NUCLEOPHILIC SUBSTITUTION REACTIONS OF BENZO[C]CINNOLINES

A THESIS

PRESENTED FOR THE DEGREE OF

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ROBERT HARVEY MONTGOMERY ROSS, B.Sc.(Hons)

Department of Organic Chemistry

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CONTENTS

SUMMARY

Benzo[c]cinnoline and the chlorobenzo[c]cinnolines have been found to react with lithium dimethylamide in dimethylamine to give, as initial products, compounds which were formed by an unexpected displacement of hydride ion from the 4- and 7- positions of the benzo[c]cinnoline nucleus. The reaction of 2-chlorobenzo[c]cinnoline was exceptional and hydride ion was displaced only from the 4- position.

The reactions of the iodobenzo[c]cinnolines and 2-, 3- and 4-chlorobenzo[c]cinnoline with potassium amide in ammonia have been studied. 1-Chloro, 2-chloro and 2-iodobenzo[c]cinnoline underwent substitution with this base to give 2-aminobenzo[c]cinnoline exclusively. 3- and 4-Chloro and 3- and 4-iodobenzo[c]cinnoline reacted with potassium amide in ammonia to form mixtures of 3- and 4-aminobenzo[c]cinnoline. Under certain conditions benzo[c]cinnoline was a product of these reactions.

Substitution reactions of some chlorobenzo[c]cinnolines with piperidine and dimethylamine are described. These reactions proceed by the addition-elimination mechanism.

The reactions of 6-chlorophthalazine with lithium dimethylamide and 4-chlorocinnoline with lithium piperidide are described.

The use of nuclear magnetic resonance spectra in identification of some benzo[c]cinnolines is discussed.

STATEMENT

This thesis contains no material previously submitted for a degree or diploma in any University, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

Robert H. M. Ross

ACKNOWLEDGEMENTS

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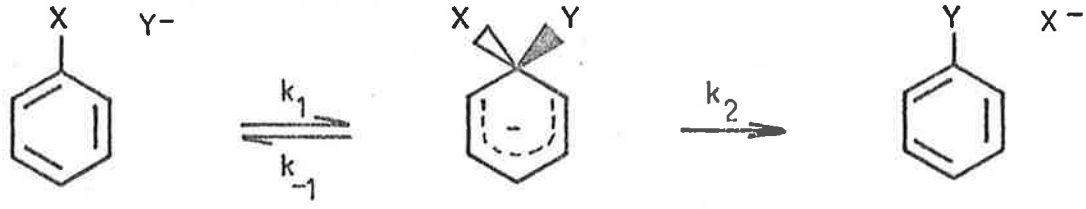
INTRODUCTION

Aromatic nucleophilic substitution reactions and their mechanisms have been studied extensively in the last two decades and the field has been well reviewed.[1-17] Most of these reactions follow a unimolecular or one of two bimolecular mechanisms. The bimolecular processes occur most frequently and may be classified into (1) the addition-elimination (AE) and (2) the elimination-addition (EA) mechanisms; a brief discussion of the principal features of each is pertinent.

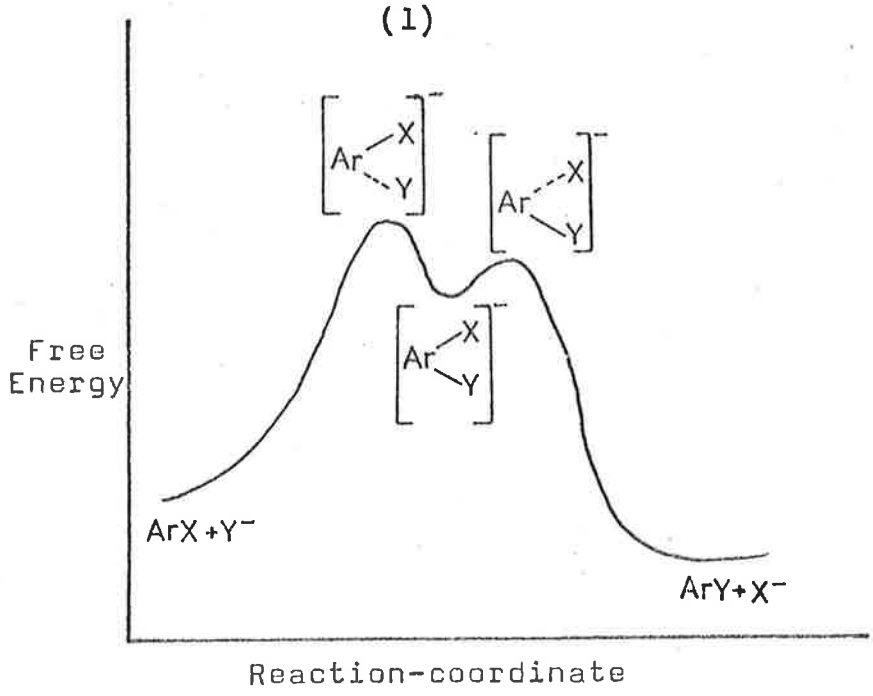
Electronic repulsion between the unshared pair of electrons of a nucleophile and the π-electron system of an aromatic compound generally disfavours aromatic nucleophilic substitution.

In AE reactions,[10-17] however, reactivity may be enhanced by suitable leaving groups, and substituents which stabilize transition states and cause one or more ring carbon atoms to become electron deficient. The reaction-coordinate of this mechanism involves an intermediate flanked by two transition states, and reaction is initiated when a nucleophile approaches the aromatic ring from above the plane. As the new bond forms, hybridization of the ring carbon at the point of attack changes from sp^2 to sp^3 in the intermediate. Loss of the leaving group and ring

rearomatization complete the reaction (Scheme 1).

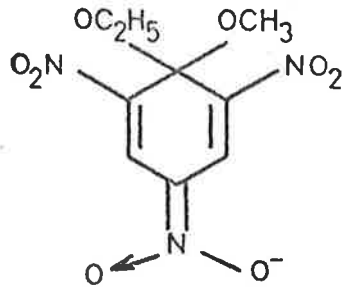


(1)



Scheme 1

Many workers have found evidence[2,4a] that the species (1) is a true intermediate and not a transition state. Compelling evidence for this is the isolation of Meisenheimer complexes,[18] compounds with structures similar to (1). For example, methoxide ion reacts with 2,4,6-trinitrophenetole to give the complex (2).[19]



(2)

Although there are strong indications that some reactions proceed by a two-step mechanism involving an intermediate, it is generally accepted that for different reactions the transition states may occur at different positions along the reaction coordinate, depending on the leaving group, the type of nucleophile and the number and types of activating substituents.

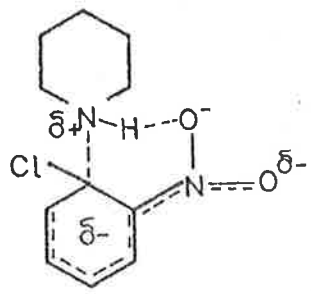
Aromatic compounds are activated towards nucleophilic substitution by electron-withdrawing substituents; such groups may activate the ring by both inductive and mesomeric effects. Activation by the mesomeric effect alone is generally considered[6a] to be slightly greater at a position para to a substituent than ortho to it, and Ingold[20] has attributed this to the greater stability of the para-activated transition state. In support of this he quotes the greater stability of p-quinones over o-quinones.

Activation by the inductive effect decreases with distance from the electron-withdrawing group along a carbon chain and so is greatest in the ortho-position.

A ring hetero-atom such as nitrogen has a similar effect to an electron-withdrawing substituent and may also activate a ring inductively and by the mesomeric effect. The same principles hold here as for activation by substituents in carbocyclic compounds. Aromatic heterocyclic compounds, however, are generally considered to be more highly activated by the mesomeric effect in a position p to the hetero-atom and more highly activated by the inductive effect in a position o to the hetero-atom. As well as these two general activating effects there are several influences which may operate to increase reactivity at a position ortho to a substituent or hetero-atom. These are known as "ortho effects" or "proximity effects" and include interaction of an ortho-substituent with nucleophile by means of hydrogen-bonding,[21-24] electrostatic effects[6b] and formation of cyclic transition states.[4b]

Nucleophiles with a hydrogen atom attached to the nucleophilic centre, such as amines and alcohols, are capable of forming hydrogen-bonds with some substituents.

Ross and Finkelstein[23] found that substitution with piperidine was faster in 2-nitrochlorobenzene than in 4-nitrochlorobenzene and accounted for this by postulating hydrogen-bonding in the transition state of the 2-nitro compound (3). In species (3) the lone pair of the piperidine nitrogen is favourably oriented for attack on the carbon ortho to the nitro group. Hydrogen-bonding such as this may also cause a levelling in the differential effect which solvents have on reaction rates. Sbar-

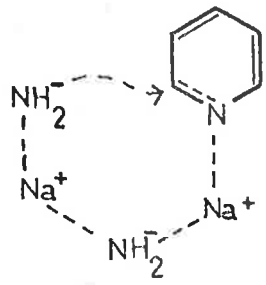


(3)

bati et al[24] showed that there was little difference in the rates of reaction of piperidine with 2-nitrochlorobenzene in benzene and in ethanol, while the 4-nitro analogue reacted faster in ethanol. This rate increase could be attributed to the greater solvation of the transition state when ethanol was solvent. The internal

hydrogen-bonding that occurs between piperidine and the 2-nitro compound would, however, mask the effect of any hydrogen-bonding between substrate and solvent.[6c]

Formation of cyclic transition states has been postulated[4b] to account for high reactivity at positions ortho to a ring nitrogen in the reactions of pyridines with lithium alkyls, amines and metal amides. For example, the transition state for the reaction of pyridine with sodium amide to give 2-aminopyridine has been envisaged[4b] as (4); in such a species electrostatic repulsion between the amide ion and the lone pair of the ring nitrogen would be substantially overcome.



(4)

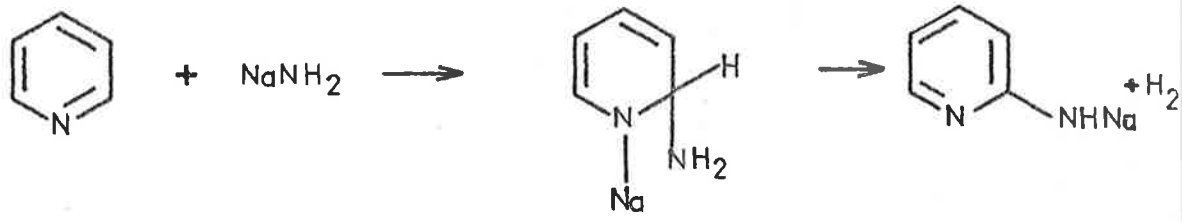
Cationization of a ring hetero-atom has an overall activating effect on nucleophilic substitution in heterocyclic compounds and has been discussed by Shepherd and Fedrick[4c] with regard to azines. Metal complexing is

one form of cationization and in some cases[25,26,27,28] this seems to promote reaction exclusively in the position ortho to the hetero-atom.

Leaving groups also affect the rate of reaction by the AE mechanism. In the present series of reactions the leaving groups are halogens. It has been shown[6d] that when the nucleophilic atom of a nucleophile is in the first Period of the Periodic Table the normal order of halogen mobility is F>Cl>Br>I.

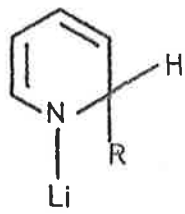
In aromatic nucleophilic substitution reactions the most suitable leaving groups are species which exist as neutral molecules or stable anions when displaced. The hydride ion does not fit either of these categories, but there are a few examples of reactions in which hydride ion is displaced.

One of these is the Tschitschibabin reaction,[2a] a well-known method for the preparation of 2-aminopyridines. The reaction is usually carried out by heating a metal amide with the pyridine at about 100-140°C; hydrogen is evolved from the mixture and the metal salt of the 2-aminopyridine is produced. The mechanism postulated[30] for this reaction (Scheme 2) involves displacement of hydride which combines with a proton from the entering amino group to give hydrogen.

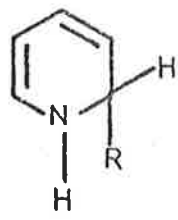


Scheme 2

A similar mechanism was proposed[30] for the reactions of aryl- and alkyllithium compounds with pyridine, which give 2-substituted pyridines.[30,31] The intermediate (5) postulated for these reactions is converted into the



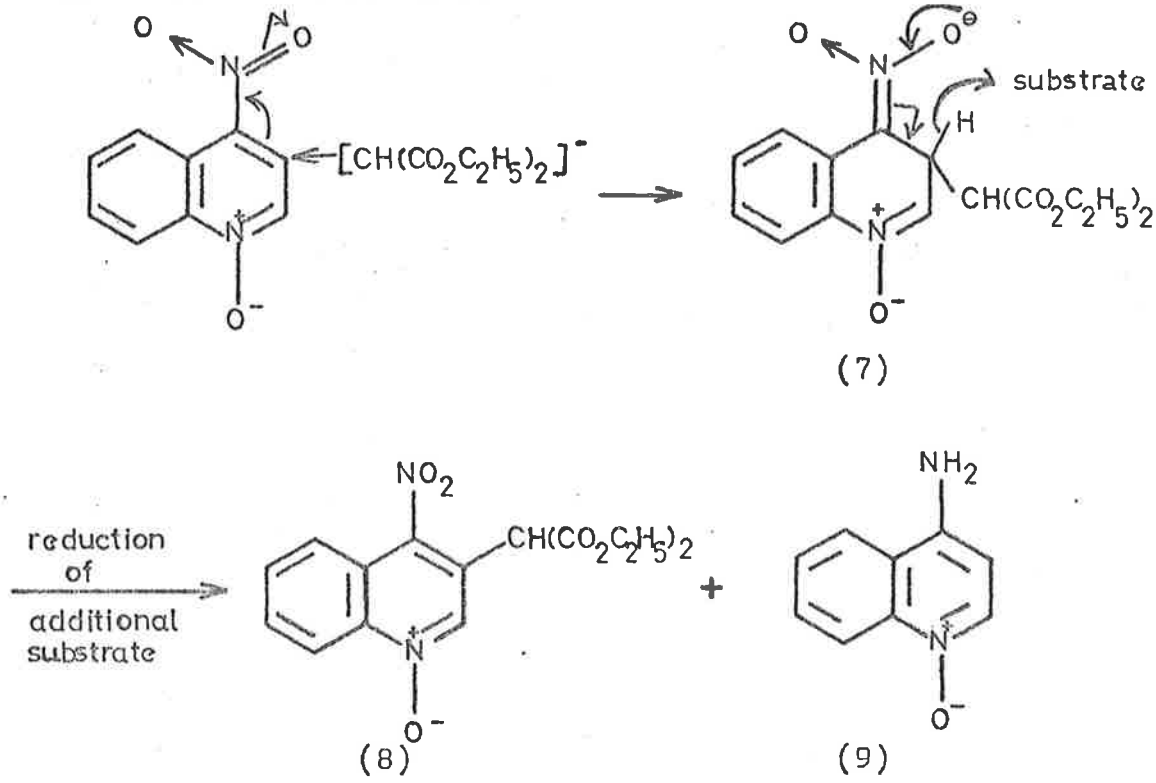
(5)



(6)

aryl- or alkyl-pyridine by direct oxidation or by heating to eliminate lithium hydride. Evidence for the existence of intermediate (5) was obtained[31] when hydrolysis of the reaction mixtures gave the dihydropyridines (6). Fraenkel and Cooper[32] found further evidence for such an intermediate when they observed that the n.m.r. spectrum of the reaction mixture of n-butyllithium with pyridine was consistent with structure (5).

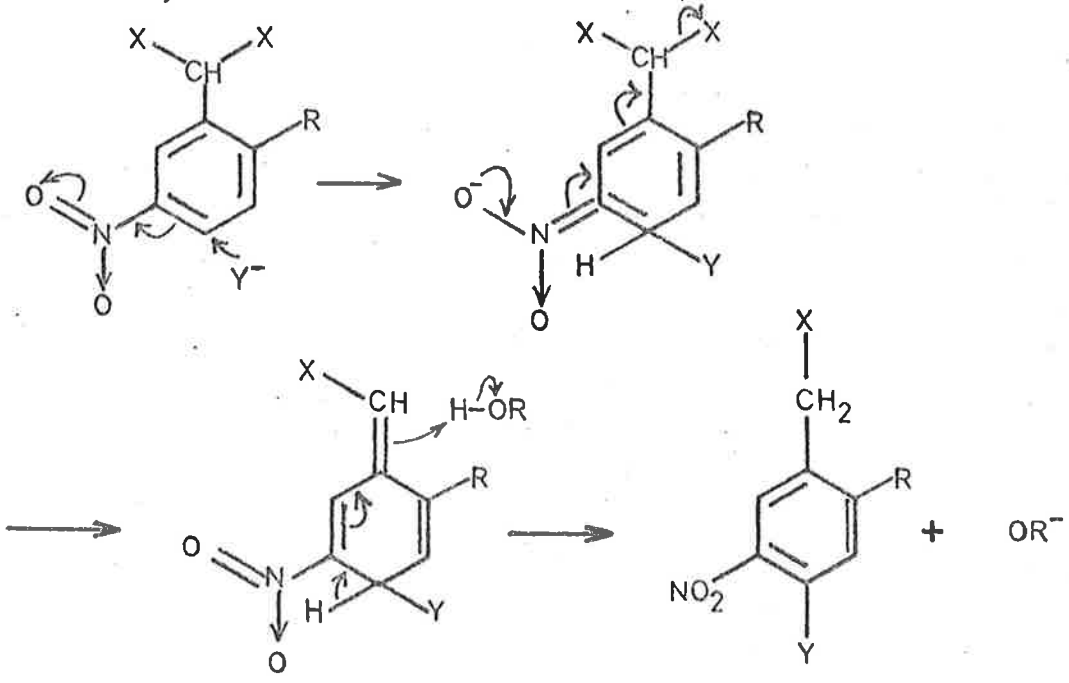
Removal of hydride ion, due to intermolecular oxidation by the substrate, is reported[33] to occur in the reaction of 4-nitroquinoline-1-oxide with diethylsodiomalonate. A mechanism put forward[33,6d] for this reaction (Scheme 3) invokes removal of hydride ion from the intermediate (7) by another molecule of substrate to give the substitution product, diethylsodio(4-nitro-3-quinoloyl)-malonate-1-oxide (8), and the reaction product, 4-aminoquinoline-1-oxide (9).



