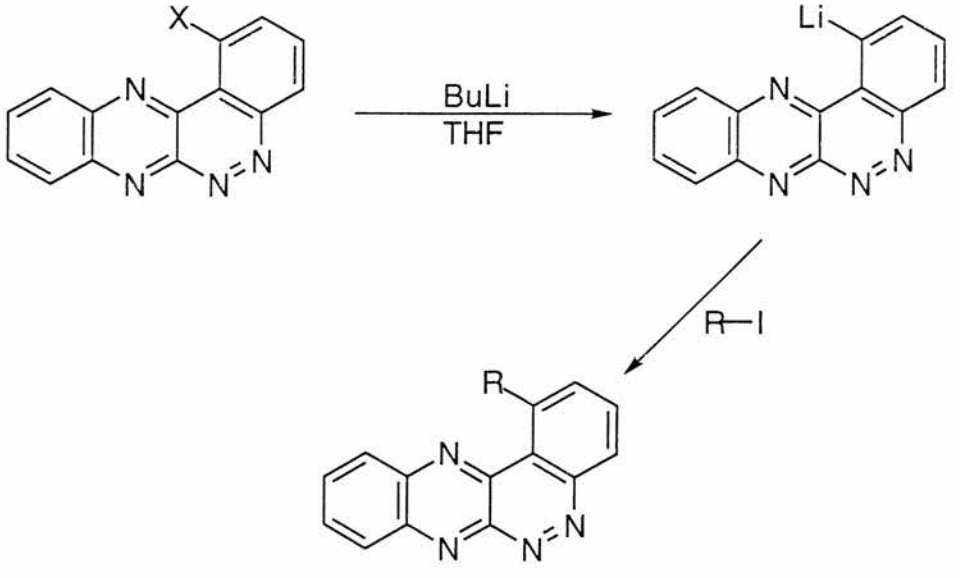


(33)

The 1-methylquinoxalino[2,3-*c*]cinnoline then precipitated out as orange/red crystals which were carefully filtered and washed free of any cyanide residues with water. The yield of the 1-methylquinoxalino[2,3-*c*]cinnoline was only 20% after recrystallisation but these low yields are not unusual for this type of cyclisation.

It was then proposed that an easy route to obtain C-1 substituted quinoxalino[2,3-*c*]-cinnolines would be via lithiation of a 1-halogenoquinoxalino[2,3-*c*]cinnoline followed by quenching with the appropriate iodo-compound (Scheme 20).

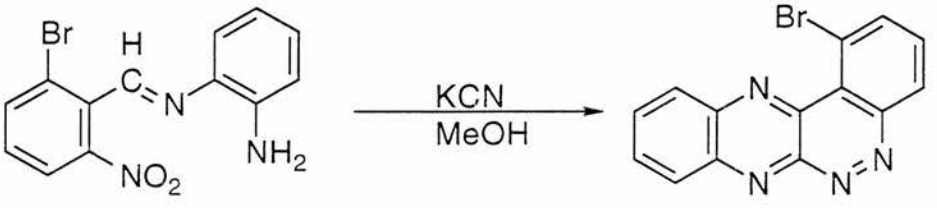
SCHEME 20



The 1-halogenoquinoxalino[2,3-*c*]cinnoline chosen was 1-bromoquinoxalino[2,3-*c*]-cinnoline (**34**) since 1-iodoquinoxalino[2,3-*c*]cinnoline had proved impossible to synthesise previously and the bromo-derivative had been made several times in the past.[19]

1-Bromoquinoxalino[2,3-*c*]cinnoline is formed from the cyclisation of *N*-(2-bromo-6-nitrobenzylidene)-*o*-phenylenediamine (**35**) in methanolic potassium cyanide (Scheme 21), the Schiff base being formed in the usual way by the reaction of *o*-phenylenediamine and 2-bromo-6-nitrobenzaldehyde (**36**) in ethanol.

SCHEME 21



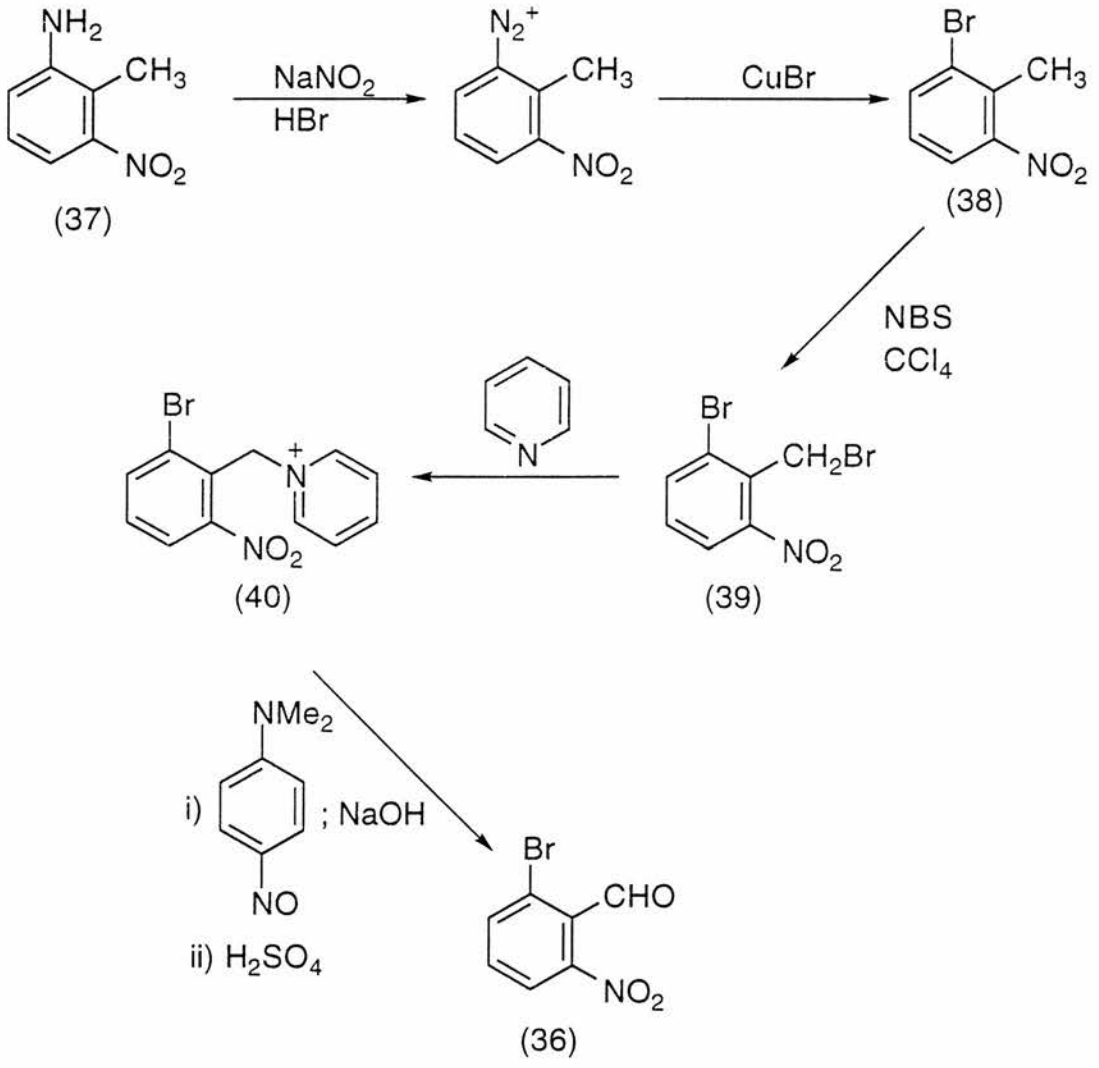
(35) (34)

The required aldehyde, 2-bromo-6-nitrobenzaldehyde, is synthesised in the route outlined below (Scheme 22).[20]

2-Methyl-3-nitroaniline (**37**) is diazotized with sodium nitrite in hydrobromic acid and then treated with copper(I) bromide. This gives 2-bromo-6-nitrotoluene (**38**), after steam distillation, in 63% yield as a low melting cream solid. The bromonitrotoluene was then oxidised using a modified Kröhnke oxidation: the 2-bromo-6-nitrotoluene reacts with *N*-bromosuccinimide in carbon tetrachloride to form the 2-bromo-6-nitrobenzyl bromide (**39**) and this is then reacted with pyridine in ethanol to give *N*-(2-bromo-6-nitrobenzyl)pyridinium bromide (**40**) in 42% yield. Reaction of the pyridinium salt with *N,N*-dimethyl-*p*-nitrosoaniline and sodium hydroxide in aqueous ethanol gives a nitrone which is then hydrolysed with dilute sulphuric acid to furnish the 2-bromo-6-nitrobenzaldehyde in 39% yield over two stages.

An alternative method for the oxidation of (**38**), involving dichlorination of the methyl group followed by hydrolysis, proved unsuccessful since the methyl group was unreactive towards *N*-chlorosuccinimide.

SCHEME 22



2-Bromo-6-nitrobenzaldehyde and *o*-phenylenediamine were then warmed in the minimum of ethanol before cooling and filtering off the product. The anil, after

recrystallisation, was then cyclised with methanolic potassium cyanide in the usual way to give 1-bromoquinoxalino[2,3-*c*]cinnoline in 85% yield.

The 1-bromoquinoxalino[2,3-*c*]cinnoline was then carefully dried and suspended in THF while *n*-butyl lithium was added at -78°C. The orange suspension then went a very dark green and at -78°C a solution of 1,1,1-trifluoro-2-iodoethane in THF was then slowly added at -78°C. The solution was then stirred at -78°C with no precipitate being formed and so was allowed to warm to room temperature where it was quenched with water. Extraction of the solution and evaporation of the solvent gave a black solid showing no sign of any starting material by T.L.C and no quinoxalinocinnoline by ^{1}H NMR . It was thought that the butyl lithium had not actually lithiated the molecule but had instead caused it to decompose. Unfortunately due to the apparent susceptibility of the quinoxalinocinnoline ring to degradation by strong base this promising route to C-1 derivatised quinoxalinocinnolines was abandoned.

CHLORINATION OF 1-METHYLQUINOXALINO[2,3-*c*]CINNOLINE.

The chlorination of 1-methylquinoxalino[2,3-*c*]cinnoline was achieved in the now standard way where a solution of the quinoxalinocinnoline was stirred while a stream of dry HCl gas was passed through. The orange solution then formed the characteristic blue/black colour and shortly afterwards a very dark precipitate formed. The passage of HCl was then continued for several more minutes to ensure complete reaction. The suspension was then stirred with dilute sodium hydroxide solution whereupon which the precipitate disappears to be replaced by an orange/red solution. This colour change then suggests the release of the free quinoxalinocinnoline from the solid protonated salt.

^{1}H NMR then showed the solid formed from the evaporation of the chloroform to be a mixture of starting material and one other component. The mass spectrum of the product suggested the presence of a chloroquinoxalinocinnoline; it is considered in greater detail on page 45. However the position of chlorination could not as yet be determined.