Scheme 3

In another reaction in which nucleophilic attack occurs at an unsubstituted position ortho to a nitro group,

3-nitrobenzylidenedichloride compounds react with methoxide and ethoxide ions to give 4-substituted products.[34] In the mechanism suggested for this reaction by Loudon and Smith[34] (Scheme 4), internal electron redistribution accompanied by loss of halide ion allows the hydrogen at the point of attachment of the nucleophile to be lost as a proton; this is usually a more favourable process than loss of hydride ion. Other nucleophilic substitution

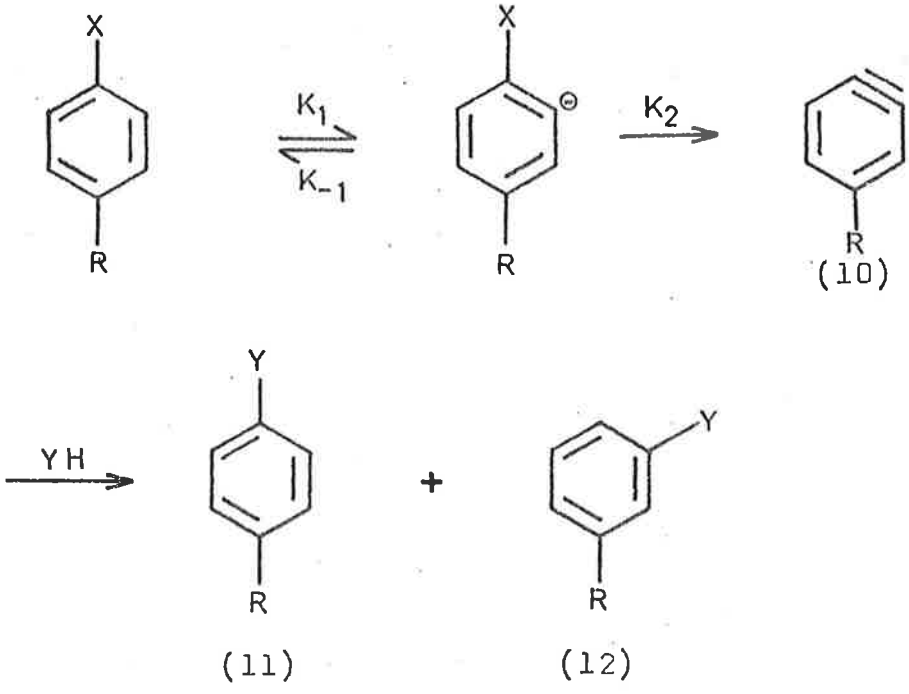


Scheme 4

reactions in which internal rearrangements allow substituted hydrogen to be lost as a proton have been reported[35,36] and include the von Richter reaction.[37]

This review of hydrogen replacement during nucleophilic substitution has particular relevance to the discussion of work described later in this thesis.

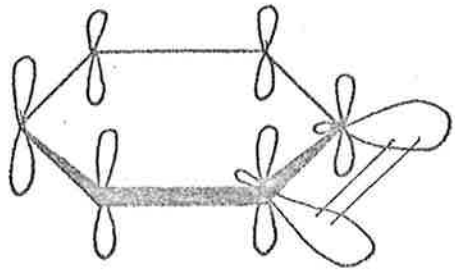
The second major pathway for aromatic nucleophilic substitution, the EA mechanism,[6-17] involves the formation of an aryne intermediate (10). This is produced when removal of a proton ortho to a leaving group and elimination of the leaving group lead to formation of a new bond, known as an aryne bond. The process may be concerted or occur in two steps depending on the mobility of the leaving group. Attack by a nucleophile at one carbon of the aryne bond and proton-capture at the other complete the reaction (Scheme 5).



Scheme 5

One of the products (11) from this reaction is the same as would be expected had substitution occurred by the AE mechanism. In the other product (12), however, the nucleophile has entered the ring in a position ortho to that originally occupied by the leaving group. Substitution with rearrangement to the ortho-position such as this is known as "cine-substitution".

The generally accepted structure of an aryne intermediate is that of an aromatic ring with an almost unperturbed π-system in which there are two orbitals (containing an electron each) on adjacent carbon atoms and in the plane of the ring. A small amount of lateral overlap between these orbitals forms the aryne bond (see structure 13).

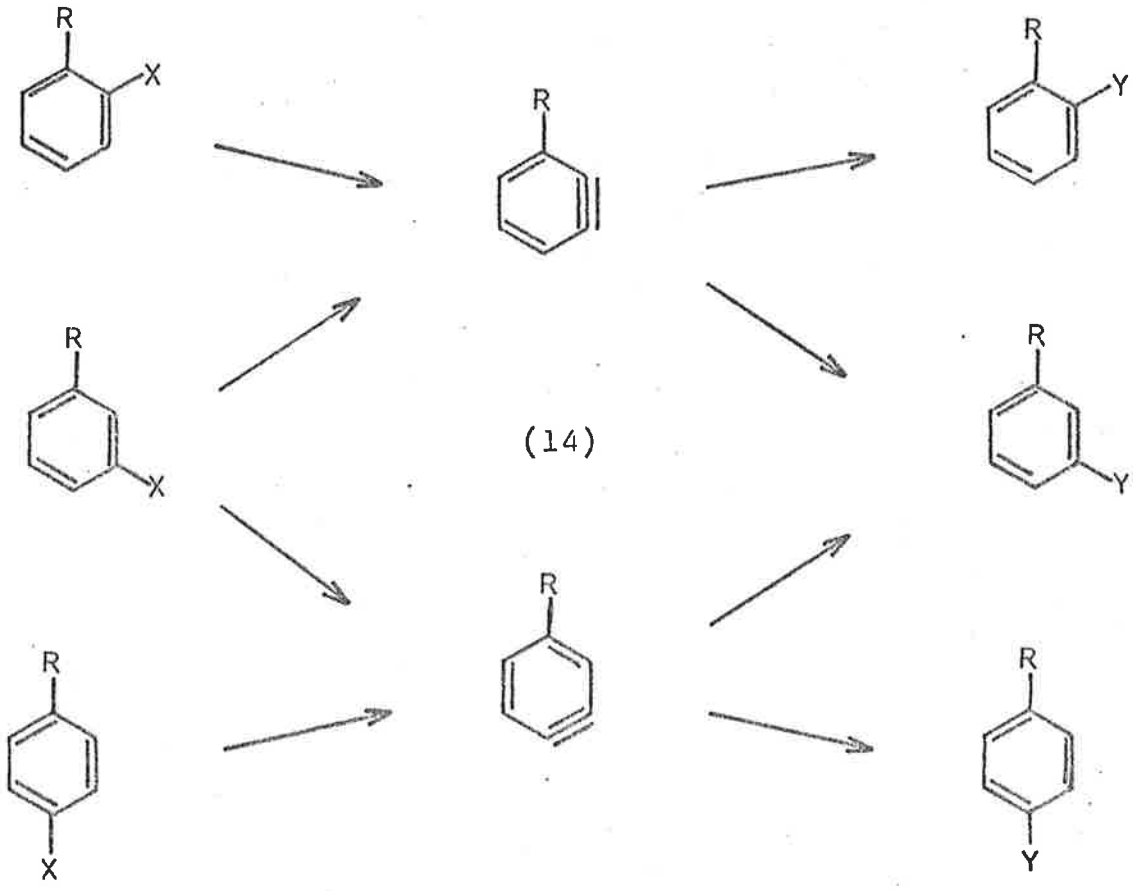


(13)

There are three main factors necessary for the EA mechanism to operate in monosubstituted aromatic compounds. These are: (1) there must be a hydrogen atom ortho to the leaving group; (2) the base used must be strong enough to remove the hydrogen as a proton; and (3) the leaving group must not be so strongly activated towards reaction by the

AE mechanism that this operates to the exclusion of the EA mechanism.

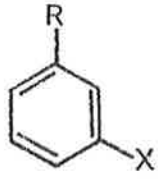
In an EA reaction involving a substrate which contains one or more substituents in addition to the leaving group, certain effects may be observed. When the substituent is ortho or para to the leaving group then only one aryne intermediate may be formed in each case (14 and 15 respectively); but when the substituent is meta to the leaving group both of these intermediates may form. The formation of a particular aryne is determined by which anion is produced initially, and this is influenced by both



(14)

(15)

the leaving group and the substituent. An anionic centre



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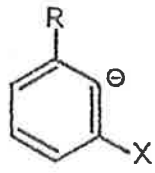

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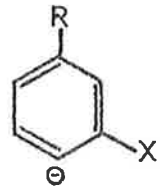
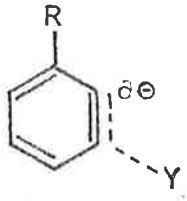


(18)

will generally be formed at the carbon with the most acidic hydrogen. In compound (16) if R is electron-withdrawing then removal of the most acidic proton will generally give the anion (17); if R is electron-donating (18) will be formed.

The orientation of nucleophilic addition to an aryne is also affected by substituents. Because the orbitals making up the aryne bond are orthogonal to the π-cloud of the aromatic ring, mesomeric effects of substituents are considered to be less important than inductive effects in influencing the position of attack by a nucleophile. Roberts[38] postulated that in nucleophilic attack on the aryne (14), if the substituent R is electron-withdrawing, then transition state (19) would be more stable than (20) because the inductive effect of R should have a greater



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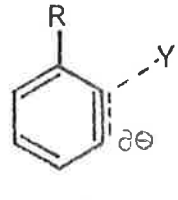


(20)

stabilizing effect on the partially formed anionic centre in species (19). Conversely, when the substituent R is electron-donating, formation of transition state (20) will be favoured over (19). These directing effects also operate, but to a lesser extent, when the aryne bond is situated 3,4- to a substituent.

Results[17] of EA substitution reactions of halogen-substituted heterocyclic compounds indicate that a ring nitrogen has a similar directing effect as an electron-withdrawing substituent.

The EA mechanism can be synchronous or proceed in two steps, and this is determined by the mobility of the leaving group. In the reaction shown in Scheme 5, if X is a good leaving group and $K_2 > K_{-1}$, then the reaction will be concerted. In the halogen series the expected[14] mobility in the second step is $I > Br > Cl > F$. Aryl bromides generally react to form an aryne bond in a concerted process, but aryl chlorides react <u>via</u> a two-step mechanism.[14]

Another factor which will affect the rate of an EA substitution reaction is the nature of the base, which has two roles in this type of reaction. Firstly it must remove a hydrogen from the substrate, and, since this hydrogen is usually weakly acidic, strong bases must be used. Commonly used bases include organometallic reagents such as butyl- and phenyllithium and metal amides such as potassium amide

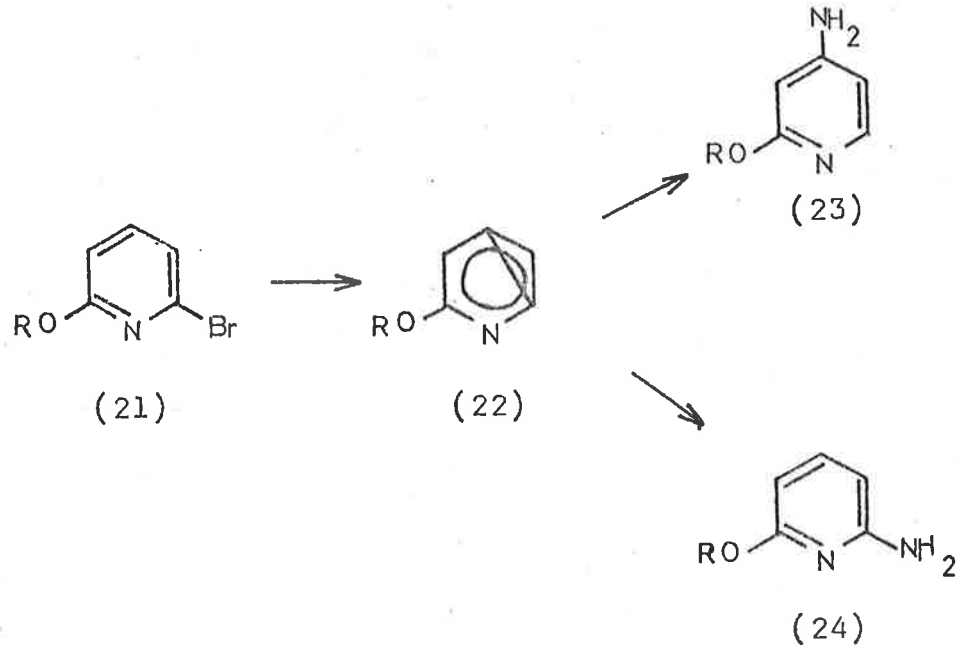
and the lithium dialkylamides.

Secondly, the base may act as a nucleophile and attack the aryne bond. When metal amides are used in the presence of free base, attack on the aryne by amide ion and by free amine may occur at a competitive rate.

The aryne intermediates discussed so far have been the 1,2-dehydroarenes. Reports of the 1,3- and 1,4-isomers are rare but 1,3- and 1,4-dehydrobenzenes have been observed[39,40] as products in the flash photolysis reactions of the corresponding benzenediazoniumcarboxylate compounds. It has been calculated[41] that the order of stability of the isomeric dehydrobenzenes is 1,2->1,3->1,4-.

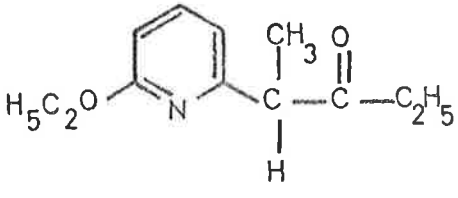
Several substitution reactions have been observed in which the nucleophile enters the ring at a position meta to the leaving group. These are known as 'tele-substitution' reactions.

For example, den Hertog et al[42,43] found that one of the products formed in the reactions of some 2-bromo-6-alkoxypyridines (21) with potassium amide in liquid ammonia was the corresponding 4-amino-6-alkoxypyridine (23). The 1,3-dehydropyridine (22) was suggested[43] as a possible intermediate in this reaction. Boer and den Hertog[43] also found that 2-bromo-6-ethoxypyridine reacted with a mixture



Scheme 7

of potassium amide and the potassium salt of pentan-3-one to give 2- 2'-(6'-ethoxypyridyl) -pentan-3-one (25) and 2- 4'-(6'-ethoxypyridinyl) -pentan-3-one (26) together with the amines (23) and (24). Reaction of the bromide (21)



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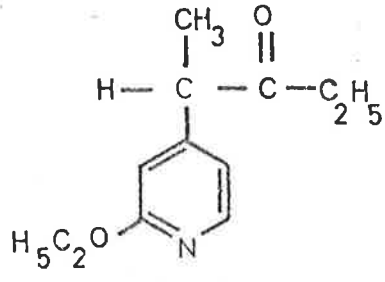
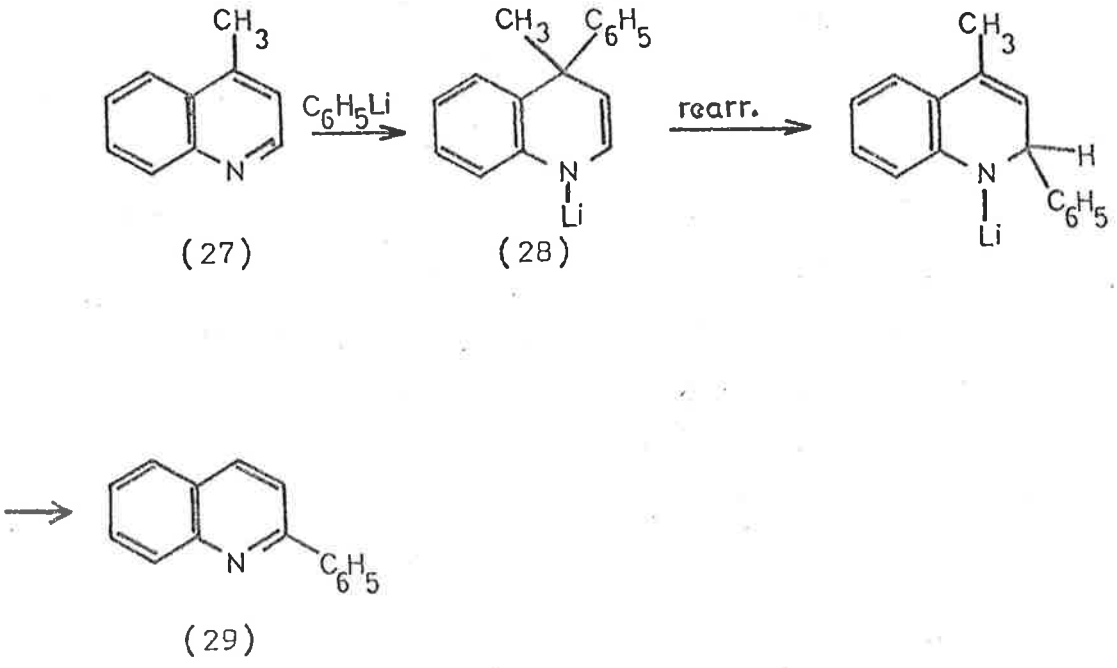


(26)

with the potassium salt of pentan-3-one, however, only

gave a small amount of compound (25) and none of (26). This adds support to the proposal of the aryne (22) as an intermediate.

Tele-substitution was also observed[44] when lepidine (27) reacted with phenyllithium to form 2-phenylquinoline (29) as one of the products. An addition-rearrangement-elimination mechanism was proposed[44] for this reaction and is shown in Scheme 8.



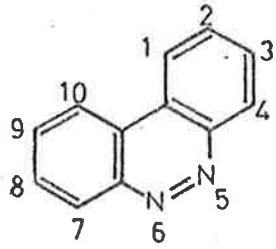
(27) (28) (29)

Scheme 8

Various reactions are known which involve cine-substitution but which do not proceed by the EA mechanism.

Some of these have already been dealt with during the discussion of hydride replacements. Others include the reaction of 2-bromothiophene with base to give 3-aminothiophene[45] and the base-catalysed isomerization of trihalogenobenzenes.[46]

The present work deals with nucleophilic substitution reactions in benzo[c]cinnoline (30) and its derivatives.



(30)

Until recently the only reactions of benzo[c]cinnoline that had been studied in any depth were the electrophilic substitution reactions. Calculations for the expected order of electrophilic attack at different ring positions of benzo[c]cinnoline have been made, based on electron density studies. The results vary, and Pullman[47] gave the order as 1>3>2>4; Longuet-Higgins and Coulson[48] as 1>3>4>2; Dewar and Maitlis[49] as 1>3>4>2 and Corbett et al[50] as 1>4>3>2.

Experimental results are not wholly consistent with the theoretical predictions. Nitration of benzo[c]cinnoline gave 1-nitrobenzo[c]cinnoline as the major product, with the 4-nitro isomer as the minor product.[51-53]

Bromination gave 4-bromobenzo[c]cinnoline as the only monobromo compound.[54] Both of these reactions, however, were carried out in strong acid and so the reacting species would be protonated benzo[c]cinnoline, in which electron distribution would be different from that in unprotonated benzo[c]cinnoline.

It might normally be predicted that the order of susceptibility of the benzo[c]cinnoline ring to nucleophilic attack would be opposite to that for electrophilic attack. Since neither theoretical calculations nor experimental results give a consistent picture for electrophilic substitution, however, no reliable prediction can be made.

In some preliminary work on the nucleophilic substitution reactions of benzo[c]cinnolines, Lewis and Reiss[55] investigated the action of dimethylamine on the chlorobenzo[c]cinnolines. They found that all four monochlorobenzo[c]cinnolines were converted into the corresponding dimethylamino compounds and that the conditions required were most vigorous for the reaction of the 1-chloro isomer and least vigorous for that of the 4-chloro isomer. Lill[56] found that in the reactions of the chlorobenzo[c]cinnolines with sodium methoxide more vigorous conditions were required for the reactions of the 1- and 3-chloro compounds than with the 2- and 4-chloro analogues. These results suggested

that the positional order of nucleophilic attack on benzo[c]cinnoline is probably 4 and 2 >3 and 1.

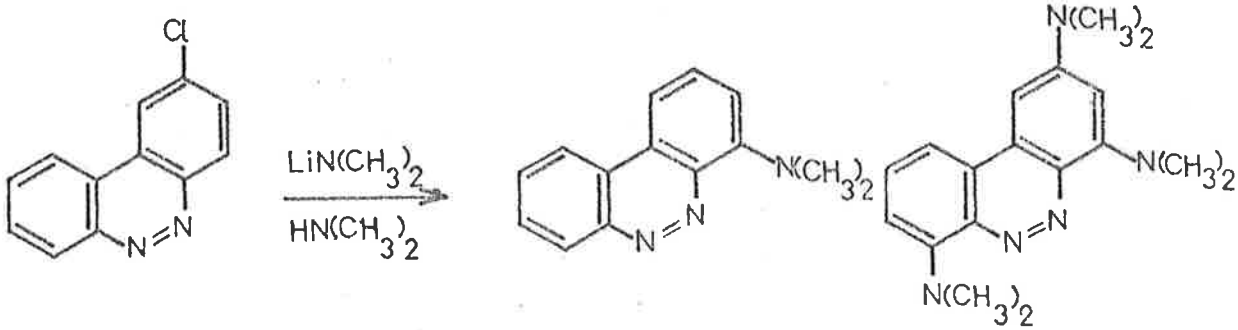
There is no report in the literature of benzo[c]-cinnolines undergoing reaction *via* an EA mechanism. Lewis and Reiss,[57] however, observed that in the reaction of 2-chlorobenzo[c]cinnoline with lithium dimethylamide in dimethylamine, 4-dimethylaminobenzo[c]cinnoline (32) was the major product. Reinvestigation of this interesting reaction led, in the present work, to further study of nucleophilic substitution reactions of benzo[c]cinnolines and of other aromatic compounds containing a diaza linkage.

RESULTS AND DISCUSSION

PART I

REACTIONS OF BENZO[c]CINNOLINE AND THE CHLOROBENZO[c]CINNOLINES WITH LITHIUM DIALKYLAMIDES

In 1968 Lewis and Reiss[57] reported that 2-chlorobenzo[c]cinnoline (31) reacted with lithium dimethylamide in dimethylamine to give two unexpected products, 4-dimethylaminobenzo[c]cinnoline (32) and 2,4,7-tris-(dimethylamino)benzo[c]cinnoline (33) (Scheme 9).



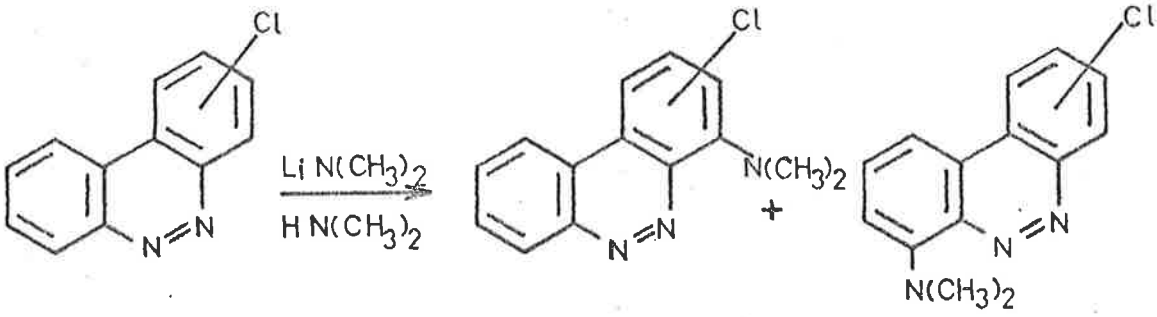
(31) (32) (33)

Scheme 9

The occurrence of substitution at the 4-position of 2-chlorobenzo[c]cinnoline was remarkable because this position is meta to that held by the displaced chloro group. This could not be explained in terms of either of the two common aromatic nucleophilic substitution mechanisms. Further investigations were obviously necessary

to shed more light on the mechanism of this reaction.

The reactions of all four chlorobenzo[c]cinnolines with lithium dimethylamide in dimethylamine have now been carried out, using shorter reaction times than those used by Lewis and Reiss. This was done because it seemed possible that the relatively long reaction times used by these workers could have had a significant bearing on the formation of the anomalous products (32 and 33). The product mixtures obtained from these reactions are complex but may be rationalized in terms of further reaction of the initial products (35) and (36) (Scheme 10). Full details of these reactions are given in Tables 7 -11, pp. 109 - 111.



(34) (35) (36)

Scheme 10

Lewis and Reiss[57] found that lithium dimethylamide in dimethylamine also reacted with benzo[c]cinnoline to give compounds (32) and (33) as products, although in different proportions to those obtained in the reaction of

2-chlorobenzo[c]cinnoline. This reaction has also been reinvestigated employing shorter reaction times. Again, 4-dimethylaminobenzo[c]cinnoline (32) was isolated.

The reactions, summarized in Scheme 10, reveal two important new points. Firstly, a hydride ion has been displaced from an aromatic nucleus in preference to a chloro substituent. Formation of product (35) indicates that hydride ion is displaced even from the aromatic ring containing the chloro group. Although not unprecedented,[58] this is surprising because chloride ion is normally a much better leaving group than a hydride ion in a nucleophilic substitution reaction. Moreover, there is ample evidence in the literature[59-61,17] to show that halide ion is usually displaced in the reactions of heterocyclic aryl halides with lithium dialkylamides. 3- and 4-Halogenopyridines, for example, react with lithium piperidide in piperidine, *via* the EA and AE mechanisms to give 3- and 4- substituted products.[59] Furthermore, the chlorobenzo[c]cinnolines react with sodium methoxide in dimethyl sulphoxide or toluene;[56] dimethylamine;[55] piperidine and potassium amide in ammonia (discussed later) giving products which appear to have been formed by the normal routes of nucleophilic substitution.

The second point to note about the short-term reactions of the chlorobenzo[c]cinnolines with lithium dimethylamide in dimethylamine is that a dimethylamino group has entered the benzo[c]cinnoline ring exclusively at the 4- or 7- positions, both of which are *peri* to the diaza linkage.

A mechanism is now proposed for these reactions (Scheme 11) which envisages displacement of hydride ion *via* an AE mechanism. Intermediates (38) and (40) are analogous to that proposed by Lewis and Reiss[57] for the reaction of benzo[c]cinnoline with lithium dimethylamide.

The features of this mechanism are:

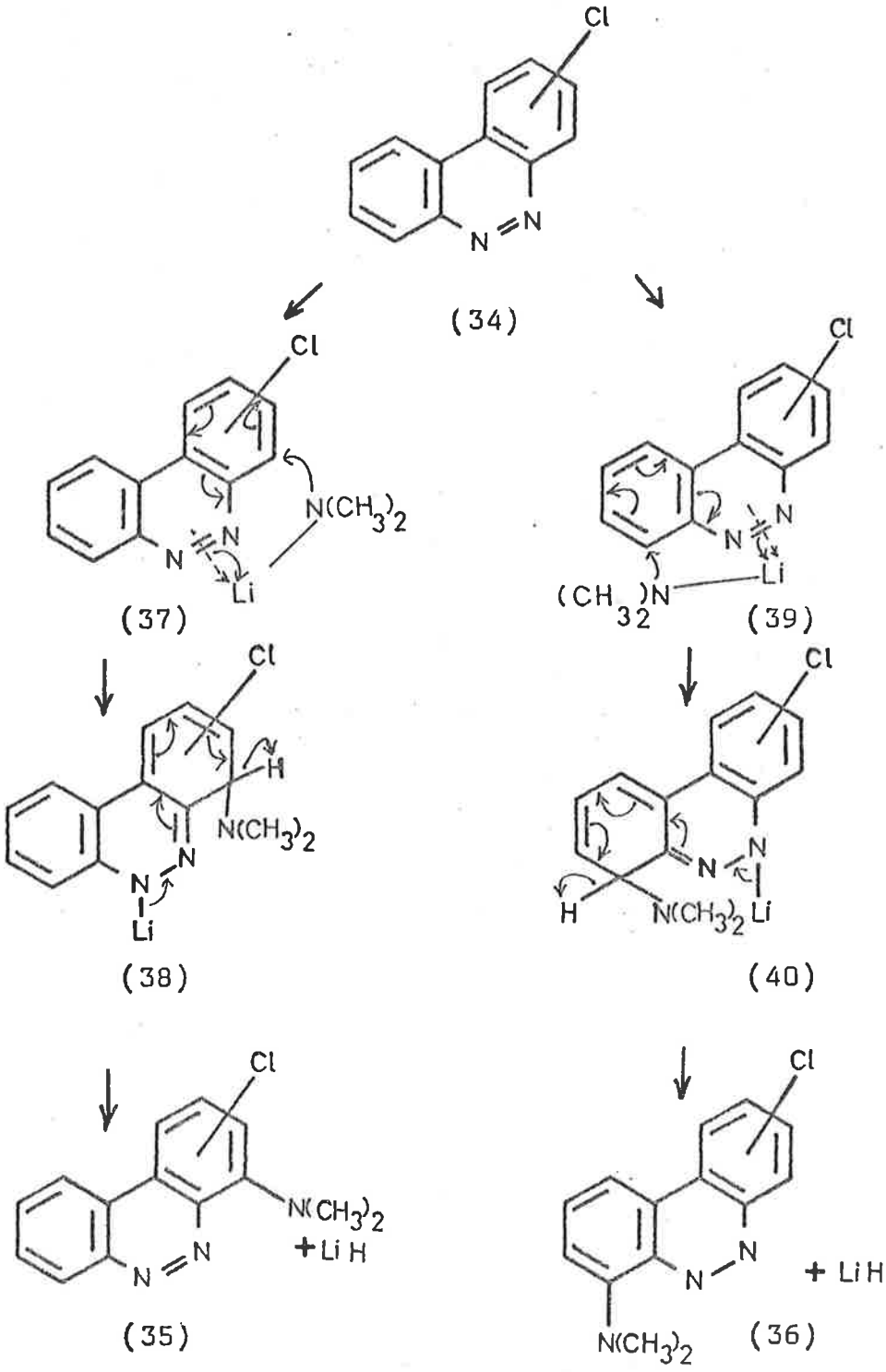
1) Formation of a π-complex between lithium dimethylamide molecules and the nitrogen atoms of the benzo[c]cinnoline diaza linkage.

2) Formation of the σ-complexes (38) and (40) by internal rearrangement of the dimethylamide groups.

3) Loss of lithium hydride or its mechanistic equivalent.

The evidence for these steps will be discussed presently.

This mechanism is different from each of those discussed in the Introduction for the replacement of aromatic hydrogen. It is different from the mechanism proposed for the reactions of alkyl- and aryllithium compounds with


Cl
N=N
(34)
Cl
N(CH3)2
N
N
Li
(37)
Cl
N
N
Li
(CH3)2N
(39)
Cl
H
N(CH3)2
N
N
Li
(38)
Cl
N
N
H
N(CH3)2
Li
(40)
Cl
N(CH3)2
N=N
+LiH
(35)
Cl
N
N
+ LiH
N(CH3)2
(36)

Scheme 11

pyridines, because in the latter reactions the initial step is addition of the nucleophile to the C-N double bond of the pyridine molecule. In the reaction under discussion, the initial step is addition of a nucleophile to a carbocyclic ring. In this respect the mechanism shown in Scheme 11 is more like the reaction that occurs between benzyllithium and pyridine to give 4-benzylpyridine,[62,63] in which addition of a nucleophile to a C-N double bond is not possible.

Intermolecular oxidation by a nitro group assists hydride removal from 4-nitroquinoline-1-oxide in its reaction with diethyl sodiomalonate (Scheme 3). The chlorobenzo[c]cinnolines are not oxidizing agents and so a comparable mechanism is untenable for their reactions with lithium dimethylamide. In support of this, no reduction products were observed in the reaction mixtures.

A mechanism comparable to the one shown in Scheme 4 has been proposed (Scheme 13) to explain the formation of 4-dimethylaminobenzo[c]cinnoline in the reaction of 2-chlorobenzo[c]cinnoline with lithium dimethylamide in dimethylamine (discussed later). This mechanism cannot explain, however, the formation of compounds (35) and (36) because these retain chloro substituents.

Clearly there must be strong influences operating in the reactions of the chlorobenzo[c]cinnolines with lithium dimethylamide in dimethylamine which make nucleophilic attack, with hydride displacement, highly favourable in the 4- and 7- positions.

Two factors are likely to be important here. Firstly, it is probable that a complex is formed between the benzo[c]cinnolines and lithium dimethylamide; and secondly, lithium dimethylamide is probably associated under the reaction conditions.

Aromatic nucleophilic substitution reactions using strong bases frequently involve highly coloured solutions. Ainscough and Caldin[64] found that ethoxide ion reacts with 2,4,6-trinitroanisole giving a yellow-coloured solution, and they attributed this to the formation of both π - and σ-complexes. When solutions of the chlorobenzo[c]cinnolines in benzene were added to solutions of lithium dimethylamide in dimethylamine a deep red-purple colouration occurred immediately, and this was then quickly replaced by an intense dark green colour which persisted until the reaction was terminated. During several preliminary reactions in which very small quantities of lithium dimethylamide were used, only the red-purple colouration was observed. In these instances starting material was recovered unchanged.

These colour formations were taken as evidence for the existence of complexes.

An indication that lithium dimethylamide in dimethylamine is associated under the reaction conditions is found in the investigation of lithium cyclohexylamide solutions in cyclohexylamine. Streitwieser *et al*[65-67] found that in this system lithium cyclohexylamide existed as aggregated ion-pairs. At the concentration of base used in the present reactions (*ca.* 0.2M) the degree of aggregation of lithium cyclohexylamide was *ca.* 3.[66] In the reactions of the chlorobenzo[c]cinnolines with lithium dimethylamide in dimethylamine benzene and ether were also used as solvents. These are less polar than dimethylamine and so the degree of aggregation of lithium dimethylamide in these solvents should be at least as great as for lithium cyclohexylamide in cyclohexylamine at the same concentrations.

If lithium dimethylamide is associated and does form a complex with benzo[c]cinnoline, then two methods of activation and attack by this base appear possible. Firstly, coordination between a lithium dimethylamide molecule and a benzo[c]cinnoline molecule may activate the ring positions to attack by a second molecule of lithium dimethylamide. Because of the possible electron shifts shown in species (37) and (39), activation will be greatest at the 2-, 4-,

7- and 9- positions, and some substitution in each of these positions could be expected. Alternatively, the coordinated lithium dimethylamide molecule may attack the aromatic ring. This would be most likely to occur at the 4- and 7- positions if lithium dimethylamide is associated. Attack by the coordinated base would be favoured by the electron shift towards nitrogen in the lithium-nitrogen bond that would occur on coordination. This shift would make the dimethylamide moiety more nucleophilic. The experimental results indicate that the initial products in these reactions are formed by this second mode of attack.

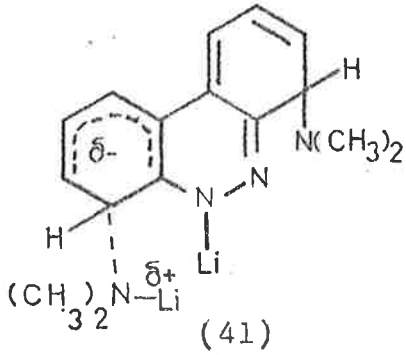
It is possible to explain the observed colourations in the reaction solutions in terms of the second reaction mechanism. The red-purple colouration is probably due to the formation of a π-complex involving an aggregate of lithium dimethylamide molecules and the π-electrons of the N-N double bond. Subsequent nucleophilic attack of the dimethylamide group at positions <u>peri</u> to the diaza linkage would form intermediates (38) and (40) and these may be responsible for the dark green colouration observed.

Conversion of the intermediates to products (35) and (36) may occur by elimination of lithium hydride during the reaction or in the working-up procedure when water is added.

In the latter case hydrogen and lithium hydroxide would be the other products formed. There is evidence that reaction proceeds by both pathways.

Maintenance of the green colour throughout the reaction indicated that some material was present as species (38) and (40).

At longer reaction times the formation of bis-(dimethylamino) compounds (e.g. 4,7-bis(dimethylamino)-benzo[c]cinnoline (66)) was observed. It is unlikely that these were formed by attack of a dimethylamide group at the 4- or 7- position of an intermediate because the transition state (41) for such a reaction cannot be stabilized by localization of partial negative charge on a ring nitrogen atom. It is more feasible that these compounds were formed by a second substitution on a monodimethylaminobenzo-[c]cinnoline. For this to happen some conversion of intermediates during the reaction must have occurred.



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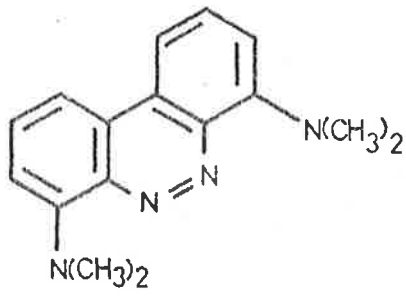
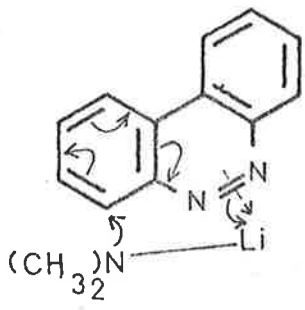


(66)

π-Complex formation may also help to clarify another aspect of these reactions. Initially, reaction rates were fast; and aliquots taken 0.1min after addition of reagents showed that in each case* the same amount of starting material (ca. 70%) had been consumed (Tables 1-4). Further reaction, however, was relatively slow, even with a 10:1 excess of base.

If π-complexes do form in these reactions, then because of the aggregation of lithium dimethylamide, all of the base could be bound up by a smaller proportion of benzo[c]-cinnoline molecules, thus allowing only those molecules which form complexes to react. Furthermore, the initial product might be expected to compete favourably for base in π-complex formation, or even σ-complex formation (42).



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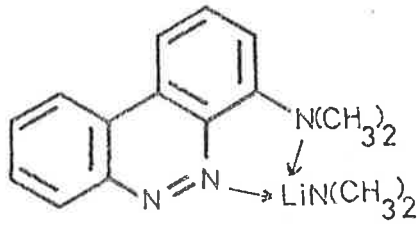

(42)

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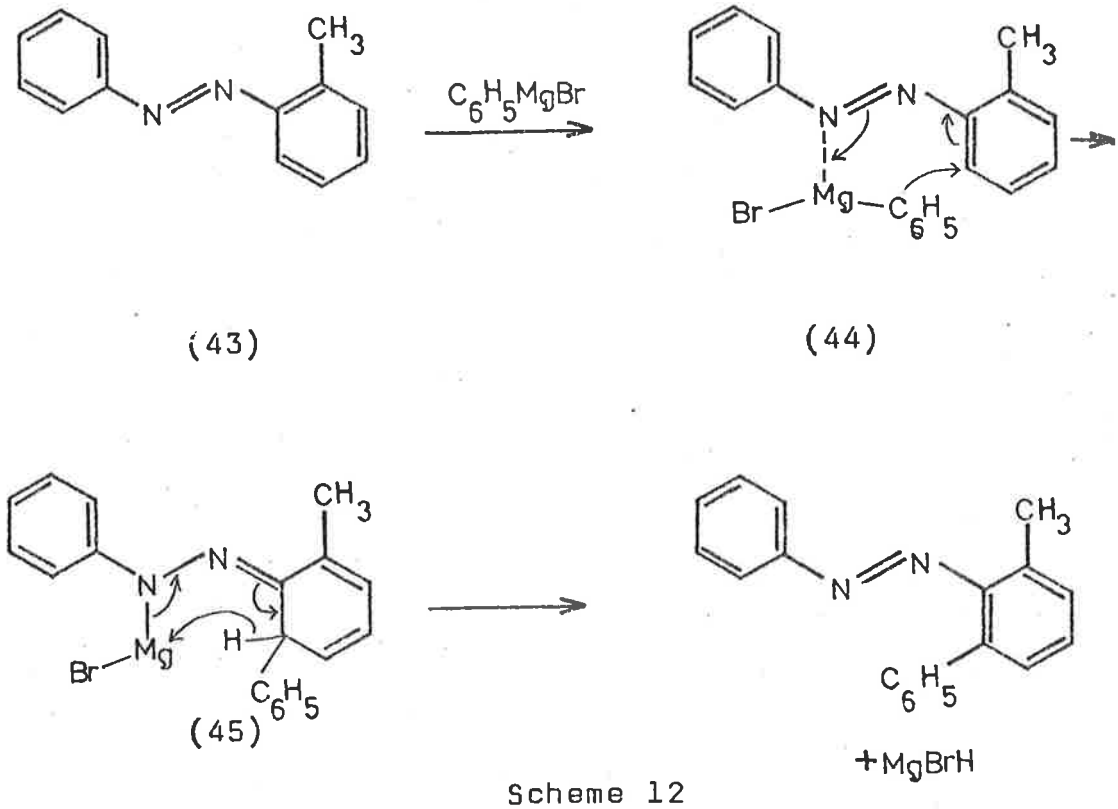
* The reaction of 2-chlorobenzo[c]cinnoline was anomalous in that all starting material had been consumed after 0.1min. Reasons for this are discussed later.