The presence of a large proportion of unchlorinated quinoxalinocinnoline in the product from the reaction with HCl suggested that the reaction had not been left long enough and that the presence of the methyl substituent in the C-1 position of the quinoxalinocinnoline had in fact slowed down the chlorination reaction. The chlorination of 1-methylquinoxalino-[2,3-*c*]cinnoline was then repeated; however this time exactly 100mg of 1-methylquinoxalino-[2,3-*c*]cinnoline was used in an attempt to obtain information regarding the rate of chlorination.

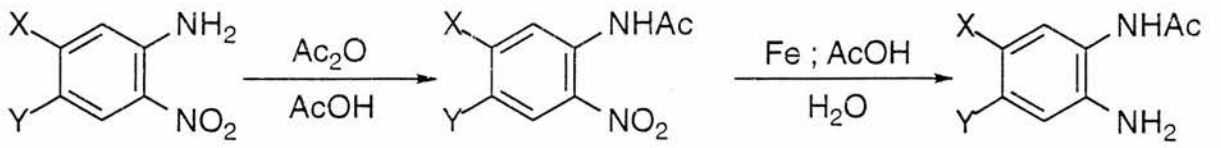
The dry HCl was passed through the solution of 1-methylquinoxalino[2,3-*c*]cinnoline in chloroform for several minutes where again the characteristic precipitate formed almost immediately. The suspension was then allowed to stand for 15 minutes and the precipitate filtered off. The mother liquors were then found to be the colour of the starting material and so this was stirred while HCl was passed through it. Again, after standing the precipitate was filtered off and the mother liquors resaturated with HCl. At this point no more precipitate was formed even though the mother liquors still maintained the orange colour of the starting material. The final solution was then evaporated down to give unchlorinated 1-methyl-quinoxalino[2,3-*c*]cinnoline in a recovery of 17%.

The blue precipitate was then subjected to the usual basic work-up and gave the orange/red solid which was again found by ^{1}H NMR to be a mixture of unreacted 1-methyl-quinoxalino[2,3-*c*]cinnoline and the chlorinated quinoxalinocinnoline in the ratio of *ca.* 5 : 3 .

The obvious way to identify the unknown chloroquinoxalinocinnoline isomer is *via* independent synthesis of both 9-chloro- and 10-chloro-1-methylquinoxalino[2,3-*c*]cinnoline, this method having been employed previously where ambiguity existed.

For both isomers the starting aldehyde is 2-methyl-6-nitrobenzaldehyde but the starting amines are obviously different. As shown in the introduction protection of one amino-group with an acetyl function will ensure the correct Schiff base will form. This means that the two other starting materials required are 2-amino-5-chloroacetanilide (**42**) and 2-amino-4-chloroactanilide (**43**). Both acetanilides are formed *via* the same route (Scheme 24).

SCHEME 24



(42) ; X = Cl , Y = H
(43) ; X = H , Y = Cl

5-(or 4-)Chloro-2-nitroaniline was acetylated by stirring in hot acetic acid with acetic anhydride and a catalytic amount of *N,N*-dimethylaminopyridine. The yields were 84% and 76% respectively.

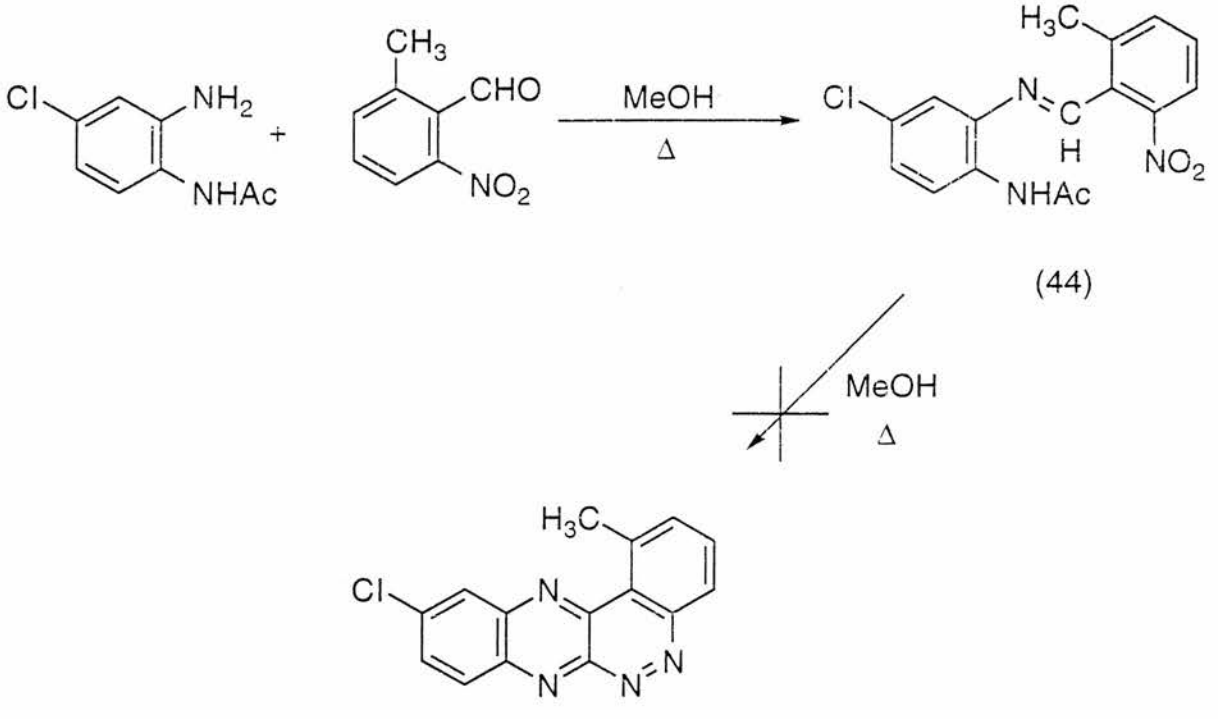
5-Chloro-2-nitroacetanilide was then reduced with iron powder in aqueous acetic acid at an elevated temperature before neutralising with potassium carbonate and filtering the hot mixture through Celite. The organic product was separated by extracting with boiling ethanol and the crude product, which was shown to be a 50 : 50 mixture of starting material and product by ^{1}H NMR, was purified by recrystallisation from toluene. The low yield (32%) was attributed to the fact that addition of the 5-chloro-2-nitroacetanilide to the aqueous suspension caused the acetanilide to aggregate and so prevent complete reaction from occurring.

The reduction of the 4-chloro-2-nitroacetanilide followed the same method and so in this case the procedure was amended so that the starting acetanilide was ground up and passed through a 250μm sieve, and the addition of the powder to the iron suspension was slowed down so as to ensure complete dispersion of the fine powder. The yield was then improved to 80% after recrystallisation.

Formation of the Schiff bases was attempted in the usual way by warming 2-amino-5-chloroacetanilide or 2-amino-4-chloroacetanilide with 2-methyl-6-nitrobenzaldehyde in ethanol, and upon cooling allowing the Schiff base to precipitate out. Unfortunately this procedure failed to produce the required anil in both cases.

Repeated attempts were made to obtain the solid Schiff base by using *p*-toluenesulphonic acid and triethylamine as catalysts and also by altering the alcohol from ethanol to isopropanol but these all proved unsuccessful in producing a crystalline product. ^{1}H NMR did, however, show the presence of the Schiff base in solution and so it was decided to try to form the Schiff base in methanol and then use this solution directly in the cyclisation step (Scheme 25).

SCHEME 25



2-Methyl-6-nitrobenzaldehyde and 2-amino-4-chloroacetanilide were heated in the minimum volume of methanol before diluting with more methanol and heating the solution to reflux with potassium cyanide for several hours. The pale green solution went to a pale pink solution but no characteristic red colour was observed. Upon cooling there was no precipitate formed and concentration of the solution failed to give a precipitate. Water was then added and

the mixture extracted. After evaporation of the solvent the ^{1}H NMR showed only the presence of the unreacted starting material 2-acetamido-5-chloro-*N*-(2-methyl-6-nitrobenzylidene)aniline (**44**).

The recovered Schiff base was then re-dissolved in methanol and heated to reflux for a further 10 hours with potassium cyanide but again after cooling no precipitate had formed and it was possible to recover the starting material (**44**).

This is the first time that any of the Schiff bases in this family have failed to cyclise to a quinoxalinocinnoline and this is thought to be due to the excessive crowding of the substituents around the C=N bond preventing access by the reagents to this reactive site.

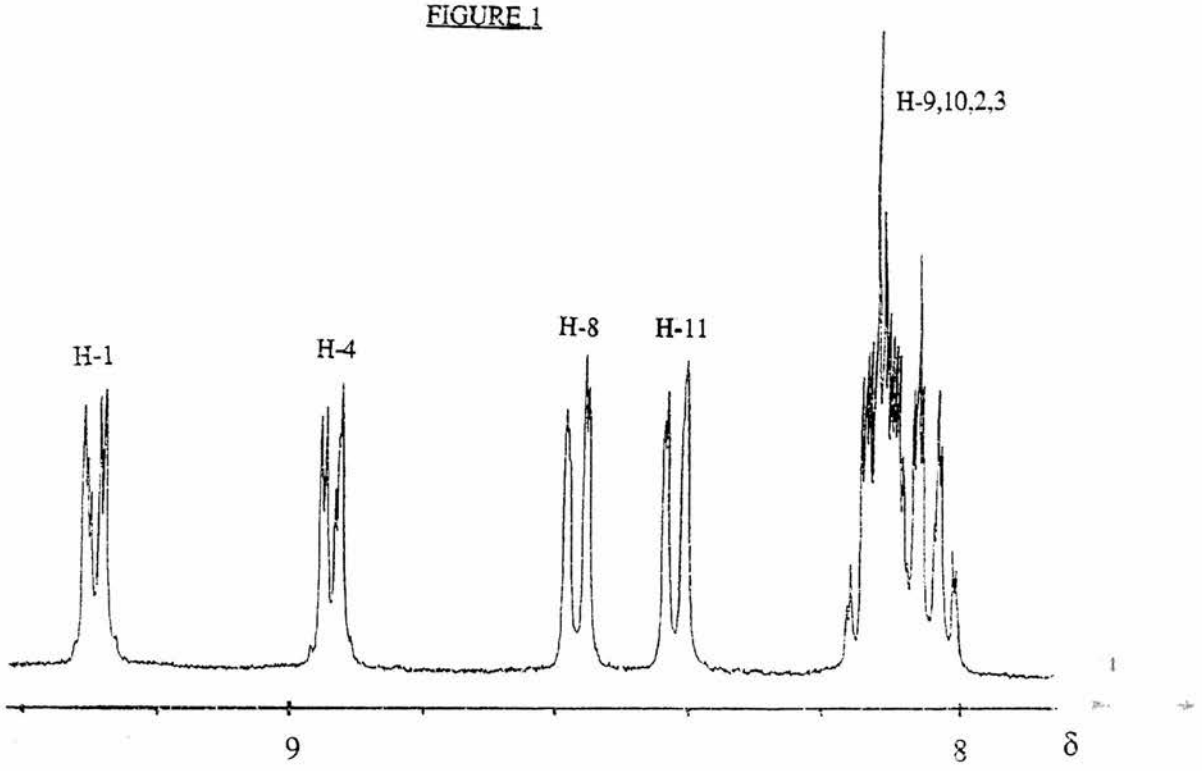
Cyclisation of the unacetylated Schiff base, *N*-(2-methyl-6-nitrobenzylidene)*o*-phenylenediamine (**33**), was successful, although it gave only a 20% yield of the 1-methylquinoxalino[2,3-*c*]cinnoline. In the case of 2-acetamido-5-chloro-*N*-(2-methyl-6-nitrobenzylidene)aniline (**44**), the chlorine will not adversely affect the reaction and so it must be concluded that the extra steric effect of the -$COCH_3$ has crowded the C=N bond to such an extent that the addition of the elements of HCN no longer takes place.