In the reaction of 4-chlorobenzo[c]cinnoline, starting material and 4-dimethylaminobenzo[c]cinnoline could not be separated by g.l.c. and so an estimate of percentage reac-

This could explain the presence of starting material in the reaction mixture.

It is pertinent to mention here that hydride ion is displaced by lithium aluminium hydride most readily from the 1-, 4- and 7- positions of the benzo[c]cinnoline molecule.[68] Corbett and Holt[68] also propose formation of a complex between the diazo linkage and the lithium compound to explain the preferential displacement at the 4- and 7- positions. These authors suggest, however, that it is the lone-pair electrons of the nitrogen atoms which coordinate with lithium aluminium hydride.

Hydride ion displacement from a position ortho to an azo linkage also occurs in the reactions of some azobenzenes with Grignard reagents. In a series of papers Risalti et al[69,70] reported that aryl magnesium bromides react with 2-methyl and 2-methoxy azobenzenes to give products from ortho substitution. The mechanism proposed[69] for the reaction of 2-methylazobenzene (43) with phenyl magnesium bromide is shown in Scheme 12. The authors do not comment on the nature of the complex (44) but it is likely to be a π-complex, in which the Grignard reagent is held above the plane of the ring. This would have a more favourable entropy of activation towards nucleophilic attack than a complex involving the lone-pair electrons on



(43) (44) (45)

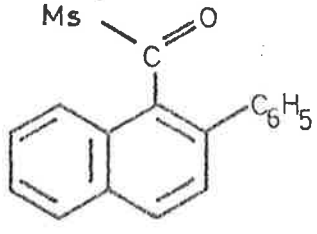
Scheme 12

nitrogen, which would hold the Grignard reagent in the plane of the ring.

There are many similarities between this mechanism and the one proposed for the reactions of the chlorobenzo-[c]cinnolines with lithium dimethylamide. For example, it is likely that coordination of the azo linkage with magnesium to give species (44) would result in activation of the azobenzene molecule towards nucleophilic attack, especially at the positions ortho and para to the azo linkage.

The results of some investigations carried out on protonated azobenzene indicate that this activation could be quite large. Bunnett et al[71] observed that protonation of the azo linkage strongly activated the aromatic rings towards nucleophilic attack. These workers found that it was even possible to hydrolyze the ether group of 4-phenylazo-1-naphthylmethylether with water when the azo group was protonated. It seems likely that the partly cationized diazo linkage of a benzo[c]cinnoline molecule (e.g. species 37 and 39) would have a similar activating effect to that of a protonated azo group. This may be another factor which helps to make the benzo[c]cinnolines so reactive towards lithium dimethylamide.

The hydride ion eliminated from the 2-position of species (45) in Scheme 12 was removed as a metal hydride (magnesium bromohydride) as may also occur for the elimination of an hydride ion from species (38) and (40). Evidence for the former elimination was shown[69] by adding 1-mesitoyl-2-phenylnaphthalene (46) to the reaction mixture.



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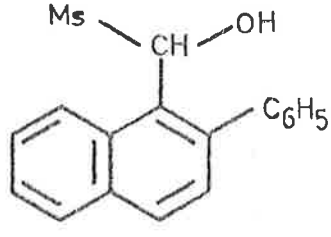

(47)

The corresponding carbinol (47) was obtained as the reduction product.

The reactions of the monochlorobenzo[c]cinnolines will now be discussed separately.

The products formed initially in the reaction between 1-chlorobenzo[c]cinnoline and lithium dimethylamide in dimethylamine were 1-chloro-4-dimethylaminobenzo[c]cinnoline (48) and 1-chloro-7-dimethylaminobenzo[c]cinnoline (49) (Table 1). These isomers could not be separated by the

TABLE* 1

Products formed initially in the reaction of 1-chlorobenzo[c]cinnoline with lithium dimethylamide in dimethylamine

Molar Ratio $LiNMe_2$	Reaction Time (min)	% Reaction	Yields (%)** 1-Cl-4-NMe_2 and 1-Cl-7-NMe_2
10	0.1	73	72

method of analysis used (g.l.c.), but an estimate of their combined yields was made using a g.l.c. column which had been calibrated with a mixture of the compounds. This may

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* Results of the reactions of the chlorobenzo[c]cinnolines with lithium dimethylamide are collected in full detail in Tables 7 -11, pp.109 -111.

** Based on unrecovered starting material.

explain why the overall yields measured for this reaction are lower than yields for the reactions of the other chlorobenzo[c]cinnolines. In earlier preparative scale reactions an n.m.r. spectrum of a mixture of the isomers indicated that 1-chloro-4-dimethylaminobenzo[c]cinnoline was the major product.

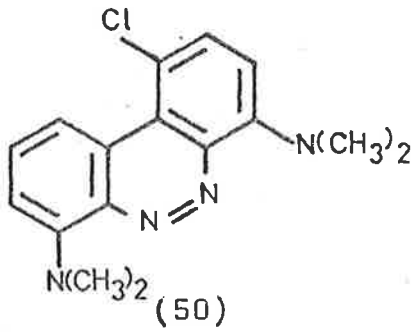
(48)

(49)

After longer reaction times a third product, 1-chloro-4,7-bis(dimethylamino)benzo[c]cinnoline (50) appeared, which most likely arose from the further reaction of products (48) and (49) with lithium dimethylamide. This reaction, too, requires displacement of a hydride ion in preference to a chloride ion and the mechanism involved would be analogous to that shown in Scheme 9.

Trace amounts of several other compounds were also observed at longer reaction times. One of these was 2,4-bis(dimethylamino)benzo[c]cinnoline (51) which was probably formed from compound (48) by an EA reaction with lithium dimethylamide. Support for an EA mechanism may be found

in the reaction of 1-chlorobenzo[c]cinnoline with potassium



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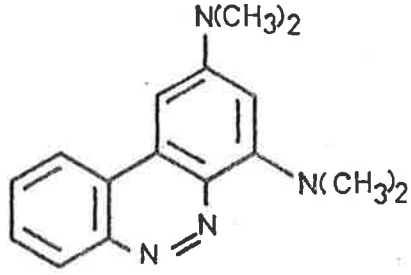
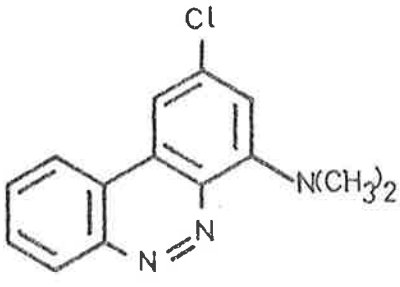


(51)

amide in ammonia (discussed in Part II) which gives a quantitative yield of 2-aminobenzo[c]cinnoline. Another of the products present in trace amounts was probably 2,7-bis(dimethylamino)benzo[c]cinnoline, which was considered to have arisen through an analogous route to that of the 2,4- isomer.

The reaction between 2-cnlorobenzo[c]cinnoline and lithium dimethylamide in dimethylamine was rapid; and an aliquot taken from the reaction mixture 0.1min after reaction commenced showed that all starting material had been consumed. This aliquot contained two products, 4-dimethylaminobenzo[c]cinnoline (32) and 2-chloro-4-dimethylaminobenzo[c]cinnoline (52). A surprising result was that no



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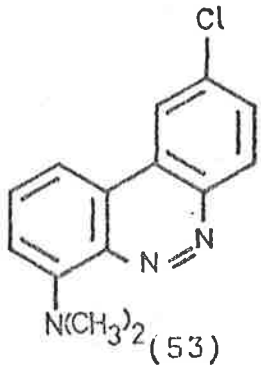

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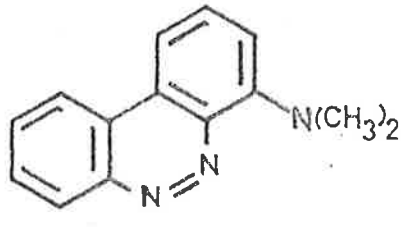


(32)

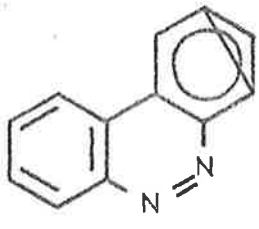
2-chloro-7-dimethylaminobenzo[c]cinnoline (53) was detected. This is the other product which could have been produced through attack of dimethylamide ion at a position peri to the diazo linkage.

In their study of this reaction, Lewis and Reiss[57] did not observe 2-chloro-4-dimethylaminobenzo[c]cinnoline. This is probably because after 2hr, the reaction time used by these workers, all of this compound would have been converted to other products (see Fig.1).

The conversion of 2-chlorobenzo[c]cinnoline into 4-dimethylaminobenzo[c]cinnoline is a tele-substitution reaction, and its mechanism can be discussed in the light of other substitutions of this kind which have been reviewed in the Introduction. Three mechanisms could be considered.

Firstly, the absence of 2-dimethylaminobenzo[c]cinnoline in the product mixture of this reaction indicates that an EA mechanism involving intermediate (54) is unlikely.

The formation of 4-dimethylaminobenzo[c]cinnoline by a reaction analogous to that shown in Scheme 7 requires the



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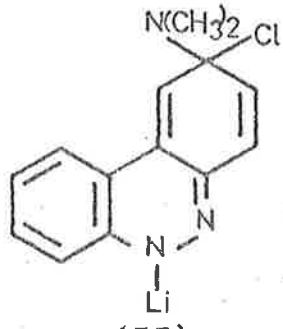

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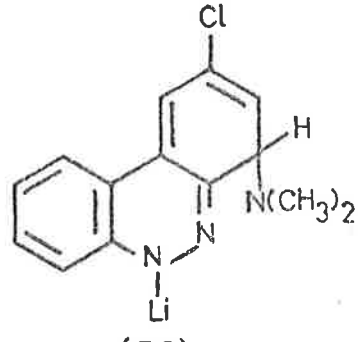
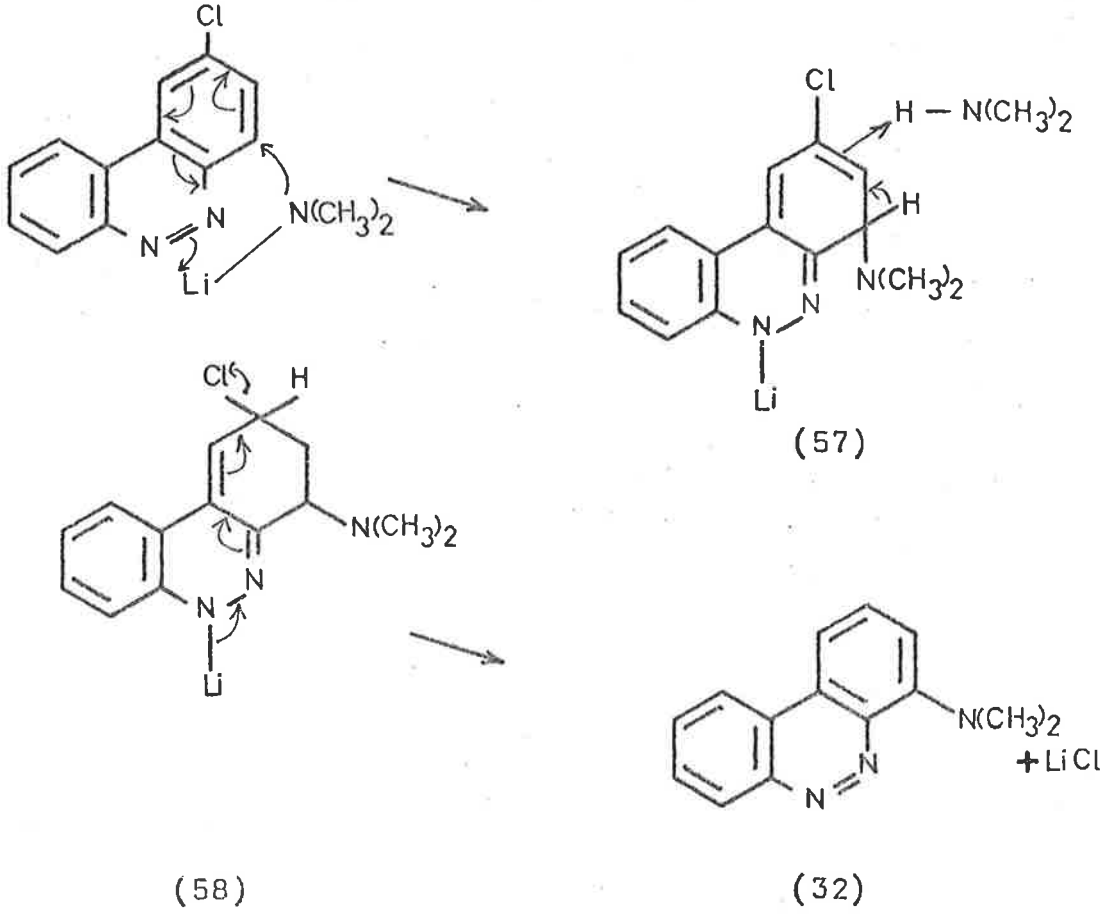


(56)

formation of intermediate (55). Rearrangement of this to species (56) which could be converted to compound (32) is allowed according to the Woodward-Hoffmann rules.[72] Elimination of chloride ion from intermediate (55) should, however, compete favourably with rearrangement, and formation of some 2-dimethylaminobenzo[c]cinnoline would be expected. Again, absence of 2-dimethylaminobenzo[c]cinnoline makes the occurrence of this mechanism unlikely.

Lewis and Reiss[57] suggested the mechanism shown in Scheme 13 and this seems to explain best the observed results.



Scheme 13

This mechanism is comparable with that for reactions mentioned earlier[34,35,36] (Scheme 4) in that loss of chloride ion from species (58) allows hydrogen to be lost as a proton.

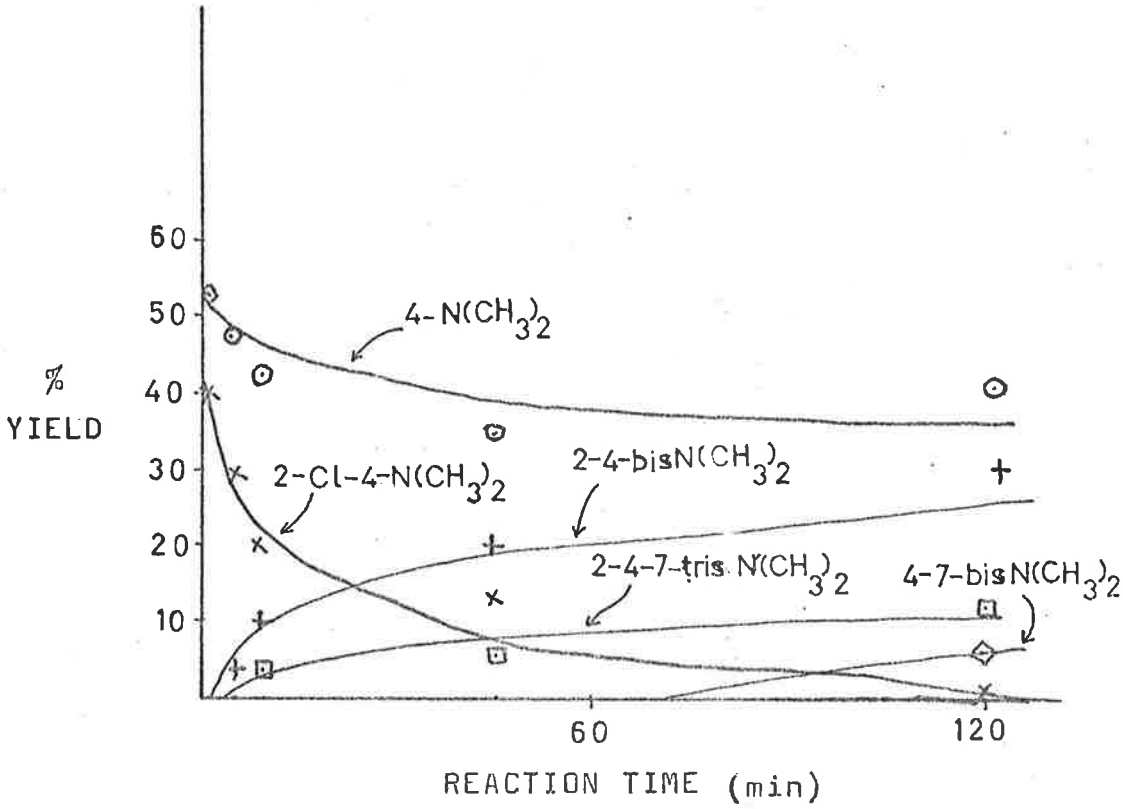
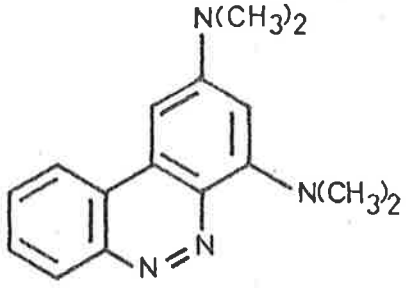


Fig.1 Yields of products from the reaction of 2-chlorobenzo[c]cinnoline with lithium dimethylamide in dimethylamine

Aliquots taken later during the reaction of 2-chlorobenzo[c]cinnoline with lithium dimethylamide contained 2,4-bis(dimethylamino)benzo[c]cinnoline (51) and 2,4,7-tris(dimethylamino)benzo[c]cinnoline (59) (Fig.1).

Since the first aliquot removed from the reaction mixture contained only 4-dimethylaminobenzo[c]cinnoline (32) and 2-chloro-4-dimethylaminobenzo[c]cinnoline (52) the bis- and tris(dimethylamino) compounds must have been formed from one or both of these.



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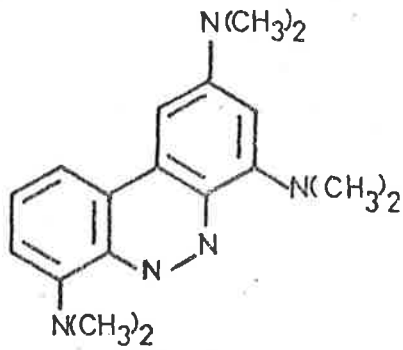


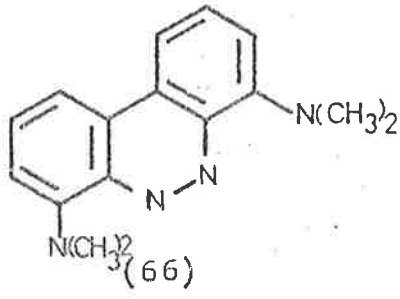
(59)

From Fig.1 it can be seen that the proportion of 4-dimethylaminobenzo[c]cinnoline in the reaction mixture decreases only slightly as the reaction proceeds. Compounds (51) and (59) must therefore mainly derive, directly or indirectly, from 2-chloro-4-dimethylaminobenzo[c]cinnoline (52).

2,4-Bis(dimethylamino)benzo[c]cinnoline most likely arose through replacement of chloride ion from the 2-position of compound (52). This could occur *via* an EA or an AE mechanism. The likelihood of either mechanism operating is dealt with during the discussion of the reaction of 2-chlorobenzo[c]cinnoline with potassium amide in ammonia in Part II.

The reaction of 2-chloro-4-dimethylaminobenzo[c]-cinnoline with lithium dimethylamide to give substitution of halide ion rather than substitution of hydride ion peri to the diazo linkage, is in contrast to the reactions of 1-chloro-4-dimethylaminobenzo[c]cinnoline and 1-chloro-7-dimethylaminobenzo[c]cinnoline with the same base. In the latter case substitution of hydride ion occurred to a greater extent than substitution of chloride ion and 1-chloro-4,7-bis(dimethylamino)benzo[c]cinnoline (50) was obtained. No 2-chloro-4,7-bis(dimethylamino)benzo[c]cinnoline was observed, however, in the reaction of the 2-chloro compound, and this is most likely due to the ease of displacement of a 2-chloro group.[55,56]

2,4,7-Tris(dimethylamino)benzo[c]cinnoline (59) was probably formed by reaction of the 2,4-bis(dimethylamino) compound (51) with lithium dimethylamide, involving a second displacement of hydride ion peri to the diazo linkage. An analogous reaction with 4-dimethylaminobenzo[c]cinnoline could conceivably occur and it is surprising that no 4,7-bis(dimethylamino)benzo[c]cinnoline (66) was obtained.



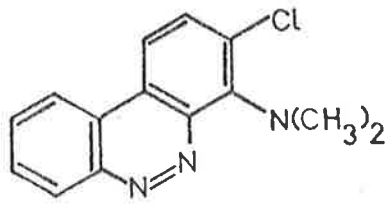
(66)

Lewis and Reiss[57] observed the tris(dimethylamino) but not the bis(dimethylamino) compound in their study of the reaction of 2-chlorobenzo[c]cinnoline with lithium dimethylamide. They used column chromatography to separate the products of the reaction. In the present work the bis- and tris(dimethylamino) compounds (51 and 59) were separated using the technique of counter-current distribution. Attempts to separate them by thin-layer chromatography, using a variety of solvents, failed. It seems likely then that the bis(dimethylamino) compound was formed in the reaction carried out by Lewis and Reiss but was not isolated. It was probably removed in the successive recrystallizations they used to purify the tris(dimethylamino) compound.

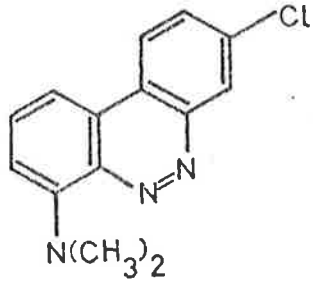
These authors proposed[57] that compound (59) was formed by further reaction of 4-dimethylaminobenzo[c]cinnoline with lithium dimethylamide. If this were so it could explain the slight decrease in the yield of 4-dimethylaminobenzo[c]cinnoline. Benzo[c]cinnoline reacts with lithium dimethylamide in dimethylamine, however, to give 4-dimethylaminobenzo[c]cinnoline and 4,7-bis-dimethylaminobenzo[c]-cinnoline (66) (discussed later). The absence of compound (66) in the reaction mixture suggests, therefore, that little,

if any, of the tris(dimethylamino) compound arises from 4-dimethylaminobenzo[c]cinnoline.

The products formed initially in the reaction of 3-chlorobenzo[c]cinnoline with lithium dimethylamide in dimethylamine were 3-chloro-4-dimethylaminobenzo[c]cinnoline (60), 3-chloro-7-dimethylaminobenzo[c]cinnoline (61), and 4-dimethylaminobenzo[c]cinnoline (32) (Table 2).



(60)



(61)

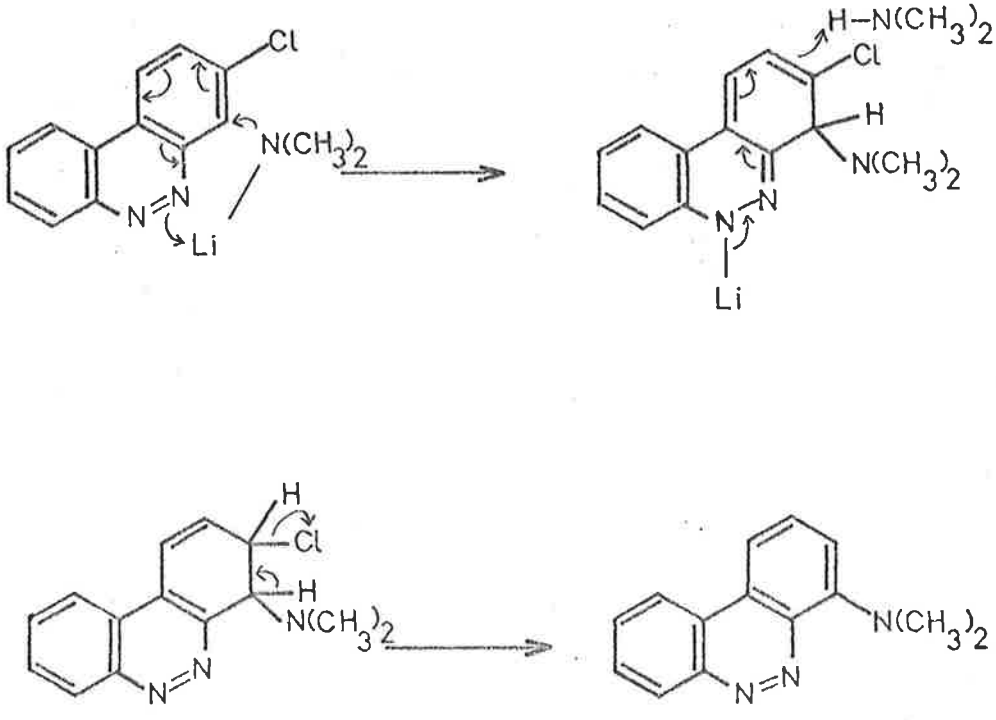
Isomers (60) and (61) were present in the ratio ca. 5:3. The inductive effect of the 3-chloro group may have caused the higher substitution rate at the 4- than at the 7- position.

TABLE 2

Products formed initially in the reaction of 3-chlorobenzo[c]cinnoline with lithium dimethylamide in dimethylamine

Molar Ratio $LiNMe_2$	Reaction Time (min)	% Reaction	Yield (%) $4\text{-}NMe_2$	3-Cl $4\text{-}NMe_2$	3-Cl $7\text{-}NMe_2$
10	0.1	69	7	51	30

3-Chlorobenzo[c]cinnoline may have been converted into 4-dimethylaminobenzo[c]cinnoline by several pathways; one possibility is outlined in Scheme 14. This mechanism is analogous to the one suggested for the formation of the 4-dimethylamino compound from 2-chlorobenzo[c]cinnoline (Scheme 13). Here, though, the species are eliminated as the elements of lithium dimethylamide and hydrogen chloride rather than lithium chloride and hydrogen.



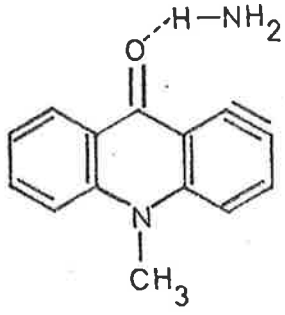
(32)

Scheme 14

A second possibility is that the aryne (62) is an intermediate in this reaction. Compound (32) is one of the products that could be obtained by attack of lithium dimethylamide or dimethylamine on intermediate (62); the

(62)

other is 3-dimethylaminobenzo[c]cinnoline, which was not observed in the reaction mixture. 4-Iodobenzo[c]cinnoline, however, reacts with potassium amide in ammonia to give 3-aminobenzo[c]cinnoline as the major product. The absence of 3-dimethylaminobenzo[c]cinnoline in the products from the reaction of 3-chlorobenzo[c]cinnoline with lithium dimethylamide therefore seems to rule out the intermediacy of the aryne (62), unless an ortho effect is operating. Such effects have been postulated in other EA reactions. Gream et al[73] suggest that hydrogen-bonding is responsible for the observed preferential attack of ammonia at the 1-position of 1,2-dehydro-10-methylacridone (63). Coordination between lithium dimethylamide and the diazo linkage of the aryne (62) may, in a similar fashion, favourably



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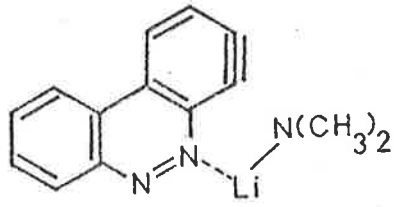
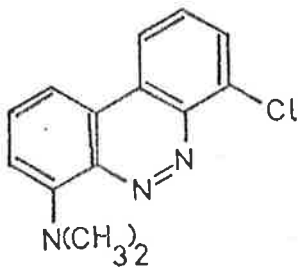


(64)

situate the base for attack at the 4- position (64). This is more likely to occur with lithium dimethylamide as base than with the more dissociated[74] potassium amide.

The reaction of 4-chlorobenzo[c]cinnoline with lithium dimethylamide gave, initially, 4-chloro-7-dimethylaminobenzo[c]cinnoline (65), 4-dimethylaminobenzo[c]cinnoline (32) and starting material (Table 3). 4-Chlorobenzo[c]cinnoline and 4-dimethylaminobenzo[c]cinnoline



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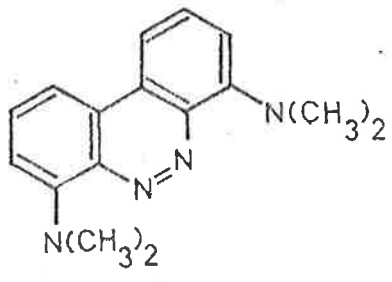

(66)

could not be separated by g.l.c. and so their yields were not calculated. An attempt to separate these compounds

by thin-layer chromatography was only partly successful but did serve to indicate that starting material was present in the reaction mixture up to 25min after addition of reagents.

TABLE 3

Products formed initially in the reaction of 4-chlorobenzo[c]cinnoline with lithium dimethylamide in dimethylamine.

Molar Ratio $LiNMe_2$	Reaction Time (min)	% Reaction	Yields (%)* $4\text{-}NMe_2$	Yields (%)* 4-Cl $7\text{-}NMe_2$
10	0.1	not known	not known	19

4-Dimethylaminobenzo[c]cinnoline is formed presumably by direct replacement of the 4-chloro group *via* an AE mechanism analogous to the one shown in Scheme 11.

The formation of 4-chloro-7-dimethylaminobenzo[c]-cinnoline in this reaction is quite remarkable since displacement of hydride and chloride ions from equivalent positions must have occurred to a similar extent. Obviously attack by the dimethylamide group has been non-selective and this suggests that the rate-determining step for the reaction is addition to the aromatic system. This could lead to the formation of a stable addition compound or immediate loss of the leaving group after the rate-determining step.

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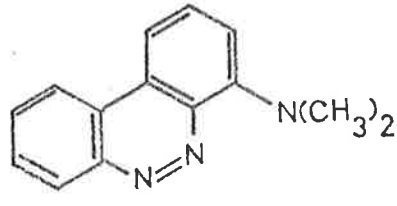
* Based on total starting material

At longer reaction times 4,7-bis(dimethylamino)-benzo[c]cinnoline (66) appeared in the reaction mixture. This could have been formed from either of the dimethylamino compounds (32) or (65). The simultaneous decrease in yield of compound (65) and increase in yield of 4,7-bis(dimethylamino)benzo[c]cinnoline indicates, however, that the latter compound is formed in large part from the chlorodimethylaminobenzo[c]cinnoline. This second substitution is slower, and therefore probably more selective than the initial fast substitution. Under these conditions it seems reasonable that displacement of chloride should occur, to some extent, in preference to hydride.

At longer reaction times also, traces of 2,4-bis-(dimethylamino)benzo[c]cinnoline (51) and 2,4,7-tris-(dimethylamino)benzo[c]cinnoline (59) were also detected. These were probably formed from compounds (32) and (66) respectively, which indicates that after the 4- and 7-positions of benzo[c]cinnolines, the 2- position is most susceptible to nucleophilic attack.



(32)

When benzo[c]cinnoline was treated with a 10:1 excess of lithium dimethylamide in dimethylamine it gave, after 0.1min, starting material and one product, 4-dimethylaminobenzo[c]cinnoline (32) (Table 4). An aliquot taken from the reaction mixture 1hr later showed little change; no other products were present.

TABLE 4

Products formed initially in the reaction of benzo[c]cinnoline with lithium dimethylamide in dimethylamine

Molar Ratio $LiNMe_2$	Reaction Time (min)	% Reaction	Yields (%) $4\text{-}NMe_2$
10	0.1	69	97

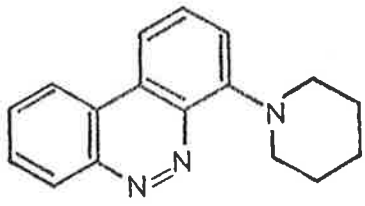
When benzo[c]cinnoline was treated with a 7:1 excess of lithium dimethylamide in dimethylamine for 15hr 4-dimethylaminobenzo[c]cinnoline and 4,7-bis(dimethylamino)-benzo[c]cinnoline (66) were obtained. The latter compound most likely formed by further reaction of initially formed 4-dimethylaminobenzo[c]cinnoline with lithium dimethylamide.

No 2,4,7-tris(dimethylamino)benzo[c]cinnoline was isolated from either of these reactions although traces of what may have been this compound were observed during chromatographic separations of the above compounds. Lewis and Reiss[57] reported that benzo[c]cinnoline reacted with a greater excess of lithium dimethylamide in dimethylamine for 3hr to give 4-dimethylaminobenzo[c]cinnoline (79%) and

2,4,7-tris(dimethylamino)benzo[c]cinnoline (12%). They also reported[57] the formation of a small amount of the tris- compound in the reaction of 4-dimethylaminobenzo[c]-cinnoline with lithium dimethylamide in dimethylamine, but they did not observe 4,7-bis(dimethylamino)benzo[c]cinnoline in either of these two reactions. In the present work the latter compound and 4-dimethylaminobenzo[c]cinnoline were found to be very difficult to separate by chromatography, even on a thin-layer plate; the technique of counter-current distribution was used to isolate these compounds. Any 4,7-bis(dimethylamino) compound produced in Lewis and Reiss's reactions would probably have been separated from 4-dimethylaminobenzo[c]cinnoline only during recrystallization and therefore would not have been observed. From the present work it seems likely that the 2,4,7-tris-(dimethylamino)benzo[c]cinnoline formed in the reaction carried out by Lewis and Reiss, arose from further reaction of the 4,7-bis(dimethylamino) compound with lithium dimethylamide.

The reactions of the chlorobenzo[c]cinnolines and benzo[c]cinnoline with lithium dimethylamide in dimethylamine were unusual and it was decided to study the scope of the reactions by treating the benzo[c]cinnolines with other metal amides.

As a first step the reaction of benzo[c]cinnoline with lithium piperidide in piperidine was investigated. This seemed to follow a similar course to that with lithium dimethylamide. At room temperature and for a reaction time of 15min the products obtained from this reaction were 4-piperidinobenzo[c]cinnoline (67) (79%) and 4,7-bis(piperidino)benzo[c]cinnoline (68) (7%). The conversion of starting material was 40%.



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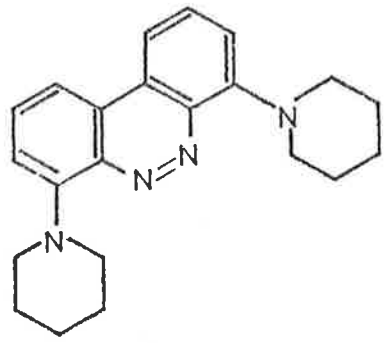


(68)

PART II

REACTIONS OF CHLORO- AND IODOBENZO[c]CINNOLINES WITH POTASSIUM AMIDE IN AMMONIA

The reactions of the chloro- and iodo- benzo[c]-cinnolines with potassium amide in ammonia followed a completely different course to the analogous reactions with lithium dimethylamide in dimethylamine. No starting material was returned in any of the reactions with potassium amide and there were no products obtained which still contained a halogeno group. With one exception, the reactions seemed to follow the general principles of aromatic nucleophilic substitution. The differences in the two groups of reactions are probably due to differences in basic strengths of the amide reagents and in their varying ability to coordinate with the diazo linkage of the benzo[c]cinnoline molecules.

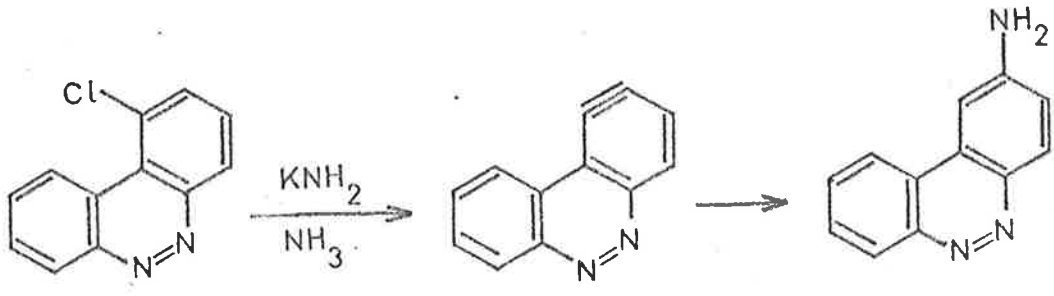
The iodobenzo[c]cinnolines reacted with potassium amide in ammonia to give brightly coloured solutions and high yields of products. In contrast, the chloro compounds gave darker coloured solutions and considerable amounts of tarry materials in the product mixtures. An exception to this was 1-chlorobenzo[c]cinnoline, which gave a quantitative yield of a product which was identified as 2-aminobenzo[c]cinnoline (70). Formation of this rearrangement

TABLE 5*

Yields (%) of products from the reactions of halogenobenzo[c]cinnolines with potassium amide in ammonia

Halogeno compd.	1-NH_2	2-NH_2	3-NH_2	4-NH_2	Total
1-Cl	0	100	0	0	100
2-Cl	0	85	0	0	85
3-Cl	0	0	40	15	55
4-Cl	0	5	20	3	30
2-I	0	95	0	0	95
3-I	0	0	90	1-2	90
4-I	0	0	80	5	85

product clearly indicates that substitution arose through the EA mechanism with the aryne (69) as an intermediate (Scheme 15).



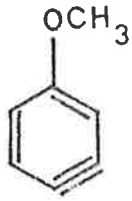
(69) (70)

Scheme 15

* Results are collected in full detail in Tables 12-13 pp. 122-123.

Attack of ammonia or amide ion at the 1- position of 1,2-dehydrobenzo[c]cinnoline (69) did not occur and possible reasons for this will now be discussed.

In the aryne (69) the diazo linkage may be considered as an electron-withdrawing substituent of the ring containing the aryne bond. According to Roberts[38] this substituent would favour reaction at the 2- position, which was in fact observed. These substituent effects, however, are usually not strong enough to cause exclusive <u>para</u>-substitution. For example, 3,4-dehydroanisole (71) reacts

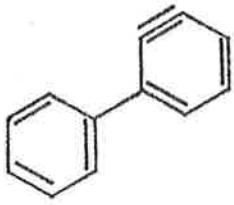


(71)

with potassium amide in ammonia to give a <u>para</u>/<u>meta</u> substitution ratio of 1.05.[38]

The non-aryne ring of intermediate (69) may also be regarded as a phenyl substituent to the aryne ring. Again, according to Roberts, substitution would be directed to the 2- position. Roberts' rule, however, only takes into account directing influences due to inductive effects and these would be small in both of the cases just mentioned. It is likely that steric effects are more important in influencing the site of attack in these reactions.