For this reason the cyanide induced cyclisation of 2-acetamido-5-chloro-*N*-(2-methyl-6-nitrobenzylidene)aniline proved impossible and so determination of the structure of the chlorination product of 1-methylquinoxalino[2,3-*c*]cinnoline was done by ^{1}H NMR.

INTERPRETATION OF THE ^{1}H NMR OF THE MONOCHLOROQUINOXALINO-[2,3-*c*]CINNOLINE

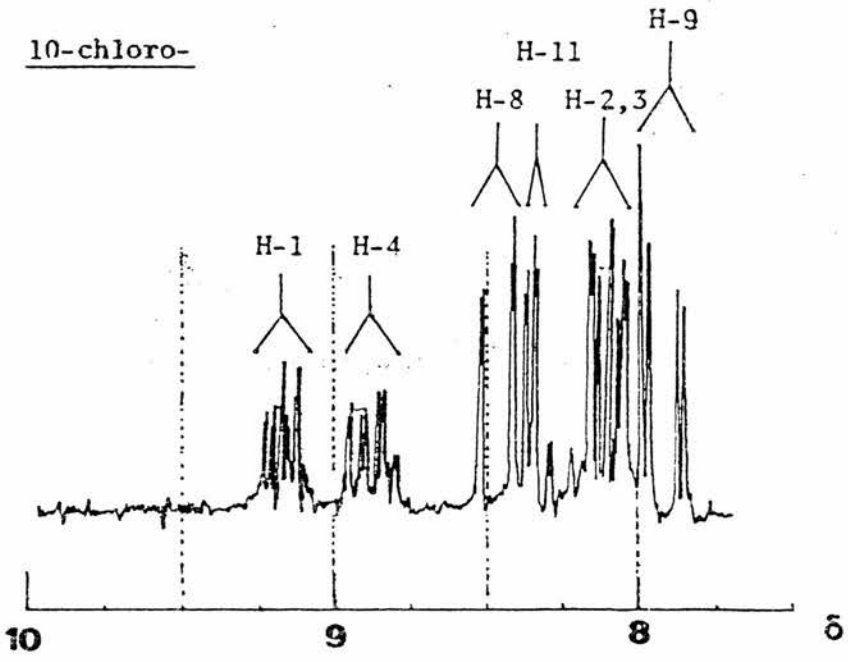
Previous studies of the ^{1}H NMR of quinoxalino[2,3-*c*]cinnolines (C-1 substituted and unsubstituted) and their 9- and 10-chloro analogues have shown a very complex arrangement of peaks. It has been possible however to identify a pattern of peaks in most of the spectra examined. In the case of unsubstituted quinoxalino[2,3-*c*]cinnoline (Figure 1) the peaks have been assigned as shown with H-1 having the highest chemical shift followed by H-4, H-8, H-11 and then finally a complex multiplet for H-9, H-10, H-2 and H-3.

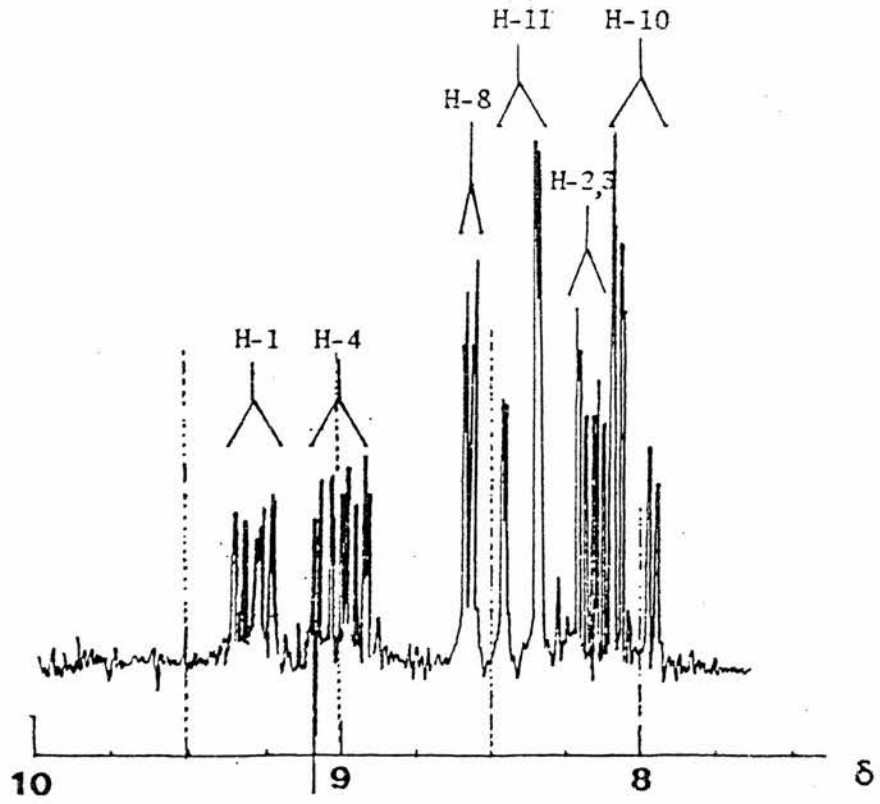
FIGURE 1



From the spectra of 9-chloro- and 10-chloroquinoxalino[2,3-*c*]cinnoline (Figure 2) it can be seen that the signals corresponding to H-1, H-4, H-8 and H-11 all remain in the same order as in the starting non-chlorinated quinoxalinocinnoline, although the chemical shifts of the signals corresponding to H-8 and H-11 have moved slightly, and their splitting patterns simplified due to the chlorine in the quinoxaline ring.

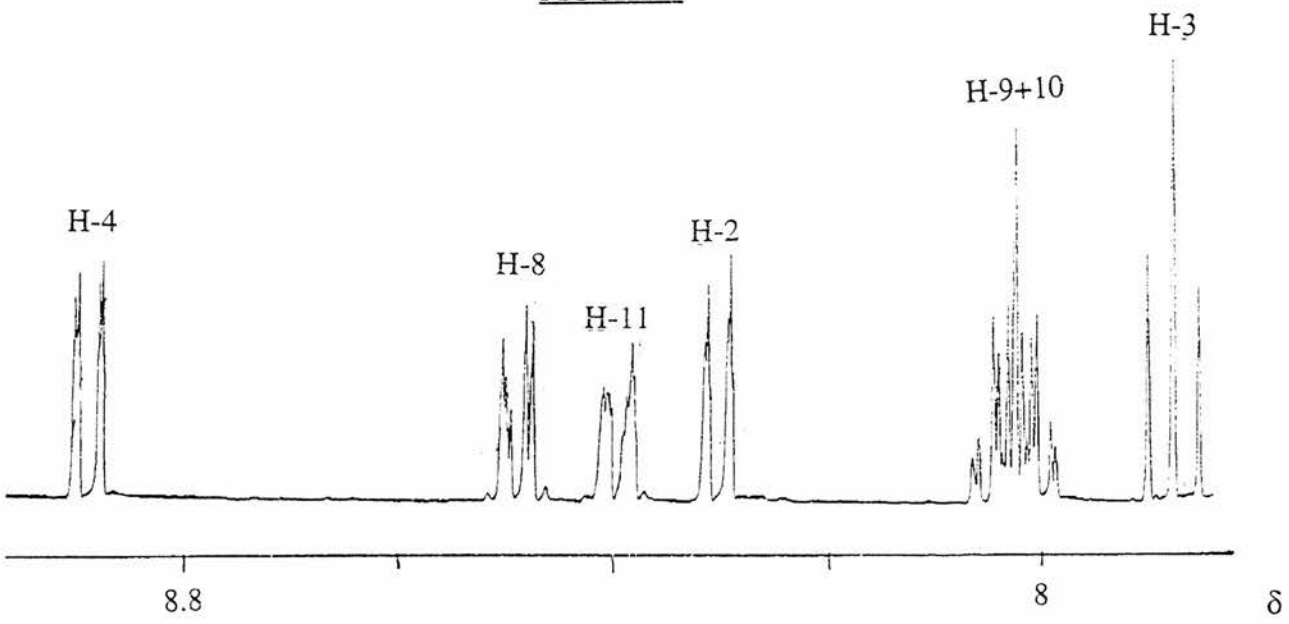
FIGURE 2


10-chloro-
H-9
H-11
H-8
H-2,3
H-1
H-4
10
9
8
δ


9-chloro-
H-11
H-10
H-8
H-2,3
H-1
H-4
10
9
8
δ

In the case of 1-bromoquinoxalino[2,3-*c*]cinnoline (Figure 3) the order of the signals corresponding to H-4, H-8 and H-11 is the same as in the unsubstituted quinoxalino[2,3-*c*]-cinnoline with the obvious loss of the signal for H-1. (The same order is found in the spectrum of the 1-chloro-analogue[10].)

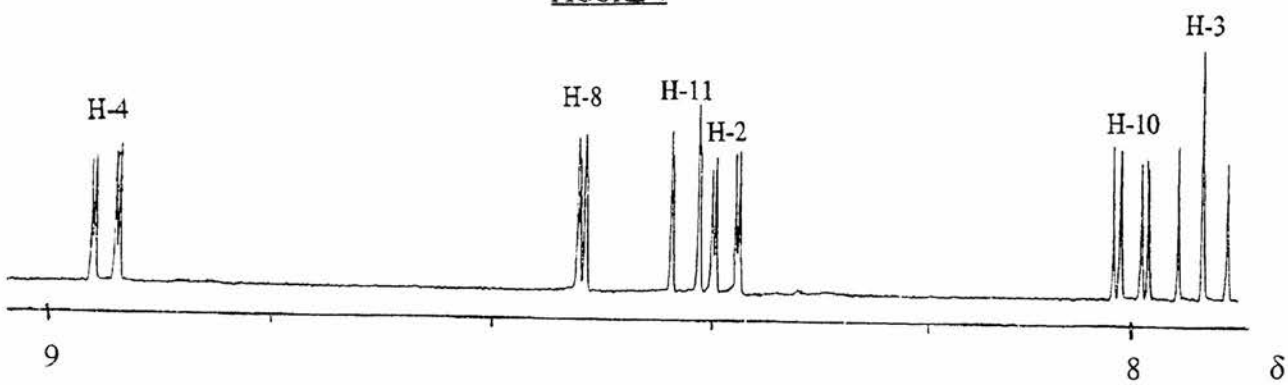
FIGURE 3



The presence of the bromine in the C-1 position results in the simplification of the upfield multiplet; the H-2 signal has moved downfield and the H-3 signal has moved upfield leaving the H-9 and H-10 signals overlapping.