Huisgen and Sauer[12] found that when 3-phenyl-1,2-dehydrobenzene (72) reacted with lithium piperidide the ratio of meta-substituted to ortho-substituted product was 32:1. In a reaction carried out by Wittig and Merkle[75]



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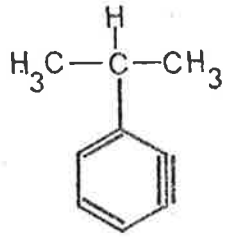


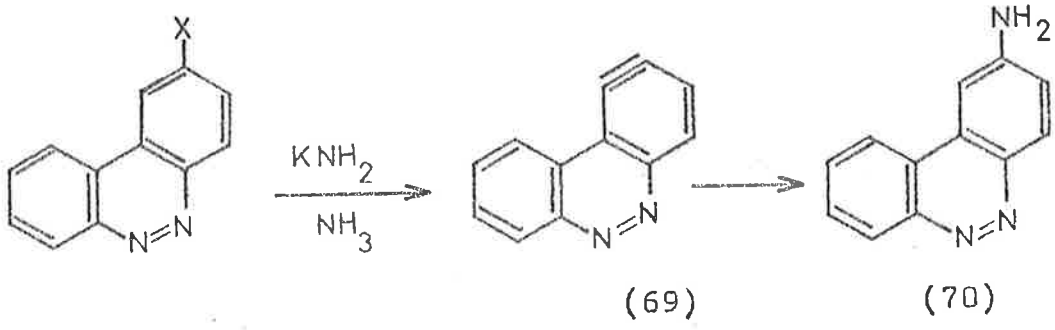
(73)

and interpreted by Hoffmann[11a] as being the reaction between (72) and phenyllithium only the meta isomer was obtained. The most rational explanation of these results seems to be that steric hindrance to nucleophilic attack at the 2- position of intermediate (72) prevents any substantial formation of 2- substituted product. Steric effects in addition reactions to arynes are discussed by Hoffmann.[11b] He interprets the greater meta addition of lithium piperidide to 2,3-dehydrocumene (73) (meta/ortho ratio 24:1) as compared to 2,3-dehydrotoluene (meta/ortho ratio 1.95:1) as being due to increase in size of the alkyl group. The results involving the phenyl substituted benzyne seem to be particularly relevant if we can compare attack of a nucleophile on intermediate (72) with a similar attack on the aryne (69). Nucleophilic attack on an aryne bond occurs in the plane of the ring.[38] Steric hindrance

would be greater, therefore, during attack on species (69) because in this situation the rings of the molecule are coplanar,[76] whereas in species (72) they would be twisted out-of-plane.[77] Steric effects, then, must strongly favour reaction at the 2- position of 1,2-dehydrobenzo[c]-cinnoline.

No 1-aminobenzo[c]cinnoline was formed in the reaction of 1-chlorobenzo[c]cinnoline with potassium amide in ammonia and so no reaction *via* an AE mechanism could have occurred. AE substitution reactions at the 1- position of benzo[c]cinnolines are subject to steric hindrance[55,56] as has already been mentioned. Release of steric strain in forming aryne (69) from 1-chlorobenzo[c]cinnoline may have been a factor which caused reaction *via* the EA mechanism to occur to the exclusion of AE substitution.

2-Chlorobenzo[c]cinnoline reacted with potassium amide in ammonia to give 2-aminobenzo[c]cinnoline (70) as the only product. The amine (70) could have been formed from 2-chlorobenzo[c]cinnoline in an EA reaction (Scheme 16, X=Cl), or *via* an AE intermediate (74); from the results it is not possible to say whether one or both of these

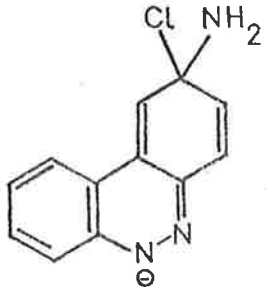


(69) (70)

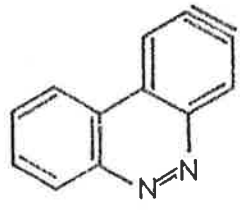
Scheme 16

mechanisms is operating. It has already been demonstrated in the reaction of 1-chlorobenzo[c]cinnoline with potassium amide in ammonia that attack of this base on the intermediate (69) gives a quantitative yield of the 2-amino compound, and so the intermediacy of this aryne is a possibility.

The other aryne from which 2-aminobenzo[c]cinnoline might arise is 2,3-dehydrobenzo[c]cinnoline (75). Reaction at the 3- position of this intermediate is not subject to the severe steric effects which operate at the 1- position of intermediate (69). If reaction <u>via</u> aryne (75) had occurred, then, formation of some 3-aminobenzo[c]cinnoline



(74)

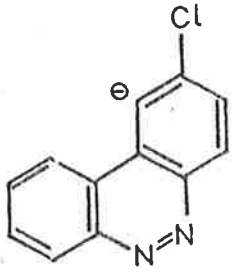


(75)

might be expected. The absence of the 3-amino compound therefore places the intermediacy of 2,3-dehydrobenzo[c]-cinnoline in doubt.

If the reaction of 2-chlorobenzo[c]cinnoline did proceed by way of an EA mechanism there should be reasons

why 1,2-dehydrobenzo[c]cinnoline (69) was formed in favour of intermediate (75). The precursors of arynes (69) and (75) are the anions (76) and (77) respectively. If the rate-determining step in this reaction is generation of the

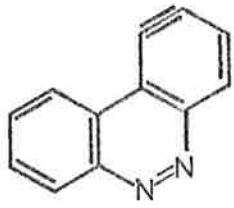


(76)

(77)

o-halogenoaryl anion then exclusive formation of intermediate (69) would imply that formation of anion (76) is favoured over (77). This cannot be explained on steric grounds; in fact the reverse situation should hold. Electron density studies[47-50] of benzo[c]cinnoline indicate that the acidities of the 1- and 3- hydrogens should be nearly identical, so explanation on these grounds is not tenable either.

Aryl halides, however, usually react via the EA mechanism in a two-step process[14] and so loss of halide ion, and not anion formation may be the rate-determining step in this reaction. If a halide ion was lost more readily from anion (76) than from anion (77), then this might explain the observed product ratio. There is evidence that such a preferential loss may occur.



(69)

(75)

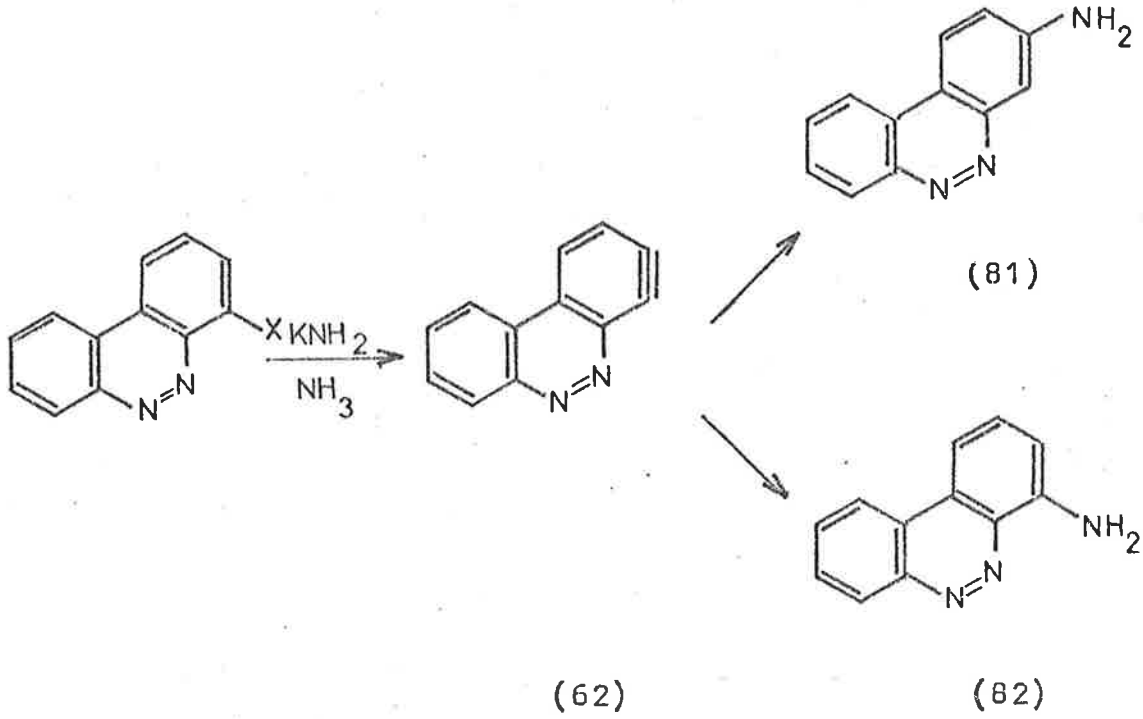
It has been calculated[78] that the dehydro bond in 1,2-dehydrobenzene is considerably shorter than a normal benzene bond, and it seems safe to assume that formation of an aryne bond will generally shorten the distance between the bonded atoms. Bond fixation in naphthalene causes the 1,2-bond to be shorter than the 1,3-bond.[79] This effect would operate in benzo[c]cinnoline to make the 1,2-bond shorter than the 2,3-bond. These factors considered together suggest that, because of the shorter 1,2-bond, aryne (69) would form from anion (76) more readily than (75) would from (77). A similar explanation could apply to the high 1:3 product ratio in the reaction of 2-chloronaphthalene with lithium piperidide in piperidine[12] and the high 5:7 product ratio in the reaction of 6-chloroquinoline with the same base.[61] These results have also been explained[12,61] in terms of relative acidities of ring hydrogen atoms.

2-Aminobenzo[c]cinnoline may also have formed from 2-chlorobenzo[c]cinnoline in an AE reaction. This could occur if the 2- position was well-activated towards AE substitution. Even 4-chloropyridine, however, which is activated towards AE substitution, reacts with potassium amide in ammonia to some extent *via* the EA mechanism.[42] It is probable, then, that 2-chlorobenzo[c]cinnoline reacts with potassium amide in ammonia at least in part *via* the EA mechanism.

2-Iodobenzo[c]cinnoline also reacted with potassium amide in ammonia, giving 2-aminobenzo[c]cinnoline as the only product. As in the case of the analogous reaction of 2-chlorobenzo[c]cinnoline, it is not possible to tell from the results whether reaction is occurring by way of the EA or AE mechanism.

4-Iodobenzo[c]cinnoline reacted with potassium amide in ammonia to give two products, 3-aminobenzo[c]cinnoline (81) and 4-aminobenzo[c]cinnoline (82). The high yield of the 3- isomer clearly indicated that reaction occurred mainly by way of the EA mechanism (Scheme 17).

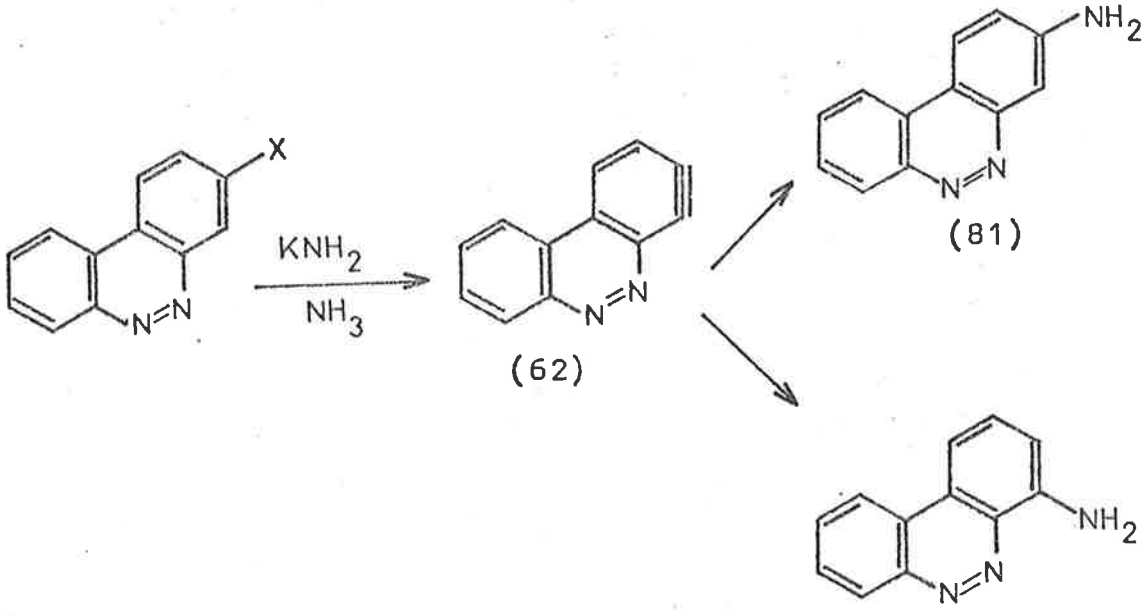
Roberts' rule predicts that nucleophilic attack on aryne (62) will occur more readily at the 3- position; this is also the site of attack favoured on steric grounds.



Scheme 17

It might have been expected that a higher proportion of 4-iodobenzo[c]cinnoline would have reacted by way of an AE mechanism because the 4- substituted benzo[c]cinnolines are the most susceptible to nucleophilic attack *via* this mechanism.[55,56]

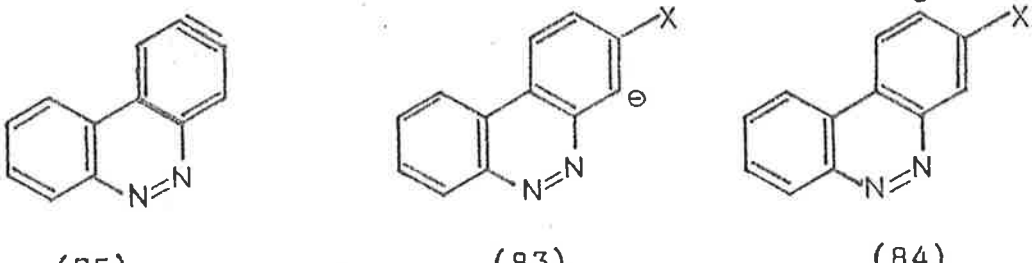
3-Iodobenzo[c]cinnoline also reacted with potassium amide in ammonia to give 3-aminobenzo[c]cinnoline (81) and 4-aminobenzo[c]cinnoline (82) as products. The formation of the 4-amino compound indicates that some reaction *via* the EA mechanism (Scheme 18, X=I) is occurring but it is not



Scheme 18

possible to guage its extent. The product ratio is similar to that obtained in the analogous reaction of 4-iodobenzo[c]cinnoline, so it is possible that this mechanism accounts for nearly all of the products in both reactions.

It is very unlikely that aryne (75) was formed in



(75) (83) (84)

these reactions. Roberts' rule predicts that reaction of this intermediate with potassium amide in ammonia would give 2-aminobenzo[c]cinnoline as the major product. The absence of this amine in the product mixture therefore rules out the formation of aryne (75). Formation of aryne (62) would be favoured over (75) for at least two reasons.

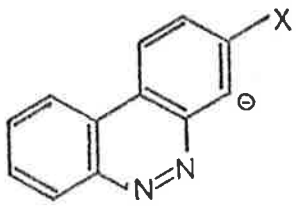
Firstly, generation of anion (83), the precursor of aryne (62), would be favoured over anion (84). This follows from the fact that the acidities of benzenoid hydrogens are determined mainly by the inductive effects of substituents;[80] therefore an aryl halide with an electron-withdrawing meta-substituent should form an anion at the 2-position since the 2- hydrogen will be the most acidic.[38]

Secondly, bond fixation would favour formation of aryne (62) for the same reasons that aryne (69) would be favoured over (75).

Both 3- and 4-chlorobenzo[c]cinnoline reacted with potassium amide in ammonia to give large quantities of intractable tars. Product stability studies showed that the tars were not produced by further reaction of the aminobenzo[c]cinnolines with potassium amide.

It has already been mentioned that the EA reactions of the chlorobenzo[c]cinnolines with potassium amide in ammonia are probably two-step reactions; the analogous

reactions of the iodo compounds are likely to be synchronous. In the former reactions, then, the anions (83), (84) and (85) may be expected to have a longer existence than in the reactions of the iodobenzo[c]cinnolines. This may result in an increased tendency for side reactions to occur and could explain the formation of polymerization products. In contrast to this, 1-chlorobenzo[c]cinnoline produced no tars when treated with potassium amide in ammonia. It seems possible, however, that this reaction would be a concerted process due to the release of steric



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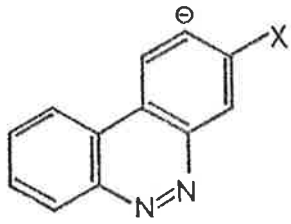

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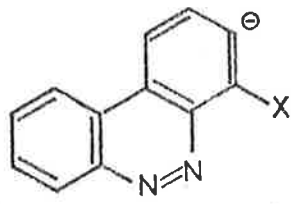


(85)

strain when chloride ion is eliminated to form 1,2-dehydrobenzo[c]cinnoline. The anion formed in this reaction, then, would be short-lived.

The products obtained in the reaction of 3-chlorobenzo[c]cinnoline with potassium amide in ammonia were 3- and 4-aminobenzo[c]cinnoline, indicating that some reaction *via* the EA mechanism (Scheme 18, X=Cl) had occurred. The relative yield of 4- isomer in this reaction was higher

than in the analogous reaction of the 3-iodo compound, indicating that the latter proceeded more *via* the AE mechanism. This is surprising because the normal order of mobility of halogens in these reactions[6d] predicts that the chloro compound would react more readily in an AE reaction.

When 4-chlorobenzo[c]cinnoline was treated with potassium amide in ammonia 2-, 3- and 4-aminobenzo[c]cinnoline were obtained as products. The 3-:4- isomer ratio was lower than in the reaction of 4-iodobenzo[c]cinnoline with the same base, suggesting that a greater proportion of AE substitution is occurring in the reaction of the chloro compound. This is expected according to the normal order of halogen mobility.[6d]

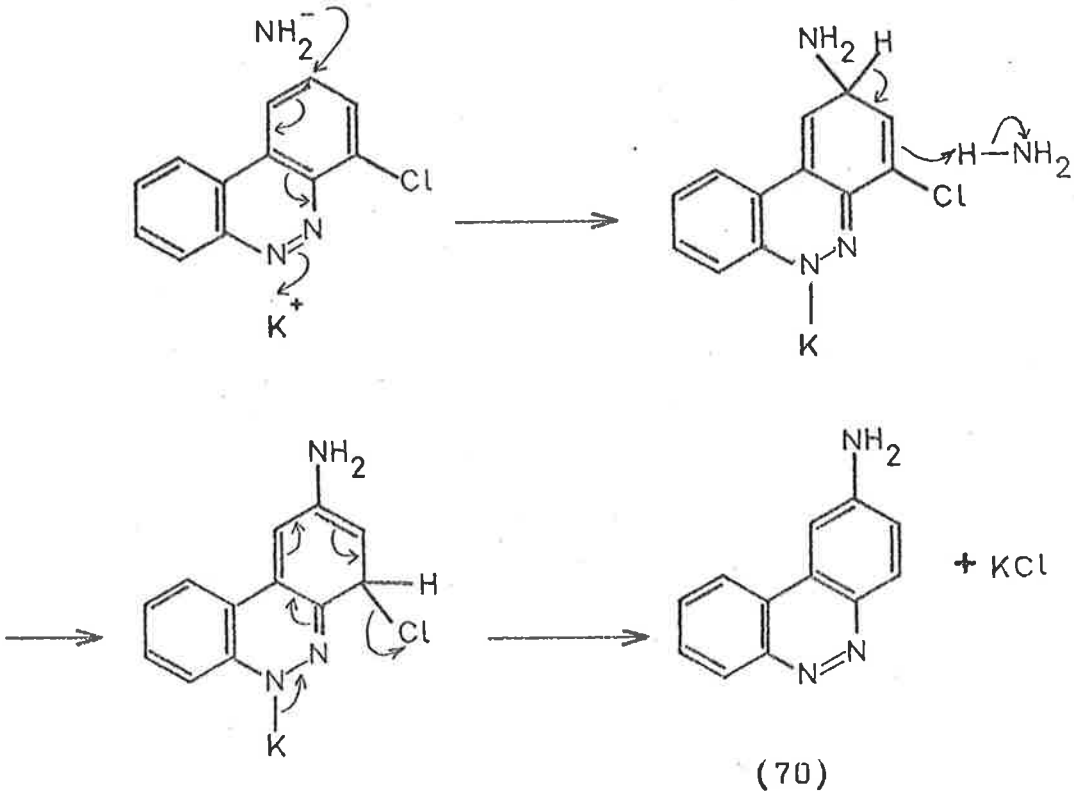
The formation of 2-aminobenzo[c]cinnoline was unexpected. This is another example of a tele-substitution reaction, and could occur in two ways.