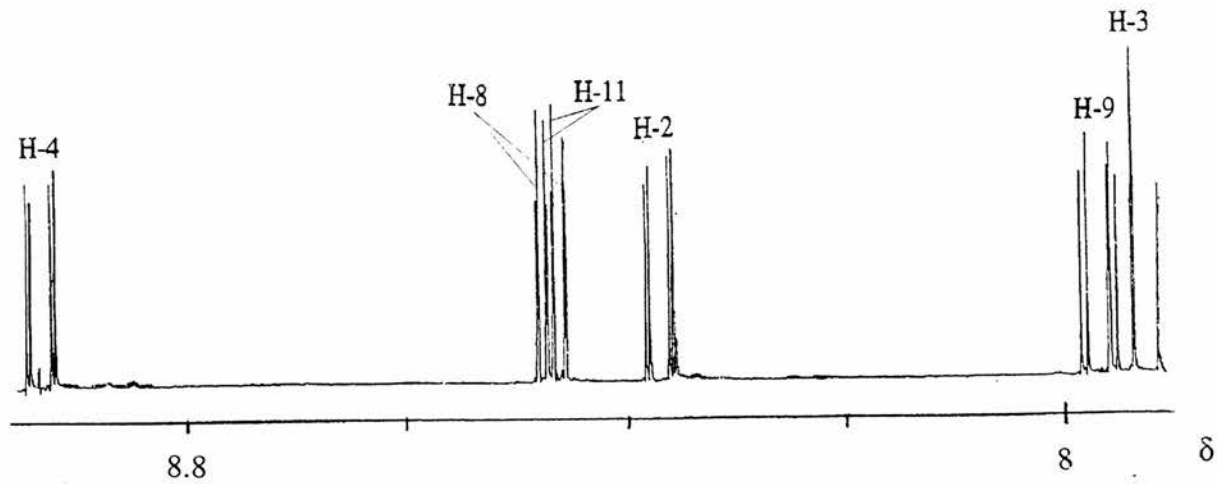
When this spectrum is compared to the one obtained from 1-bromo-9-chloroquinoxalino[2,3-*c*]cinnoline (Figure 4) it can be seen that the signals corresponding to the protons H-4, H-8, H-11, H-2, H-10 and H-3 all remain in the same order as they appear in the spectrum of the starting 1-bromoquinoxalino[2,3-*c*]cinnoline with the obvious loss of H-9 and the simplification of the splitting pattern of the H-8, H-10 and H-11 signals.

FIGURE 4



Comparison of the ^1H NMR spectra obtained from 1-bromo-10-chioro-quinoxalino[2,3-*c*]cinnoline (Figure 5) and the non-chlorinated 1-bromoquinoxalino[2,3-*c*]-cinnoline shows a different pattern for the H-8 and H-11 signals in the former. The H-8 and H-11 signals have converged to give the appearance of a quartet of doublets which is in fact two double doublets with the doublet corresponding to H-11 lying almost in the middle of the doublet corresponding to H-8.

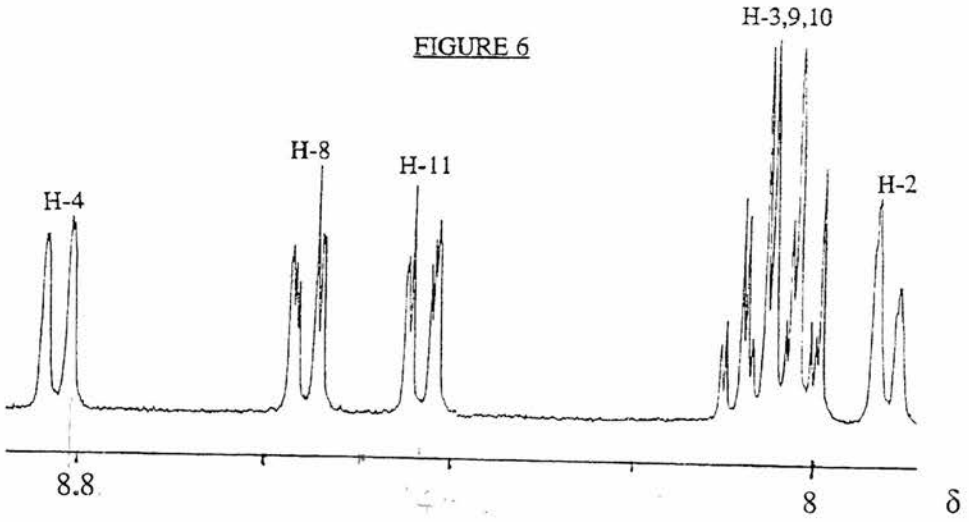
FIGURE 5



1-Bromo-10-chloro-quinoxalino[2,3-*c*]cinnoline is the only case so far examined in which the positions of the signals relating to protons H-8 and H-11 had converged. In other 9- and 10-chloroquinoxalino[2,3-*c*]cinnolines the relative positions of the signals relating to H-8 and H-11 are always the same, with H-8 having the higher chemical shift. There has been no evidence for a chlorine substituent at either C-9 or C-10 producing an inversion of this order. This evidence suggests that generally the chlorine in either the C-9 or C-10 position has very little effect on the shifts of protons H-8 or H-11.

The ^{1}H NMR of 1-methylquinoxalino[2,3-*c*]cinnoline (figure 6) shows a distribution of signals very similar to those found in 1-bromoquinoxalino[2,3-*c*]cinnoline and quinoxalino[2,3-*c*]cinnoline itself, with the signal for H-4 being the furthest downfield followed by H-8, H-11, then a multiplet comprising H-3, H-9 and H-10 and finally the signal for H-2 is the furthest upfield of the aromatic protons.

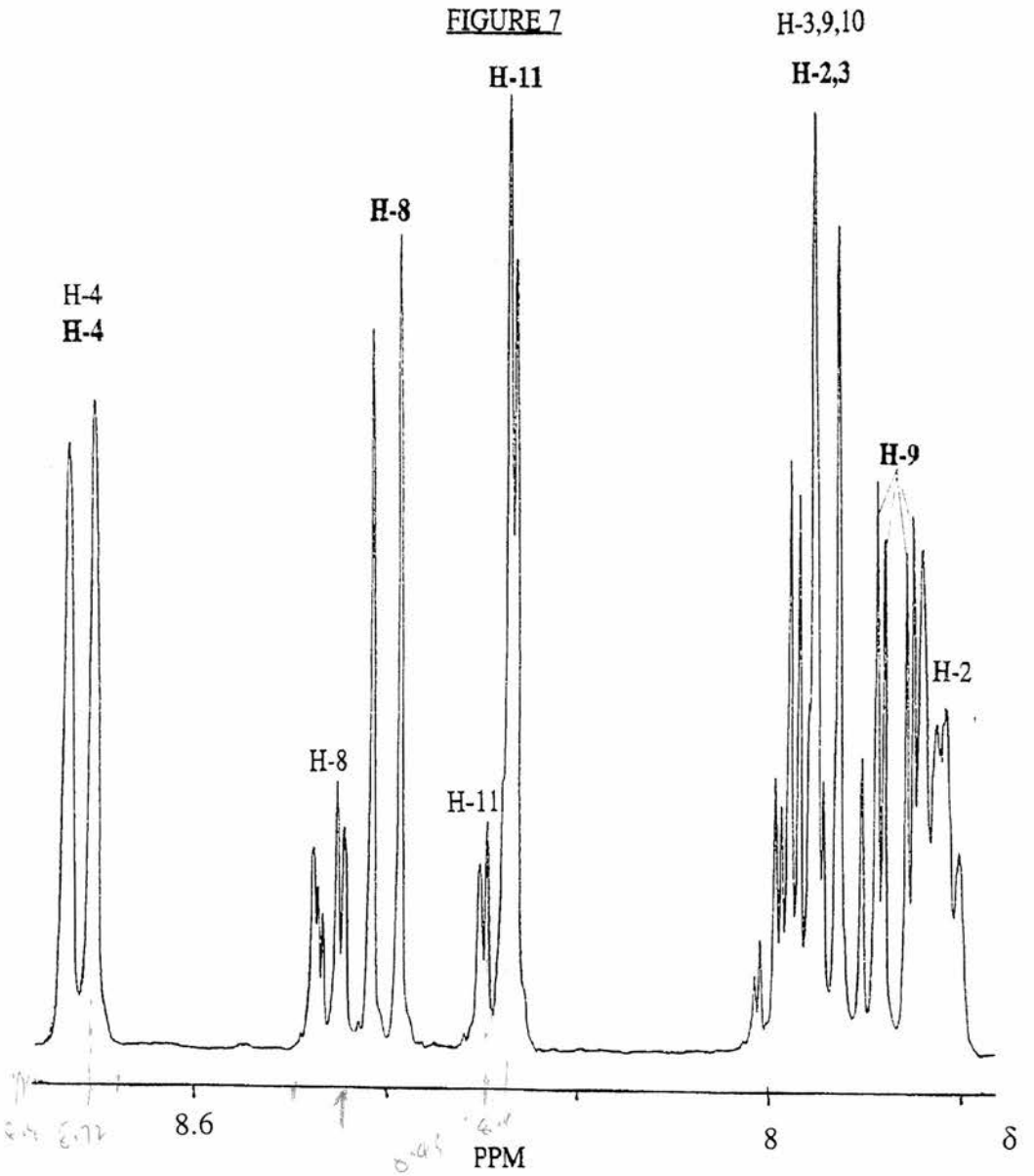
FIGURE 6



Upon chlorination of 1-methylquinoxalino[2,3-*c*]cinnoline in the now standard way the ^{1}H NMR shows that the product comprises a mixture of monochlorinated 1-methyl-quinoxalino[2,3-*c*]cinnoline and non-chlorinated starting material (see previous sections for explanation). The signals arising from the non-chlorinated starting material can be clearly seen in the ^{1}H NMR spectrum of the product from chlorination (figure 7) although the multiplet at 7.80-8.02ppm has been further complicated by signals from the chlorinated product.

The signals arising from H-8 and H-11 in the starting material can be clearly seen with their familiar splitting pattern and these are now joined by two sets of peaks resulting from protons in the chlorinated product.

FIGURE 7



BOLD = SIGNALS FROM CHLORINATED PRODUCT

NORMAL = SIGNALS FROM STARTING MATERIAL

By comparison with Figures 1, 2 and 4, and noting that the shielding effect of a methyl group on neighbouring protons in an aromatic system lies between the effects of a bromine and a hydrogen atom, it is reasonable to conclude that the new signals adjacent to those arising from H-8 and H-11 in the starting material are from H-8 and H-11 in the chlorinated product.