One possibility is that 2,4-dehydrobenzo[c]cinnoline (54) is an intermediate in a reaction similar to the one shown in Scheme 7, p.17. Under the conditions used this

(54)

could react to produce 2- and 4-aminobenzo[c]cinnoline.

Secondly, 4-aminobenzo[c]cinnoline could arise from 2-chlorobenzo[c]cinnoline by way of the mechanism shown in Scheme 19. This mechanism is comparable to the one



(70)

Scheme 19

shown in Scheme 13, p.40, for the formation of 4-dimethylaminobenzo[c]cinnolines from 2-chlorobenzo[c]cinnoline.

In some preliminary reactions of the chlorobenzo[c]cinnolines with potassium amide in ammonia quite high yields

of benzo[c]cinnoline were obtained (e.g. Table 6). Several mechanisms for these reduction reactions can be considered.

It is unlikely that benzo[c]cinnoline was formed by the intermolecular rearrangement of the chloro group as has been observed[46,81] in the reactions of bromo- and iodobenzenes with alkali metal amides in ammonia. If this type of reaction had occurred, then a dichlorobenzo[c]cinnoline or its amino derivatives should have been formed in the reaction mixture. These were not observed.

Gream et al[73] reported that 1-, 2- and 4-bromo-10-methylacridone reacted with potassium amide in ammonia to give 10-methylacridone as one of the products. They proposed[73] that the reaction proceeded by direct attack of amide ion on a bromine atom. Benzo[c]cinnoline may have

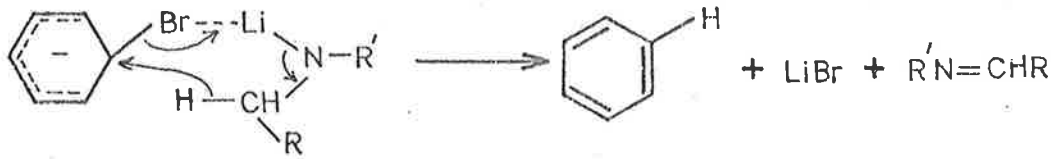
Table 6

Yields (%) from preliminary reaction of 3-chlorobenzo[c]cinnoline with potassium amide in ammonia.

Chloro compd.	Benzo[c] cinn.	Yields (%) $3\text{-}NH_2$	$4\text{-}NH_2$
3-Cl	28	31	28

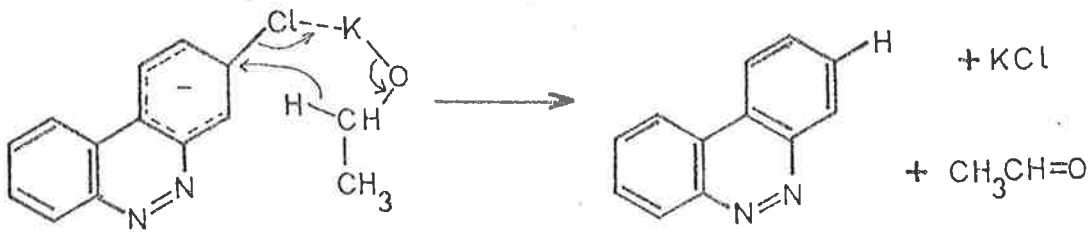
been produced by a similar route in the preliminary reactions of the chlorobenzo[c]cinnolines with potassium amide in ammonia.

In many of these reactions, ethanol was used to render the reaction mixture inactive. In these cases the halide reductions may have involved potassium ethoxide as base. There have been numerous reports[11] of the reduction of aryl halides by substituted lithium amides. Benkeser and de Boer[82] proposed that these reductions require the loss of hydride from an alkyl group *via* the six-membered transition state (87). A transition state (88), analogous



(87)

to (87), may be envisaged for these reactions in which a hydride from the ethyl group of an ethoxide ion displaces a chloro group from the benzo[c]cinnoline ring. This mechanism is comparable to the one proposed for the reduction of



(88)

4-chlorobenzo[c]cinnoline with ethanol and copper sulphate (discussed in Part III).

It is also possible that reduction involving ethanol in a radical mechanism may be involved. Hodgeman and Prager[83] found that when the bromo-10-methylacridones are treated with sodium methoxide in methanol they are reduced to 10-methylacridone *via* a radical reaction.

The reactions of potassium amide in ammonia with halogenobenzo[c]cinnolines proceed *via* the EA or AE mechanisms, whereas lithium dimethylamide in dimethylamine reacts to give an unusual elimination of hydride ion. The main factor responsible for the changeover in mechanism is probably the degree of dissociation of these bases under the reaction conditions. It has already been mentioned that lithium dimethylamide in dimethylamine probably exists as aggregated ion-pairs. Caruso *et al*[74] state that potassium amide in ammonia forms electrostatically associated ion-pairs whereas lithium amide in the same solvent is more associated and may even contain a covalent bond. The reactions with lithium dimethylamide in dimethylamine were carried out using benzene and ether as solvents; the more polar dimethoxyethane was the co-solvent in the reactions with potassium amide in ammonia. These factors all indicate that, under the reaction conditions, lithium dimethylamide was less dissociated than potassium amide. This,

coupled with the ability of lithium dimethylamide to coordinate with the diazo linkage of the benzo[c]cinnoline nucleus, is probably the major reason for the different mechanisms observed in these two groups of reactions.

PART III

FURTHER AROMATIC NUCLEOPHILIC SUBSTITUTION REACTIONS

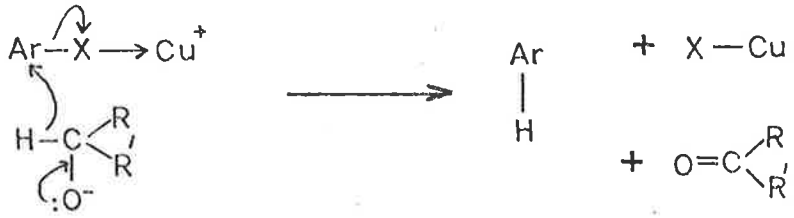
Reaction of 4-chlorobenzo[c]cinnoline with ammonia

4-Aminobenzo[c]cinnoline was required for product studies in the reaction of 4-chlorobenzo[c]cinnoline with potassium amide in ammonia. As reasonable quantities of 4-chlorobenzo[c]cinnoline were available, it was decided to attempt a preparation of the 4-amino compound by direct substitution with ammonia rather than by a longer route.[52] This method seemed feasible as Lewis and Reiss[55] had prepared 4-dimethylaminobenzo[c]cinnoline from 4-chlorobenzo-[c]cinnoline and dimethylamine in good yield, and 4-piperidinobenzo[c]cinnoline has been prepared by a similar method (discussed later). Copper sulphate was added to the reaction mixture because catalysis by copper and copper salts is common in such reactions. The Ullmann reaction,[84] for example, is a well-known method of preparation of carboxydiarylamines in which the halide ion of an o-halocarboxylic acid is substituted by an aniline; the reaction is catalysed by small amounts of copper or copper salts. More relevant, perhaps, are the reactions of bromopyridines[85]

and halogenocinnolines[86] with ammonia and copper sulphate to give the corresponding amino compounds.

When 4-chlorobenzo[c]cinnoline was heated with ammonia, ethanol and copper sulphate in a sealed tube at 190° 4-aminobenzo[c]cinnoline (32%) and benzo[c]cinnoline (54%) were obtained. The formation of benzo[c]cinnoline was unexpected and probably occurred through a reduction of the halide involving ethanol.

Substitutive reductions of this kind are common in copper catalysed reactions[87] and are discussed in a review by Bacon and Hill.[88] Common hydride donors in such reactions are alcohols, amines, alkoxides and aromatic compounds. A mechanism has been proposed[88] for the substitutive reduction of aryl halides by alkoxides with copper salts as catalyst (Scheme 20), and a similar mechanism could be



Scheme 20

envisaged for the reaction of 4-chlorobenzo[c]cinnoline with ethanol, ammonia and copper sulphate. Bacon and Rennison[89] noted, however, that the alcohols were less active

than their corresponding alkoxides in these reductive processes and the yield of reduction product obtained in the present reaction must be regarded as high. Substitutive reductions in which hydrogen transfer from the nucleus of an aromatic compound occurs have also been observed,[90] but seem less likely here as none of the other products which might have been expected from such a reaction, (e.g. coupling products), were obtained.

The high yield of benzo[c]cinnoline produced in this reaction is probably better explained by a radical mechanism (Scheme 21). Although this requires Cu^{I} compound and only copper sulphate was used, it is likely that some of the former would be present at the high temperature (190^{o}) of this reaction.

$$ArCl + Cu^{+} \rightarrow Ar^{\cdot} + (CuCl)^{+}$$

$$Ar^{\cdot} + RCH_2OH \rightarrow ArH + R\dot{C}HOH$$

$$ArCl + R\dot{C}HOH \rightarrow Ar^{\cdot} + RCHO + Cl^{-} + H^{+}$$

$$Cu^{++} + RCHOH \rightarrow Cu^{+} + RCHO + H^{+}$$

Scheme 21

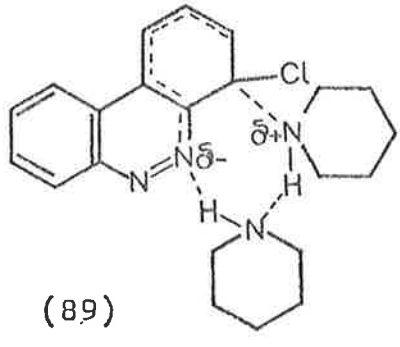
Reaction of the chlorobenzo[c]cinnolines with piperidine

The reactions of the chlorobenzo[c]cinnolines with refluxing piperidine indicated that these compounds have

the relative reactivity towards nucleophiles which is predicted by electron density studies[47-50] and as shown in experiments carried out by Lewis and Reiss[55] and Lill.[56]

1- and 3-Chlorobenzo[c]cinnoline were completely unreactive in a 1000:1 excess of refluxing piperidine. 2-Chlorobenzo[c]cinnoline reacted with refluxing piperidine to give 2-piperidinobenzo[c]cinnoline in 10% yield. The rest of the material was unchanged 2-chlorobenzo[c]cinnoline. Under the same conditions 4-chlorobenzo[c]cinnoline gave 4-piperidinobenzo[c]cinnoline in 54% yield, the rest of the material being unchanged 4-chlorobenzo[c]cinnoline.

These results demonstrate once again that the 2- and 4- positions of the benzo[c]cinnoline ring are the most reactive in AE substitution reactions. The reactivity of the 4-chloro compound is likely to be enhanced by hydrogen-bonding in the transition state (89) between the N-hydrogen of piperidine and the lone pair of a diazo linkage nitrogen atom. Hydrogen-bonding involving a cyclic transition

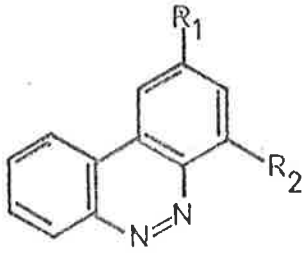


(89)

state such as (89) has been proposed by Shepherd and Fedrick.[4b]

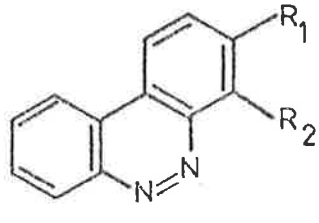
The reactions of 2,4- and 3,4-dichlorobenzo[c]cinnoline with dimethylamine

The results obtained from the reactions of 2,4-dichlorobenzo[c]cinnoline (90) and 3,4-dichlorobenzo[c]-cinnoline (91) with dimethylamine affirm the order of reactivities at different ring positions which was mentioned above. When 2,4-dichlorobenzo[c]cinnoline is heated with dimethylamine in a sealed tube 2,4-bis(dimethylamino)benzo-[c]cinnoline (51) is obtained as the major product. Under similar conditions 3,4-dichlorobenzo[c]cinnoline gives mainly 3-chloro-4-dimethylaminobenzo[c]cinnoline (60). This demonstrates once more that nucleophilic substitution proceeding by the AE mechanism occurs more readily at the 2- and 4- positions in benzo[c]cinnoline than at the 3-position.



(90) $R_1 = R_2 = Cl$

(51) $R_1 = R_2 = N(CH_3)_2$

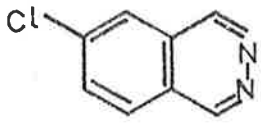


(91) $R_1 = R_2 = Cl$

(60) $R_1 = Cl$; $R_2 = N(CH_3)_2$

Reactions of 6-chlorophthalazine and 4-chlorocinnoline with lithium dialkylamides

In Part I it was postulated that coordination between lithium dimethylamide and the diazo linkage of benzo[c]cinnoline was one of the factors which caused selective entry of the dimethylamide group into the 4- and 7- positions of that molecule. To find if this effect operated with other compounds containing the diazo linkage, the reactions of lithium dialkylamides with 6-chlorophthalazine (92) and 4-chlorocinnoline (93) were investigated.



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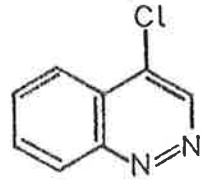
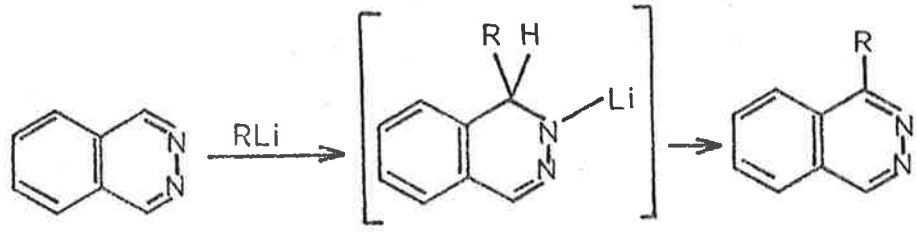


(93)

In phthalazine, the 1- position is the most susceptible to nucleophilic attack and 1-chlorophthalazines react with a number of nucleophiles to give 1- substituted products.[91-93] Phthalazine also reacts with organolithium compounds[94] and Grignard reagents[95] to give 1- substituted phthalazines, and the mechanism proposed[94,95] for these reactions is similar to that for addition of these reagents to the carbon-nitrogen double bond in pyridine.[30,31]



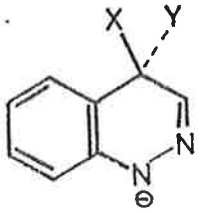
Scheme 22

Scheme 22 shows the mechanism proposed[94] for the reaction of phthalazine with organolithium reagents.

6-Chlorophthalazine was chosen for the attempted reaction with lithium dimethylamide in the present work because this compound has a chloro group in the carbocyclic ring. If substitution occurred at the 1- position of this compound and the chloro group was unaffected, then this would perhaps be an indication that coordination was occurring between the diaza linkage and the base. Although this reaction was attempted several times, however, only starting material was obtained in each case. This was surprising because phthalazine undergoes reaction with the Grignard reagent phenylmagnesiumbromide.[95] The conditions used in the latter reaction are, however, more vigorous than those used in the present reaction.

The other compound chosen for this study, 4-chlorocinnoline, reacts with a variety of nucleophiles to give 4- substituted products.[93] By considering transition

states (94) and (95) for reactions of nucleophiles with 3- and 4- substituted cinnolines as Miller did for 2- and 4-quinazoline,[6f] it seems likely that substitution at the 4- position of a cinnoline compound is the more



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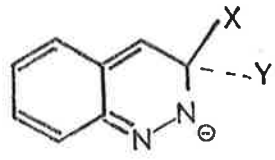


(95)

favourable. This is because in species (94) one aromatic ring remains fully benzenoid while in (95) neither ring is benzenoid. Experimental results[96] seem to support this view. If, therefore, 4-chlorocinnoline reacted with a lithium dialkylamide to give a 3- substituted cinnoline, this would be good evidence of coordination between the cinnoline and the lithium compound.

4-Chlorocinnoline reacted with piperidine to give a compound which, although not fully characterized, is probably 4-piperidinocinnoline. This was expected since 4-chlorocinnoline reacts with other amines directly to give the corresponding 4-amino compounds.[97,98]

In the reaction of 4-chlorocinnoline with lithium piperidide, two major products were obtained. Thin layer chromatography indicated that one of them was the compound thought to be 4-piperidinobenzo[c]cinnoline but the other,

which was obtained as an oil, could not be identified.

Obviously further investigations are necessary to clarify the results of these reactions.

PART IV

PREPARATION AND IDENTIFICATION OF SOME BENZO[c]CINNOLINES

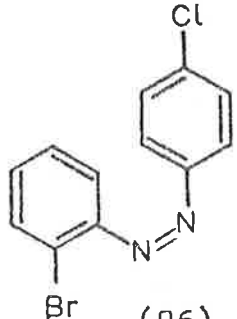
At one stage in this project an investigation was made into the feasibility of independently synthesising the products from the reactions of the chlorobenzo[c]cinnolines with lithium dimethylamide in dimethylamine. The best method for preparing these compounds seemed to be *via* the dihalogenobenzo[c]cinnolines.

The most widely used method for the preparation of the benzo[c]cinnolines has been the reduction of 2,2'-dinitrobiphenyls; a variety of reduction methods has been used.[99] The 2,2'-dinitrobiphenyls are usually prepared by the Ullmann synthesis,[100,101] and this can limit the usefulness of the route in the preparation of benzo[c]cinnolines because yields from this reaction are often low, especially for the preparation of unsymmetrical 2,2'-dinitrobiphenyl compounds. The use of this route in the preparation of halogenobenzo[c]cinnolines is also restricted because of the possibility of participation of the halogeno group during the step involving the Ullmann reaction.

Benzo[c]cinnolines have also been prepared by oxidation of 2,2'-diaminobiphenyls,[102] although the yields are generally lower than in the preparations from the 2,2'-dinitrobiphenyls; furthermore these compounds are generally prepared from the 2,2'-dinitrobiphenyls and so their use is subject to the same limitations as those which apply to dinitro compounds.