Similarly it is reasonable to conclude that these signals are in the same order as seen in other chlorinated quinoxalino[2,3-*c*]cinnolines, i.e. the downfield signals are from H-8 and the upfield signals are from H-11.

The downfield doublet at δ 8.40 arising from H-8 in the chlorinated product shows *ortho*- splitting (*J* 9Hz) and the upfield doublet at δ 8.28 shows *meta*- splitting (*J* 2.2Hz) indicating that **the chlorinated product contains the chlorine at C-10.**

Another observation which may lend further weight to the above conclusion relates to the actual chemical shifs for H-9 and H-10 in the ^{1}H NMR spectra of 10- and 9-chloroquinoxalino-[2,3-*c*]cinnolines respectively. In the 10-chloro series the signals arising from H-9 have moved slightly upfield relative to the non-chlorinated starting materials. In their 9-chloro isomers, however, the chemical shift of the H-10 signal is unchanged relative to the non-chlorinated starting materials. (Figures 2 - 5).

In Figure 7, it is possible within the complex multiplet between δ 7.80 and 8.02 to observe a double doublet at δ 7.96 which has coupling constants (*J* 9 and 2.2 Hz) different to those found in the starting material. Since the multiplet is known to arise from H-9 or H-10 in the chlorinated product, H-9 and H-10 in the starting material, and H-2 and H-3 in both compounds, and since the new double doublet lies upfield from those peaks attributed to H-9 and H-10 of the unchlorinated compound, it is possible to conclude that this double doublet arises from H-9 in the chlorinated product.

The recovery of a significant amount of the unreacted 1-methylquinoxalino[2,3-*c*]-cinnoline and the fact that the precipitate formed was a mixture of chlorinated and unchlorinated quinoxalinocinnoline salts shows that the methyl group in the C-1 position must be having a disruptive influence on the reaction sequence. It may recalled from Section 1 (p.18) that chlorination of 1-bromoquinoxalino[2,3-*c*]cinnoline also occurs slowly and gives the

chlorinated product in greatly reduced yield by comparison with the 1-chloro and less substituted analogues.

The presence of unreacted starting 1-methylquinoxalino[2,3-*c*]cinnoline in the product was very unexpected. The recovery of starting material from these reactions has previously been observed only in examples where the starting material already contains a chlorine substituent at C-10. The presence of the starting material in the present case is therefore an interesting result which requires further investigation.

In the case of simple quinoxalino[2,3-*c*]cinnolines the chain of events leading to chlorination is believed to be as follows (Scheme 10, p.16):

1. Protonation at N-12.
2. Attack by a chloride nucleophile at C-10.
3. Protonation of one of the azo-nitrogens (N-5 or N-6) to form the hydrochloride salt.
4. Precipitation of the salt as the characteristic blue/black solid.
5. Formation of a chlorodihydroquinoxalinocinnoline by base treatment of the blue salt.
6. Oxidation of the product of step 5.

Upon chlorination of 1-bromoquinoxalino[2,3-*c*]cinnoline the reaction with HCl is slower and lower-yielding than with the unsubstituted quinoxalinocinnoline although there is no evidence of any starting material as a contaminant of the final bromochloro-quinoxalinocinnoline. In the case of the chlorination of 1-methylquinoxalinocinnoline the reaction is again low-yielding; however the precipitate formed, when filtered and subjected to a basic work-up, does not give the pure chloromethylquinoxalinocinnoline but a mixture of starting material and chlorinated product. This result can be explained in a number of ways which all appear reasonable at this time, although there is no firm evidence to support one over the remainder.

1) If the chlorination of both 1-bromo- and 1-methylquinoxalinocinnoline follow the above chain of events, and if the effect of the C-1 substituents is only steric, it is difficult to conceive of different outcomes for the two reactions. However, the bromine may function in two ways: inhibition of protonation at N-12 on steric grounds, but at the same time *assistance* of protonation through hydrogen bonding. This hydrogen bonding is not possible with the

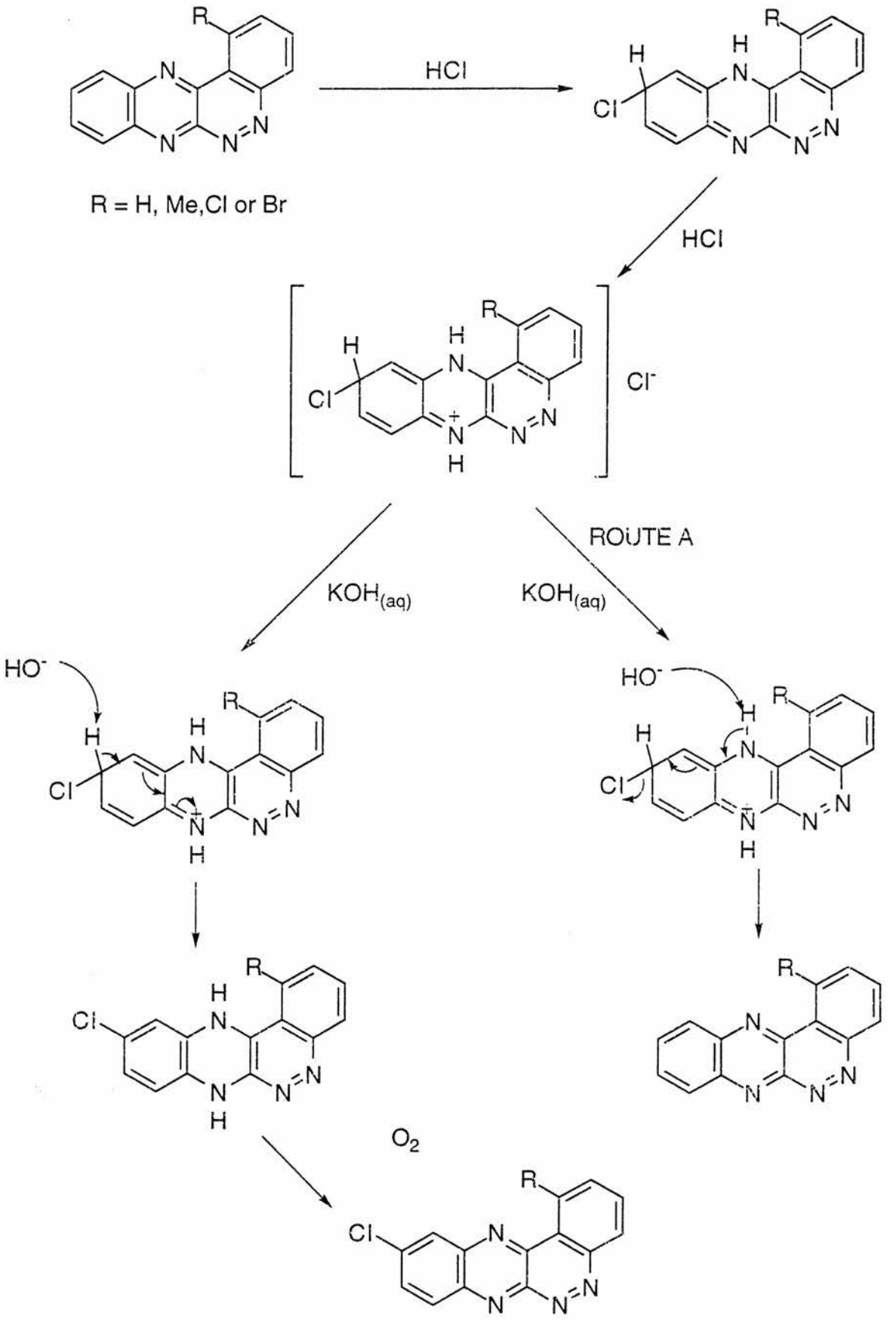
methyl substituent. N-12 may then become less favoured for protonation and other sites may compete for protonation. Protonation at another nitrogen may lead to a salt which precipitates out of solution along with the blue compound, and upon work-up regenerates the starting material.

2) Protonation of 1-methylquinoxalinocinnoline, even at N-12, may lead to a simple hydrochloride salt which is more sparingly soluble in chloroform than other analogous salts, and this has a tendency to precipitate from solution before nucleophilic attack by chloride can occur.

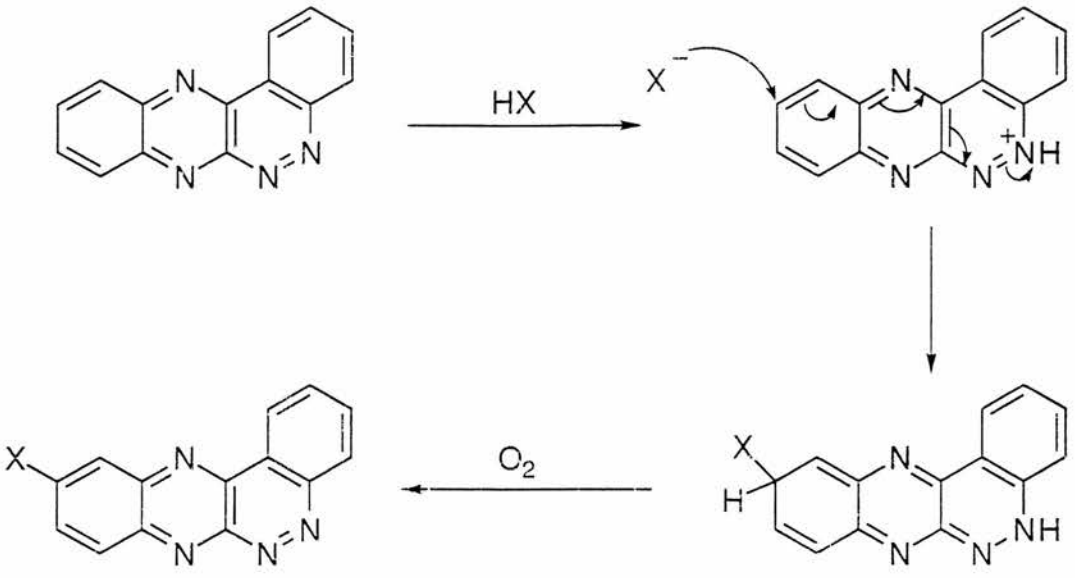
3) The chlorination may well follow the proposed mechanism, but in the basic work-up the intermediate blue salt is reconverted into the starting material. Due to the fact that the methyl group cannot form a hydrogen bond to the proton on N-12, as a bromine can, and therefore cannot give the N-H bond the same stability, it is possible that the basic work-up may simply remove the proton at N-12 in preference to another (e.g. the one bound to C-10, Route A) and so cause the elimination of the chloride and give rise to the unchlorinated starting material (Scheme 26).

4) A further possible explanation is that the methyl is having more of a disruptive effect on the protonation at N-12 than might have been predicted due to its size, and this is causing a second nitrogen to become more favoured as the site for protonation. It is possible to write a mechanism for chlorination at C-10 which involves initial protonation at N-5 (Scheme 27), although the MNDO calculations suggest otherwise. The apparently low basicity of this nitrogen may result in a reduced rate of reaction.

SCHEME 26



SCHEME 27

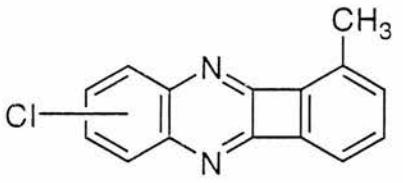


It is, of course, still possible that the first step in chlorination of *any* quinoxalinocinnoline is *not* protonation of N-12, and that the accepted mechanism is incorrect. Whether or not protonation of N-12 is indeed crucial to the chlorination of the ring system as a whole can probably best be determined by removal of this heteroatom and study of quino[2,3-*c*]cinnolines.

INTERPRETATION OF THE MASS SPECTRUM OF THE CHLORINATION PRODUCT OF 1-METHYLQUINOXALINO[2,3-*c*]CINNOLINE

The mass spectrum obtained from the product of the reaction of 1-methylquinoxalino-[2,3-*c*]cinnoline and HCl gas suggested the presence of a monochlorinated species, the parent ion peaks being at *m/z* 282 and 280, and the fragmentation pattern being similar to those observed for other monochloroquinoxalino[2,3-*c*]cinnolines.[21]

The ion with *m/z* 246 is the molecular ion of the starting material. It has been shown in previous work that monochlorinated quinoxalinocinnolines will fragment in a predictable way, which does not involve loss of the chlorine direct from the molecular ion. The first fragment obtained is usually from the loss of dinitrogen. This leads to a peak at $(M-28)^{+\cdot}$ and is thought to arise from the loss of the azo-nitrogens leading to the fragment (**45**).



(45)

For a monochlorinated methylquinoxalinocinnoline this fragment would give rise to two peaks, one at *m/z* 252 and the other at *m/z* 254. For the unchlorinated compound, the corresponding fragment has *m/z* 218. These fragments can all be clearly seen on the mass spectrum (intensities 92%, 31% and 85% respectively). In previous work it has been found that the fragment corresponding to (**45**) would then lose the chlorine atom hence leading to a single fragment at *m/z* 217 which is also clearly seen with an intensity of 45%. The next major peak in the mass spectrum of the chloro-compound (intensity 61%) is at *m/z* 190. This could arise from the loss of HCN from the previous fragment and the literature shows this to be a favoured reaction in the mass spectra of most of the monochloroquinoxalino-[2,3-*c*]cinnolines.[21]

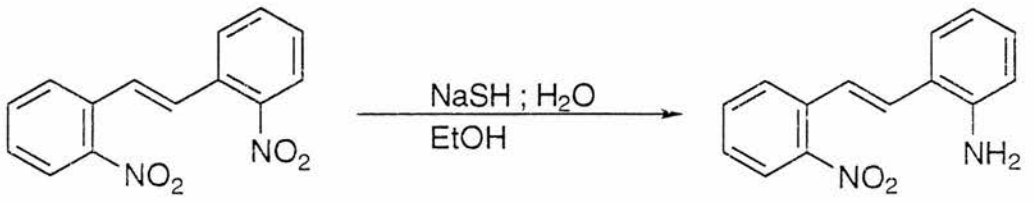
The mass spectrum of the product from the reaction of HCl and 1-methylquinoxalino[2,3-*c*]cinnoline leads to the conclusion that chlorination has taken place (to some extent) and that the fragmentation pattern from that spectrum agrees very well with the fragmentation pattern from previous spectra obtained from monochloroquinoxalino[2,3-*c*]-cinnolines.

QUINO[2,3-*c*]CINNOLINES

The other route to preventing protonation at N-12 was to remove N-12 altogether. It was hoped to achieve this by the cyclisation of 2-amino-2'-nitrostilbene in methanolic cyanide, following the same pathway as in the cyclisation of the Schiff bases, to give quino[2,3-*c*]-cinnoline (**28**), and to use this as the species to be chlorinated.

2,2'-Dinitrostilbene was formed in 50% yield by dissolving 2-nitrobenzyl chloride in ethanol and adding a solution of potassium hydroxide in ethanol.[12] Heberlein and Ehrenspergen have shown that one nitro-group in 2,2'-dinitrostilbene can be selectively reduced, using sodium hydrogen sulphide in aqueous ethanol, without the reduction of the second nitro-group (Scheme 28).

SCHEME 28



2-Amino-2'-nitrostilbene was obtained by the above method as an orange solid in a very poor 29% yield. It was hoped that cyanide induced cyclisation of the stilbene would follow the same mechanism as that of the corresponding Schiff base; however T.L.C of the product showed the starting material to have been recovered unchanged, with no other products being visible. ^{1}H NMR then confirmed this result, showing no quino[2,3-*c*]cinnoline. This result thus confirms the earlier fear that the C=C bond, even between presumably electron-deficient and electron-rich benzene rings, did not have an electrophilic "end" capable of being attacked by the cyanide nucleophile.

An alternative route to the quino[2,3-*c*]cinnoline was then examined by attempting the coupling of 2-nitrobenzyl chloride and 2-nitrobenzyl cyanide (Scheme 12, p.23). Sodium hydride in THF was used to deprotonate the 2-nitrobenzyl cyanide: the solution went bright purple instantly and also began to evolve hydrogen. After the evolution had ceased, the 2-nitrobenzyl chloride was added. Work-up of the resulting brown solution, however, led only to intractable products, with no quino[2,3-*c*]cinnoline being found by ^{1}H NMR.

SECTION 3

EXPERIMENTAL

Materials and apparatus

Melting points were determined on an Electrothermal model 9100 apparatus and are uncorrected.

All infra-red spectra were recorded as Nujol mulls.

Unless otherwise indicated NMR spectra were recorded in $CDCl_3$ solution, ^1H NMR at 200MHz and ^{13}C NMR spectra at 50.3 MHz, on a Varian Gemini spectrometer with tetramethylsilane as an internal reference.

Mass spectra were generated by electron impact on a Finnegan Mat. Incos 50 mass spectrometer.

'Ether' refers to diethyl ether, and 'petrol' to the fraction of b.p. 40-60°C

Symbols and Abbreviations

NMR	nuclear magnetic resonance
δ	chemical shift (ppm)
s	singlet
bs	broad singlet
d	doublet
dd	double doublet
m	multiplet
i.r.	infra-red
m.p.	melting point
m/z	mass-to-charge ratio
THF	tetrahydrofuran
DMF	*N,N*-dimethylformamide

2-METHYL-6-NITROBENZYL ALCOHOL (**32**)

A suspension of 2-methyl-6-nitrobenzoic acid (**31**) (8.0 g; 44.2 mmol), thionyl chloride (15.8 g; 132.5 mmol) and DMF (1.0 g; 13.7 mmol) was heated at reflux for 5 hours under nitrogen before cooling and evaporating off the excess thionyl chloride.

The crude 2-methyl-6-nitrobenzoyl chloride was then dissolved in dry THF (30 ml) and added to a slurry of sodium borohydride (6.35 g; 172.8 mmol) in THF (30ml) over 30 mins with the temperature being kept below 5°C. This mixture was then stirred under nitrogen for 20 hours before adding water (200 ml) then hydrochloric acid (15 ml conc. HCl + 30 ml water).

The solution was then extracted with ether (5 x 50 ml), the ether layers combined, dried and evaporated to give a brown oil which was chromatographed (silica gel; dichloromethane eluent) to give the alcohol (**32**).

Yield, 4.63g (63%); m.p. 62-64.5°C [lit.,[13] 58-62°C]; ν_{max} 3390 (OH), 1510 and 1350 cm^{-1} (NO_2); δ_H 2.52 (3H, s, CH_3), 2.81 (1H, bs, OH), 4.70 (2H, s, CH_2), 7.32 (1H, t, H-4), 7.45 (1H, d, H-3), 7.65 (1H, d, H-5); δ_C 19.8 (CH_3), 58.3 (CH_2), 122.5 (C-3), 129.0 (C-2), 133.0 (C-5), 135.8 (C-1), 141.0 (C-6), 151.3 (C-4).

2-METHYL-6-NITROBENZALDEHYDE (**30**)

To a stirred solution of 2-methyl-6-nitrobenzyl alcohol (**32**) (0.91 g; 5.45 mmol) in dichloromethane (10 ml) was added a solution of pyridinium chlorochromate (1.77 g; 8.17 mmol) in dichloromethane (10 ml). The solution was stirred for 48 hours before diluting with ether (50 ml) and filtering the supernatant liquid through Celite. The residue was then extracted again with ether (5 x 50 ml), filtered through Celite, the extracts combined and evaporated down to yield a dark brown/black waxy solid. Purification may be attained by chromatography of the crude product (silica gel; eluent, ether) to give a white crystalline solid.

Yield, 0.90g (100%); m.p. 41.5-43°C (crude), 46-47°C (chromatographed) [lit.,[13] 47.5-48.5°C]; $\nu_{max.}$ 1690 (C=O), 1510 and 1350 cm^{-1} (NO_2); δ_H 2.52 (3H, s, CH_3), 7.50-7.71 (2H, m, H-3 + H-4), 7.98 (1H, d, H-5), 10.39 (1H, s, CHO); δ_C 19.9 (CH_3), 122.2 (C-1), 131.6 (C-5), 132.3 (C-2), 132.4 (C-3), 137.2 (C-4), 139.4 (C-6), 190.6 (CHO).

OTHER SYNTHETIC ROUTES TO 2-NITRO-6-METHYLBENZYL ALCOHOL (**32**)

METHOD A

METHYL 2-NITRO-6-METHYLBENZOATE

A suspension of 2-methyl-6-nitrobenzoic acid (**31**) (1.00 g; 5.52 mmol), methanol (3.5 ml) and thionyl chloride (1.32 g; 11.04 mmol) was heated to reflux for 5 hours before cooling to room temperature and adding another portion of thionyl chloride (1.0 g; 8.36 mmol) before reheating to reflux for a further hour before again cooling to room temperature and evaporating off the excess thionyl chloride an methanol. The cream solid was then dissolved in ethyl acetate (15 ml) and washing repeatedly with aqueous potassium hydroxide (5 x 25 ml). The organic layer was then dried ($MgSO_4$) and evaporated to yield an orange solid (95 mg) which was shown to contain methyl 2-nitro-6-methylbenzoate (ca. 60% by ^1H NMR).

The aqueous layer was then acidified to pH 2 with dilute hydrochloric acid (2M), extracted with ethyl acetate (5 x 10 ml), and the organic layer dried ($MgSO_4$) and evaporated to give the acid in a recovery of 82%.

METHOD B

A suspension of 2-methyl-6-nitrobenzoic acid (**31**) (1.00 g; 5.52 mmol), methyl iodide (0.862 g; 6.07 mmol), potassium carbonate (0.839 g, 6.07 mmol) and DMF (10 ml) was

stirred at room temperature for 5 days before adding water (50 ml) and extracting with ethyl acetate (2 x 50 ml). The extracts were then dried ($MgSO_4$) and evaporated to give a yellow oil. The remaining DMF was distilled off and the resultant solid recrystallised from ether/hexane to afford pale yellow crystals.

Yield 0.63g (59%); m.p. 44-45°C; $\nu_{max.}$ 1700 (C=O), 1510 and 1355 cm^{-1} (NO_2); δ_H 2.42 (3H, s, Ar-CH_3), 3.99 (3H, s, CO_2CH_3), 7.35-7.60 (2H, m, H-3 + H-4), 8.02 (1H, d, H-5).

LITHIUM BOROHYDRIDE

A stirred suspension of sodium borohydride (0.57 g; 15 mmol) and lithium bromide (1.30 g; 15 mmol) in dry THF (13 ml) was heated to reflux for 20 hours before cooling and filtering off the solids. The solution of lithium borohydride must then be used immediately.

REDUCTION OF METHYL 2-NITRO-6-METHYLBENZOATE

A stirred suspension of methyl 2-nitro-6-methylbenzoate (0.85 g;4.35 mmol), sodium borohydride (0.33 g; 8.71 mmol) and lithium bromide (0.76 g; 8.71 mmol) in THF was heated to reflux for 7 hours before cooling to room temperature and carefully acidifying with dilute hydrochloric acid. The mixture was then extracted with diethyl ether (5 x 10 ml), the organic layer dried ($MgSO_4$) and evaporated to give a purple oil which appeared to be ca. 75% of the required alcohol (**32**)by ^1H NMR.

METHOD C

ATEMPTED REDUCTION OF 2-METHYL-6-NITROBENZOIC ACID.

To a suspension of 2-methyl-6-nitrobenzoic acid (1.0 g; 5.52 mmol) and sodium borohydride (0.21 g; 5.52 mmol) in dry diglyme (5.6 ml) was added a solution of aluminium chloride (0.25 g; 1.90 mmol) in dry diglyme (1.9 ml). The suspension was stirred at 25°C for 3 hours before carefully adding dilute HCl (2M) and extracting the mixture with diethyl ether (5 x 20 ml), drying ($MgSO_4$) and evaporating to give a yellow oil which was found to be only diglyme and the starting acid by ^1H NMR.

N-(2-METHYL-6-NITROBENZYLIDENE)-*o*-PHENYLENEDIAMINE (**33**)

2-Methyl-6-nitrobenzaldehyde (**30**) (0.100g; 0.61mmol) and *o*-phenylenediamine (0.065 g; 0.61 mmol) were dissolved in the minimum of hot ethanol (ca. 1 ml). After 2 minutes the solution was allowed to cool in ice and the precipitate filtered off.

Yield 0.14g (91%); m.p. 69-70°C (from propan-2-ol); $\nu_{max.}$3490 (NH_2), 1610 (CH=N), 1510 and 1355 cm^{-1} (NO_2); δ_H 2.62 (3H, s, CH_3), 4.10 (2H, bs, NH_2), 6.65-6.85 (2H, m, H-6 + H-3), 7.05-7.20 (2H, m, H-4 + H-5), 7.38-7.52 (2H, m, H-4' + H-3'), 7.75 (1H, d, H-5'), 8.81 (1H, s, CH=N).

Repetition of the above procedure on 8 times the scale shown did not result in the formation of a precipitate. The solution, upon ice-cooling and scratching finally gave a solid which on attempted recrystallisation from propan-2-ol gave first a small quantity of a high-melting (ca. 260°C) solid, presumed to be 2-(2-methyl-6-nitrophenyl)benzimidazole, and then the more soluble Schiff base (0.37g; 30%) m.p. 75-76°C. The analytical sample had m.p. 77-78°C (from ethyl acetate/petrol) (Found: C, 65.8; H, 4.7; N, 16.2. $C_{14}H_{13}N_3O_2$ requires C, 65.9; H, 5.1; N, 16.5%.)

1-METHYLQUINOXALINO[2,3-*c*]CINNOLINE

A suspension of *N*-(2-methyl-6-nitrobenzylidene)-*o*-phenylenediamine (**33**) (2.70 g; 10.59 mmol) and potassium cyanide (1.42 g; 21.18 mmol) in methanol (250 ml) was heated at reflux for 5.5 hours before cooling the solution, filtering off the orange precipitate, washing with water and drying *in vacuo*.

Yield, 0.51 g (20%); m.p. 236-237°C (from toluene). (Found: C, 73.2; H, 3.7; N, 22.6. $C_{15}H_{10}N_4$ requires C, 73.2; H, 4.1; N, 22.8%.) δ_H 3.45 (3H, s, CH_3), 7.91 (1H, dd, H-2), 7.98-8.10 (3H, m, H-3 + H-9 + H-10), 8.43 (1H, m, H-11), 8.55 (1H, m, H-8), 8.82 (1H, dd, H-4). *m/z* 246 (100%), 218 (86), 190 (22), 149 (10), 115 (13), 109 (10), 89 (11), 77 (39), etc.

2-BROMO-6-NITROTOLUENE (**38**)

2-Methyl-3-nitroaniline (**37**) (15.00 g; 98.59 mmol) was heated to reflux with concentrated hydrobromic acid (48%; 48 ml; 423.10 mmol) and water (120 ml) for 15 mins. The solution was then ice cooled and a solution of sodium nitrite (6.80 g; 98.55 mmol) in water (38 ml) was slowly added, the temperature being kept below 3°C. After the addition was complete, the solution was warmed to room temperature and a solution of copper(I) bromide (21.92 g; 98.59 mmol) in hydrobromic acid (48%; 33 ml; 290.90 mmol) and water (78 ml) was slowly added. The solution was then stirred for 30 mins before steam distillation. The distillate was then extracted with ether, dried ($MgSO_4$), combined and evaporated down to give a cream solid. Yield 13.31g (63%); m.p. 39.5-42°C [lit.,[20] 42°C].

2-BROMO-6-NITROBENZYL BROMIDE (**39**)

2-Bromo-6-nitrotoluene (**38**) (10 g; 46.27 mmol), *N*-bromosuccinimide (8.24 g; 46.27 mmol) and benzoyl peroxide (2.24 g; 9.23 mmol) in carbon tetrachloride (800 ml) were heated

to reflux for 10 hours before cooling to room temperature and filtering off the solids. The solvent was evaporated off to give a yellow oil which was then taken crude to the next stage.

N-(2-BROMO-6-NITROBENZYL)PYRIDINIUM BROMIDE (**40**)

A solution of 2-bromo-6-nitrobenzyl bromide (**39**) (13.65 g; 46.27 mmol) and pyridine (5.49 g, 69.41 mmol) in ethanol (7 ml) was stirred at room temperature for 48 hours before filtering off the precipitate and washing the solid with ether. Yield 7.22 g (42%) ; m.p. 209-210°C [lit.,[20] 210°C].

p-NITROSO-*N,N*-DIMETHYLANILINE

To a stirred solution of *N,N*-dimethylaniline (30.00 g; 0.25 mol) in concentrated hydrochloric acid (37 wt%; 105 ml; 1.28 mol) at 5°C was added a solution of sodium nitrite (18.00 g; 0.26 mol) in water (30 ml) maintaining the temperature at less than 5°C.

The solution was then allowed to stand for 1 hour at room temperature before filtering the *p*-nitroso-*N,N*-dimethylaniline hydrochloride and washing with dilute hydrochloric acid (5M). Yield 40.60 g (87%).

The hydrochloride was converted into the free base, as follows, only when required.

A suspension of *p*-nitroso-*N,N*-dimethylaniline hydrochloride (30.00 g; 0.16mol) in water (100 ml) was shaken with sodium hydroxide solution (10% w/w) until the mixture was bright green and the supernatant liquid basic. The free base was then extracted with toluene (3 x 60 ml) before drying (K_2CO_3). When the extract was evaporated to half volume, the free base then crystallised out as bright green flakes which were filtered off to give an almost quantitative yield. M.p. 83-84°C [lit.,[22] 85°C].

2-BROMO-6-NITROBENZALDEHYDE (**36**)

METHOD A

To a solution of *N*-(2-bromo-6-nitrobenzyl)pyridinium bromide (5.00 g; 13.4 mmol) and *N,N*-dimethyl-*p*-nitrosoaniline (2.01 g; 13.4 mmol) in ethanol (60 ml) at 2°C was added a sodium hydroxide solution (1M; 39 ml) so the temperature did not rise above 2°C. The mixture was then stirred at room temperature for 48 hours before addition of water (70 ml) and ice-cooling. The nitrone then precipitated out as orange needles and was filtered off and washed with water. It was then stirred with sulphuric acid (3M; 561 ml) for 12 hours before ice-cooling and the resultant precipitate filtered off. The cream solid was then recrystallised from ethanol. Yield 1.21 g (39%); m.p. 81-82°C [lit.,[20] 82°C]; δ_H 7.55 (1H, t, H-4), 8.00 (2H, dd, H-3 + H-5), 10.30 (1H, s, CHO).

METHOD B

A solution of 2-bromo-6-nitrotoluene (**38**) (1.00 g; 4.63 mmol), *N*-chlorosuccinimide (1.85 g; 13.88 mmol) and dibenzoyl peroxide (0.22 g; 0.93 mmol) in carbon tetrachloride (80 ml) were heated to reflux for 7 hours before cooling and stirring the solution with hydrochloric acid (3M; 15 ml). The mixture was then extracted with ether (3 x 50 ml), the ether layers combined, dried ($MgSO_4$) and evaporated, to give the recovered 2-bromo-6-nitrotoluene with no chlorinated product (or aldehyde) detectable.

N-(2-BROMO-6-NITROBENZYLIDENE)-*o*-PHENYLENEDIAMINE (**35**)

A solution of 2-bromo-6-nitrobenzaldehyde (**36**) (1.00 g; 4.35 mmol), *o*-phenylenediamine (0.47 g; 4.35 mmol) and *p*-toluenesulphonic acid (2 crystals) in ethanol was heated at reflux for 5 mins before cooling and evaporating off the solvent. The red solid was then recrystallised form ethanol. Yield 1.03 g (74%); m.p. 102-102.5°C [lit..[20] 101-

102°C]; δ_H 4.05 (2H, bs, NH_2), 6.60-6.85 (2H, m, H-3 + H-5), 7.00-7.22 (2H, m, H-4 + H-6), 7.39 (1H, t, H-4'), 7.64 (1H, d, H-3'), 7.82 (1H, d, H-5'), 8.80 (1H, s, CH=N).

1-BROMOQUINOXALINO[2,3-*c*]CINNOLINE (**34**)

A suspension of *N*-(2-bromo-6-nitrobenzylidene)-*o*-phenylenediamine (**35**) (1.00 g; 3.13 mmol) and potassium cyanide (0.42 g; 6.25 mmol) in methanol (75 ml) was heated at reflux for 5.5 hours before cooling the solution, filtering off the orange precipitate, washing with water and drying *in vacuo*. Yield 0.70g (85%); m.p. 233-233.5°C [lit.,[19] 237-238°C]; δ_H 7.87 (1H, t, H-3), 7.95-8.15 (2H, m, H-9 + H-10), 8.29 (1H, d, H-2), 8.40 (1H, d, H-11), 8.49 (1H, m, H-8), 8.87 (1H, dd, H-4).

ATTEMPTED LITHIATION OF 1-BROMOQUINOXALINO[2,3-*c*]CINNOLINE

To a stirred suspension of 1-bromoquinoxalino[2,3-*c*]cinnoline (**34**) (200 mg, 0.76 mmol) in dry THF (10 ml) at –78°C was added a solution of *n*-butyl-lithium (1.5M; 0.76 ml, 1.14 mmol) in hexane. The solution then changed, almost instantly, to a very dark green colour; this was then stirred at –78°C for 15 minutes.

ATTEMPTED PREPARATION OF 1-(2,2,2-TRIFLUOROETHYL)QUINOXALINO-[2,3-*c*]CINNOLINE

To the above solution of the (supposed) lithiated compound was added, under nitrogen, a solution of 1,1,1-trifluoro-2-iodoethane (320 mg, 1.52 mmol) in dry THF (10 ml) at –78°C. The resulting solution,which was still green, was stirred at –78°C for 1 hour, then allowed to warm slowly to room temperature; it was then black. It was then quenched with water (10 ml), extracted with dichloromethane (3 x 50 ml), dried ($MgSO_4$), and evaporated, to yield a black solid which was insoluble in chloroform, and gave only a black base-line spot on TLC.

REACTION OF 1-METHYLQUINOXALINO[2,3-*c*]CINNOLINE WITH HCl

Dry hydrogen chloride gas was bubbled into a stirred solution of 1-methyl-quinoxalino[2,3-*c*]-cinnoline (100 mg; 0.407 mmol) in chloroform (10 ml). A blue/black solid was instantly precipitated, but passage of the gas was continued for 15 minutes and the mixture left to stand for 15 minutes. The precipitate was then filtered off and the mother liquors retreated with HCl following the above procedure. This procedure was then repeated for a third time. The combined precipitates were then stirred with aqueous sodium hydroxide (10 ml; 2M) and dichloromethane (15 ml) for 10 minutes before removing the aqueous layer, drying the dichloromethane ($MgSO_4$) and evaporating the solvent to give an orange/red solid. Yield 92 mg; m.p. 252-253°C; δ_H (300 MHz) for the chlorinated product: 3.30 (3H, s, CH_3), 7.80-8.02 (3H, m, H-2 + H-3 + H-9), 8.28 (1H, d, H-11), 8.40 (1H, d, H-8), 8.72 (1H, d, H-4). Resonances corresponding to 1-methylquinoxalinocinnoline (see above) were also observed. For the mixture, *m/z* 282 ($M^{+\cdot}$, 35%), 280 ($M^{+\cdot}$, 100), 254 (31), 252 (92), 246 (93), 218 (85), 217 (45), 190 (61), 141 (20), 115 (33), 89 (28), 77 (40), 75 (52), etc.

The original reaction mother-liquor, when evaporated, gave unreacted 1-methyl-quinoxalinocinnoline (17 mg; 17% recovery).

4-CHLORO-2-NITROACETANILIDE

To a stirred solution of 4-chloro-2-nitroaniline (20.00 g; 115.9 mmol) in acetic acid (30 ml; 524.5 mmol) was added acetic anhydride (30 ml; 318.2 mmol) and a catalytic amount of *N,N*-dimethylaminopyridine (DMAP). The solution was then heated to 95°C for 1 hour before cooling to room temperature and filtering off the product. The product was then recrystallised from ethanol to give 4-chloro-2-nitroacetanilide as yellow needles. Yield 18.80g (76%); m.p 100-101°C [lit.,[24] 103°C]; δ_H 2.30 (3H, s, CH_3); 7.60 (1H, dd, H-5), 8.19 (1H, d, H-3), 8.76 (1H, d, H-6), 10.22 (1H, bs, N<u>H</u>Ac).

5-CHLORO-2-NITROACETANILIDE

The same method as above, using 5-chloro-2-nitroaniline (5.00 g; 29.0 mmol), acetic acid (7.5 ml; 131.1 mmol), acetic anhydride (7.5 ml; 79.6 mmol) and DMAP (2 mg), gave 5-chloro-2-nitroacetanilide as straw coloured needles. Yield 5.20 g (84%); m.p. 117.5-118.5°C (from ethanol: lit.,[25] 117-118°C); δ_H 2.31 (3H, s, CH_3), 7.11 (1H, dd, H-4), 8.12 (1H, d, H-3), 8.82 (1H, d, H-6), 10.35 (1H, bs, NH).

2-AMINO-4-CHLOROACETANILIDE (**43**)

To a stirred suspension of iron powder (8.46 g; 151.52 mmol) in water (32 ml) and acetic acid (2.0 ml) at 80°C was added the 4-chloro-2-nitroacetanilide (10.00 g; 46.62 mmol) which had first been passed through a 250μm sieve. After 40 minutes the acid was neutralised with potassium carbonate (4.0 g) in water (20 ml). The hot solution was then filtered through Celite and the Celite extracted with boiling ethanol (10 x 70 ml). The ethanol was evaporated and the product recrystallised from toluene to give 2-amino-4-chloroacetanilide as a brown solid. Yield 6.88 g (80%); m.p. 142-143°C [lit.,[23] 145°C]; δ_H 2.05 (3H, s, CH_3), 3.50 (2H, bs, NH_2), 6.49-6.60 (1H, m, H-5), 6.72-6.77 (1H, m, H-3), 7.15-7.23 (1H, m, H-6), 9.17 (1H, bs, NHAc).

2-AMINO-5-CHLOROACETANILIDE (**42**)

To a stirred suspension of iron powder (4.23g; 75.76mmol) in water (13.5ml) and acetic acid (0.5ml) at 80°C was added the 5-chloro-2-nitroacetanilide (5.00g; 23.31mmol) over 15 minutes. Water (20ml) and acetic acid (1ml) were then added and the mixture then stirred for 10 minutes before neutralising the acid with potassium carbonate (1.2 g) in water (10 ml). The hot solution was then filtered through Celite and the Celite extracted with boiling ethanol

(10 x 50 ml). The ethanol was then evaporated and the product recrystallised from toluene to give 2-amino-5-chloroacetanilide as a brown solid. Yield 1.32 g (32%); m.p 140-142°C [lit.,[9] 144-145°C]; δ_H 2.08 (3H, s, CH_3), 3.31 (2H, bs, NH_2), 6.72 (1H, d, H-3), 6.91 (1H, dd, H-4), 7.36 (1H, d, H-6), 9.11 (1H, s, NHAc).

2-ACETAMIDO-5-CHLORO-*N*-(2-METHYL-6-NITROBENZYLIDENE)ANILINE (**44**)

A solution of 2-amino-4-chloroacetanilide (190 mg; 1.02 mmol) and 2-methyl-6-nitrobenzaldehyde (169 mg; 1.02 mmol) in methanol (2 ml) was heated to reflux for 2 minutes before being cooled. The Schiff base did not crystallise from the solution, but the NMR spectrum showed its presence in the solution, and it was therefore used crude for the cyclisation stage. δ_H 1.21 (3H, s, CH_3-Ar), 2.42 (3H, s, $COCH_3$), 6.64 (1H, dd, H-5), 6.77 (1H, d, H-3), 7.07 (1H, d, H-6), 7.50 (1H, t, H-4'), 7.58 (1H, m, H-3'), 8.00 (1H, dd, H-5'), 8.84 (1H, bs, NHAc).

ATTEMPTED CYCLISATION OF 2-ACETAMIDO-5-CHLORO-*N*-(2-METHYL-6-NITRO-BENZYLIDENE)ANILINE (**44**)

A suspension of 2-acetamido-4-chloro-*N*-(2-methyl-6-nitrobenzylidene)aniline (**44**) (538 mg; 1.62 mmol) and potassium cyanide (218 mg; 3.25 mmol) in methanol (40 ml) was heated to reflux for 10 hours before being cooling to room temperature. Water (10 ml) was added, and the solution extracted with dichloromethane (30 ml). The organic layer was then removed and the solution dried ($MgSO_4$) and evaporated to give a pale pink solid which was shown to be exclusively starting material (**44**) by ^1H NMR.

2,2'-DINITROSTILBENE

To a solution of 2-nitrobenzyl chloride (10.00 g; 58.28 mmol) in ethanol (40 ml) was added dropwise a solution of potassium hydroxide (9.81 g; 174.85 mmol) in ethanol (100 ml) at room temperature. The mixture was stirred for 4 hours before the orange solid was filtered off, washed firstly with cold ethanol, then hot water, and finally with cold ethanol before being recrystallised from toluene. Yield 3.95g (50%); m.p. 198°C [lit.,[12] 197.5-198.0°C]; δ_H 7.50 (2H, t, H-4), 7.59 (2H, s, CH=CH), 7.69 (2H, t, H-5), 7.84 (2H, d, H-6), 8.06 (2H, d, H-3).

2-AMINO-2'-NITROSTILBENE (**28**)

To a solution of 2,2'-dinitrostilbene (3.50 g; 12.96 mmol) in ethanol (450 ml) heated at reflux was added a solution of sodium hydrogen sulphide (4.90 g; 66.20 mmol) in water (15 ml). The solution was then maintained at reflux for a further 25 minutes until the suspension went brown and the mixture was then allowed to cool to room temperature and filtered.

The solid was then washed with dichloromethane (100 ml) and the filtrate evaporated to a quarter volume, water (50 ml) was added and the solution extracted with dichloromethane (4 x 150 ml). The organic solutions were then combined, dried ($MgSO_4$) and evaporated. The orange solid was then recrystallised from ethanol. Yield 0.88 g (29%); m.p. 103.5-105°C [lit.,[12] 105-105.5°C]; δ_H 3.70 (2H, bs, NH_2), 6.75 (3H, m, H-3 + H-4 + H-5), 7.12 (2H, m, H-6 + H-4'), 7.34 and 7.50 (2H, AB, CH=CH), 7.59 (1H, t, H-5'), 7.72 (1H, d, H-6'), 7.95 (1H, d, H-3').

ATTEMPTED CYCLISATION OF 2-AMINO-2'-NITROSTILBENE (**28**)

A suspension of 2-amino-2'-nitrostilbene (500 mg; 2.1 mmol) and potassium cyanide (284 mg; 4.2 mmol) in methanol (40 ml) was heated to reflux for 5 hours before cooling to

room temperature, evaporating the solution to one-quarter volume and adding water (20 ml). The red precipitate was then filtered off and was shown to be starting material by TLC and ^1H NMR.

ATTEMPTED PREPARATION OF 2,3-BIS(2-NITROPHENYL)PROPANONITRILE

To a cooled suspension of sodium hydride (148 mg, 6.17 mmol) in dry THF (10 ml) was added a solution of 2-nitrobenzyl cyanide (1.0 g, 6.17 mmol) in dry THF (10 ml). The solution then turned bright purple and hydrogen was evolved. When evolution had stopped, a solution of 2-nitrobenzyl chloride (1.06 g, 6.17 mmol) in dry THF (10 ml) was added dropwise, and the mixture was then stirred at room temperature for 2 hours, during which time it developed a brown colour. It was then quenched with water; the product was completely insoluble in chloroform, and TLC showed only a base-line spot.

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