A method of preparation of the benzo[c]cinnolines which has proved to be satisfactory in the preparation of both symmetrically and asymmetrically substituted products is the cyclization of azobenzenes. Wolfram[103] prepared benzo[c]cinnoline by carrying out the cyclization of azobenzene in an aluminium chloride eutectic melt; and a variety of benzo[c]cinnolines, including halogenobenzo[c]-cinnolines, have been prepared in good yield by the photochemical cyclization of azobenzenes in sulphuric acid.[104]

An attempt was made to prepare 4-bromo-9-chlorobenzo[c]cinnoline (97) by photochemical cyclization of 2-bromo-4'-chloroazobenzene (96) in sulphuric acid. It was hoped that reaction of the halogeno compound (97) with



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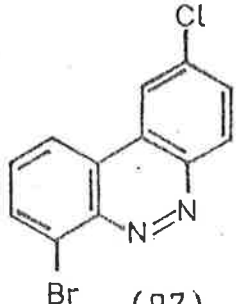

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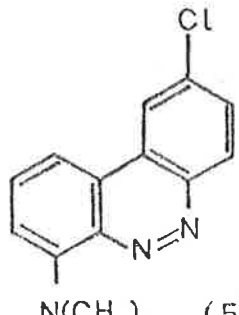


(53)

dimethylamine under selected conditions might give 2-chloro-7-dimethylaminobenzo[c]cinnoline (53). The small amount of product obtained from this reaction, however, could not be purified because of its insolubility in several different solvents. Attempts to prepare several other bromochlorobenzo[c]cinnolines also met with solubility problems and this method was abandoned.

The products obtained in the reactions of the chlorobenzo[c]cinnolines with lithium dimethylamide proved too difficult to synthesize independently and so some other method of identification had to be found.

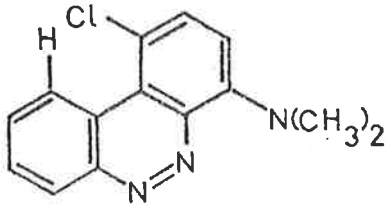
1- and 3-Chlorobenzo[c]cinnoline each reacted with lithium dimethylamide in dimethylamine, giving two isomeric chlorodimethylaminobenzo[c]cinnolines. Mass spectral data could not be used to differentiate between the members of each pair of isomers because the mass spectra of the six isomeric chlorodimethylaminobenzo[c]cinnolines prepared in the reactions with lithium dimethylamide are almost identical. Ultraviolet spectrometry could not be used either because the spectra of each of the isomers in three different solvents were very similar, each being almost identical to those of 4-dimethylaminobenzo[c]cinnoline[55] in the same solvents. Structures were eventually assigned to the isomers using their n.m.r. spectra.

There were three main factors that led to differentiation between the isomers using their n.m.r. spectra. Firstly, it has been shown[105] that a dimethylamino group in an aromatic ring causes a considerable upfield shift in the signal of a proton ortho or para to it. This shift is ca. 3.5ppm. A chloro group, on the other hand, has a very much smaller effect.[105] It was found that in the n.m.r spectra of the isomers under discussion the signal of the proton ortho to the dimethylamino group was shifted upfield sufficiently to be separated from the other aromatic protons. It was possible to tell from the splitting pattern of this proton whether there was a chloro group in the same ring, and if so, in which position.

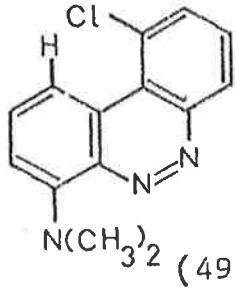
Secondly, the n.m.r. spectrum of unsubstituted benzo[c]cinnoline shows two multiplets, each containing four protons. The lower-field multiplet has been assigned[106] to protons 1, 4, 7 and 10 and the higher-field multiplet to protons 2, 3, 8 and 9. In the chlorodimethylamino compounds studied, the chemical shifts of these protons remained approximately the same as in unsubstituted benzo[c]cinnoline unless influenced by a dimethylamino group ortho or para to them.

The only exception to this was the signal for the 10-proton, which underwent a large downfield shift when

there was a chloro group in the 1- position. In the n.m.r. spectrum of 1-chloro-4-dimethylaminobenzo[c]cinnoline (48), for example, the signal for the proton at the 10- position was at 9.6ppm. The signal for the 10- proton in 1-chloro-



(48)



(49)

7-dimethylaminobenzo[c]cinnoline (49) occurred at 9.0ppm. In 1-chlorobenzo[c]cinnoline itself the signal for the 10-proton appears at 9.7ppm. These signals are well downfield from the region where most aromatic protons appear and this can be attributed to a considerable through-space interaction between the 10-hydrogen and the 1-chloro groups. "Peri-effects" such as this are well known in aromatic polycyclic compounds.[107] In the isomeric chlorodimethylaminobenzo[c]cinnolines which do not contain a chloro group in the 1- position and hence have reduced interactions between the 1- and 10- positions, the lowest proton signals are at 8.3-8.7ppm.

EXPERIMENTAL

General

Melting points were determined on a Reichert hot stage microscope and are uncorrected.

Ultraviolet-visible spectra were determined with a Unicam SP.800 or an Optica CF-4 recording spectrophotometer.

Infrared spectra were determined with a Unicam SP.200 recording spectrophotometer.

Nuclear magnetic resonance spectra were determined with a Varian DP-60 or a T-60 spectrometer at 60MHz. The spectra were measured in deuterochloroform solution and chemical shifts were measured relative to tetramethylsilane as an internal standard. Each signal is described in terms of chemical shift in ppm from tetramethylsilane, multiplicity, intensity and assignment in that order, with use of the following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; and dd, doublet of doublets.

Mass spectra were determined with an Hitachi Perkin-Elmer RMU 6D mass spectrometer at 70eV.

Microanalyses were carried out by the Australian Microanalytical Service, Melbourne.

Quantitative gas-liquid chromatographic analyses were carried out using a Perkin-Elmer 881 gas chromatograph fitted with a Perkin-Elmer 194B printing integrator. Nitrogen was used as the carrier gas at a flow rate of 30ml/min. Calibration graphs were made by analysing accurately made mixtures of an internal standard and independently synthesised products. The columns used were:- A and B: 5% Silicon GE XE-60 (82-001565) on 100-120 mesh Varaport-30 in silanized glass tubing (5ft x 0.125in); C: 3% Silicon GE XE-60 (82-001565) on 100-120 mesh Varaport-30 in silanized glass tubing (5ft x 0.125in). Where counter-current distribution was used to separate mixtures, a Quickfit automatic 50-tube apparatus with stationary and moving phases of 25ml each was employed.

Spence alumina was used for column chromatography. Thin layer chromatography was carried out on 0.25mm layers of Merck silica gel G. Preparative plate chromatography was carried out using 2mm layers of silica gel G on glass plates (20 x 20 x 0.4cm).

Light petroleum used had a boiling range of 40-60^{o} unless otherwise stated.

Reactions with potassium amide in ammonia were carried out in liquid ammonia.

PART I

REACTIONS OF BENZO[C]CINNOLINE AND THE CHLOROBENZO[C]CINNOLINES WITH LITHIUM DIALKYLAMIDES

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1. Starting materials

1.1 Nitrosobenzene

This was prepared from nitrobenzene by the method of Vogel.[108a] It was recrystallized from ethanol and obtained as white crystals, m.p. 64-66° (lit.[108a] 68°).

1.2 o-Bromonitrosobenzene

This was prepared in 61% yield from o-bromonitrobenzene by the method of Lutz and Lytton.[109] A portion of the product was recrystallized from ethanol to give o-bromonitrosobenzene as white needles, m.p. 97° (lit.[109] 97°).

1.3 Chloroazobenzenes

2-, 3-, and 4-Chloroazobenzene were prepared from nitrosobenzene and the appropriate chloroaniline by the method of Badger et al.[110] Yields and melting points were consistent with literature values.

1.4 2,4-Dichloroazobenzene

This was prepared in 30% yield from 2,4-dichloroaniline and nitrosobenzene by the method of Stieglitz et al.[111] It was recrystallized from light petroleum and obtained as orange plates, m.p. 105° (lit.[111] 105°).

1.5 Benzo[c]cinnoline

This was prepared from azobenzene by the method of Lewis.[112] It was recrystallized from ethanol and obtained as yellow needles, m.p. 157-158° (lit.[112] 156°).

1.6.1 Chlorobenzo[c]cinnolines

1-, 2-, 3- and 4-Chlorobenzo[c]cinnolines were prepared by the photochemical cyclization of the appropriate chloroazobenzene in 11M sulphuric acid using the method of Badger et al.[110] Yields and melting points were consistent with literature values.

1.6.2 1-Chlorobenzo[c]cinnoline

This was also prepared from 1-aminobenzo[c]-cinnoline according to the method in Vogel[108b] for the

preparation of p-toluidine. A solution of cuprous chloride in concentrated hydrochloric acid was prepared from copper sulphate (627mg), sodium chloride (175mg), sodium metabisulphite (139mg), sodium hydroxide (96mg) and concentrated hydrochloric acid (1ml). A solution of sodium nitrite (300mg) in water (5ml) was added slowly and with stirring to a solution of 1-aminobenzo-[c]cinnoline (700mg) in concentrated hydrochloric acid (0.9ml) and water (10ml). The temperature was kept between -5^{o} and 0^{o}. This solution was then added slowly to the solution of cuprous chloride and the mixture allowed to warm to room temperature. The mixture was heated on a water bath for 10min, shaken with chloroform and filtered. The chloroform filtrate was washed, dried, and chromatographed on a column of alumina. 1-Chlorobenzo[c]cinnoline (480mg, 61%) was obtained as pale yellow needles from the first yellow-green band. This was used without further purification (thin layer chromatographic analysis showed one spot) in the preparation of 1-chloro-4,7-bis(dimethylamino)benzo-[c]cinnoline.

1.7 2,4-Dichlorobenzo[c]cinnoline

This was prepared in 8% yield from 2,4-dichloroazobenzene by the method of Lewis.[112] Recrystallization from ethanol gave 2,4-dichlorobenzo[c]cinnoline as yellow needles, m.p. 236-237° (Found: C, 58.0; H, 2.5; N, 11.1. $C_{12}H_6Cl_2N_2$ requires C, 57.8; H, 2.4; N, 11.3%). Mass spectrum: m/e 250, 248 (M^+). ($C_{12}H_{16}Cl_2N_2$ requires M^+ 250, 248).

1.8 Attempted preparation of 4-Bromo-9-chlorobenzo[c]cinnoline

a) A solution of o-bromonitrosobenzene (1.5g) and p-chloroaniline (1g) in glacial acetic acid (2ml) was warmed on a water bath; the mixture became solid after 30sec. The solid was added to a solution of dilute sodium hydroxide and the mixture extracted with chloroform. The solvent was removed and the residue was chromatographed on a column of alumina, using light petroleum as the eluant. The first (main) band was collected and the solvent evaporated to give an orange-red solid, (1.2g), thought to be 2-bromo-4-chloroazobenzene. Analysis of this by thin layer chromatography showed that

the material contained only one compound, and it was used without purification for the next step.

b) The product obtained in part a), (1.2g), was dissolved in sulphuric acid (130ml, 11M) and irradiated with a Philips HP 125-W high pressure mercury-quartz lamp for 72hr. The mixture was made basic with dilute sodium hydroxide and extracted with chloroform, and the chloroform extract was subjected to chromatography on a column of alumina. Attempts to purify the small amount of product obtained were made difficult by its insolubility in a range of solvents, and the method was abandoned.

1.9 n-Butyllithium in hexane

In the reactions described in sections 2.6-3.1 a stock solution of n-butyllithium in hexane was used which was prepared according to the method of Gilman and Morton.[113] The solution was stored under an atmosphere of nitrogen and analysed by the double-titration technique[114] prior to reaction.

2. Products

The preparations described in sections 2.1-2.4 were carried out in an atmosphere of dry nitrogen. A similar procedure was followed in each reaction. All ether and benzene used was dried over sodium wire. Yields are based on unrecovered starting material.

2.1 1-Chloro-4-dimethylamino- and 1-chloro-7-dimethylaminobenzo[c]cinnoline

A solution of n-propyllithium was made by adding n-propylbromide (5.92g) in ether (30ml) to lithium (1.2g) in ether (15ml) at -10^{o} over 30min. The mixture was stirred for a further 1hr at room temperature. The n-propyllithium solution (35ml, 0.85M) was added to anhydrous dimethylamine (ca. 25ml) in ether (10ml) at -10^{o} over 5min. The mixture was stirred for a further 30min at room temperature. 1-Chlorobenzo[c]cinnoline (469mg) in benzene (30ml) was added at -10^{o} over 5min. The ratio of lithium dimethylamide to 1-chlorobenzo[c]cinnoline was 13:1. On addition of the chlorobenzo[c]cinnoline solution the reaction mixture turned an intense red-purple colour which gave way within 0.5min to a dark green colour. The mixture was stirred for a further 5min at room temperature and then water was added. The mixture was

extracted with chloroform and the chloroform layer washed with water and dried over magnesium sulphate. The solvent was removed and the residue chromatographed on a plate of silica developing with ether/light petroleum/benzene, (3:3:1). The material in the upper fraction was isolated and subjected to counter-current distribution between 0.05M hydrochloric acid and benzene/light petroleum (3:17). The material in the tubes nearest the solvent front was 1-chlorobenzo[c]cinnoline (69mg, 15% recovery). The material (369mg, 77%) in the tubes closer to the starting tube was a mixture of 1-chloro-4-dimethylamino- and 1-chloro-7-dimethylaminobenzo[c]cinnoline. These two compounds could not be completely separated from each other but were contained in a band which was separated from starting material and other products. By isolating the contents of several tubes at either end of the band, pure samples of the two compounds were obtained. An n.m.r. spectrum of the material in the remainder of the tubes was identical to a spectrum of 1-chloro-4-dimethylaminobenzo[c]cinnoline. In this band the tubes nearest the solvent front contained 1-chloro-7-dimethylaminobenzo-[c]cinnoline. This compound was the minor product. It was recrystallized from chloroform/hexane and obtained as orange-red needles, m.p. 122-123.5° (Found: C, 65.4;

H, 5.0; N, 16.5. $C_{14}H_{12}ClN_3$ requires: C, 65.3; H, 4.7; N, 16.3%). N.m.r. spectrum: ∂ 3.3 (s, 6H, $N-CH_3$); 6.9 (d, 1H, aromatic H); 7.5-8.0 (m, 3H, aromatic H); 8.3-8.7 (m, 1H, aromatic H); 9.5-9.7 (m, 1H, aromatic H). The ultraviolet-visible spectra of the compound in neutral, moderately acidic and strongly acidic ethanolic solutions showed absorption maxima as follows: EtOH: 240, 295, 350, 460nm; 20% EtOH/0.2M sulphuric acid: 245, 275, 320nm; 20% EtOH/ 98% sulphuric acid: 255, 380nm. Mass spectrum: m/e 259, 257 (M^+). ($C_{14}H_{12}ClN_3$ requires M^+ 259, 257). In the same band, the tubes nearest the starting tube contained 1-chloro-4-dimethylaminobenzo[c]cinnoline. This was recrystallized from chloroform/hexane and obtained as dark red needles, m.p. 100-101.5° (Found: C, 65.4; H, 4.8; N, 16.1. $C_{14}H_{12}ClN_3$ requires C, 65.3; H, 4.7; N, 16.3%). N.m.r. spectrum: ∂ 3.3 (s, 6H, $N-CH_3$); 7.2 (d, 1H, aromatic H); 7.4-7.8 (m, 3H, aromatic H); 8.6 (dd, 1H, aromatic H); 9.0 (dd, 1H, aromatic H). Ultraviolet-visible spectra: λ max EtOH: 245, 280, 315, 350, 460nm; 20% EtOH/0.2M sulphuric acid: 250, 325, 620nm; 20% EtOH/98% sulphuric acid: 260, 390nm. Mass spectrum: m/e 259, 257 (M^+). ($C_{14}H_{12}ClN_3$ requires M^+ 259, 257). Other products from this reaction were not present in sufficient quantities to warrant further investigation.

2.2 2-Chloro-4-dimethylaminobenzo[c]cinnoline and 4-dimethylaminobenzo[c]cinnoline

A solution of n-propyllithium in ether (35ml, 0.61M) was prepared by the procedure described in 2.1. This was added to a solution of dimethylamine (ca. 25ml) in ether. 2-Chlorobenzo[c]cinnoline (389mg) in benzene (50ml) was added at -30° over 2.5min. The ratio of lithium dimethylamide to 2-chlorobenzo[c]cinnoline was 10:1. The mixture developed a dark green colouration which persisted until work-up. The cooling-bath was removed and the mixture stirred for 2min. The mixture was rendered inactive by the addition of water; and after the usual working-up procedure it was chromatographed on a plate of silica, developing with ether/light petroleum/benzene (3:3:1). The material in the two fractions with highest Rf values was isolated and subjected to counter-current distribution between 0.1M sulphuric acid and benzene/light petroleum (1:4). The material in the tubes nearest the solvent front was 2-chlorobenzo[c]cinnoline (37mg. 9% recovery). The material in tubes nearer the starting tube was 2-chloro-4-dimethylaminobenzo[c]cinnoline (234mg, 56%). This was recrystallized from chloroform/hexane and obtained as orange-yellow needles, m.p. 146.5-148.5° (Found: C, 65.3; H, 4.7; N, 16.2. $C_{14}H_{12}ClN_3$ requires C, 65.3; H, 4.7; N, 16.3%). N.m.r. spectrum: δ

3.3 (s, 6H, N-CH_3); 6.9 (d, 1H, aromatic H); 7.6-7.8 (m, 3H, aromatic H); 8.2-8.6 (m, 2H, aromatic H). Ultraviolet-visible spectra: λ max EtOH: 245, 310, 345, 445nm; 20% EtOH/0.2M sulphuric acid: 245, 320, 580nm; 20% EtOH/98% sulphuric acid: 255, 380nm. Mass spectrum: m/e 259, 257 (M^+). ($C_{14}H_{12}ClN_3$ requires M^+ 259, 257). The material in the tubes nearest the starting tube was 4-dimethylaminobenzo[c]cinnoline (175mg, 48%). This was recrystallized from chloroform/hexane and obtained as orange-yellow plates, m.p. 93-96° (lit.[55] 97.5-98°). When a sample of this compound was mixed with a sample of authentic 4-dimethylaminobenzo[c]cinnoline, obtained from earlier work[55] done in this Department, the mixture also melted at 93-96°. No other compounds were isolated from the reaction mixture.

2.3 3-Chloro-4-dimethylamino- and 3-chloro-7-dimethylaminobenzo[c]cinnoline

A solution of n-propyllithium (35ml, 0.65M) was prepared by the procedure described in 2.1. This was added to a solution of dimethylamine (ca. 25ml) in ether. 3-Chlorobenzo[c]cinnoline (936mg) in benzene (85ml) was added at -10° over 5min. The ratio of lithium dimethylamide to 3-chlorobenzo[c]cinnoline was 5:1. The mixture developed a dark green colouration which persisted until

work-up. The cooling-bath was removed and the mixture was stirred for a further 10min. Water was added and after the usual working-up procedure the mixture was chromatographed on a plate of silica, developing with ether/light petroleum/benzene (3:3:1). Three fractions were obtained. The material from the fraction of highest Rf value was subjected to counter-current distribution between 0.5M hydrochloric acid and hexane. Only one compound was present. This was 3-chloro-4-dimethylaminobenzo[c]cinnoline (212mg, 23%). It was recrystallized from chloroform/hexane and obtained as lemon-yellow needles, m.p. 130.5-131.5° (Found: C, 65.4; H, 4.5; N, 16.2. $C_{14}H_{12}ClN_3$ requires C, 65.3; H, 4.7; N, 16.3%). N.m.r. spectrum: ∂ 3.3 (s, 6H, N-CH_3); 7.6-8.1 (m, 3H, aromatic H); 8.3-8.7 (m, 3H, aromatic H). Ultraviolet-visible spectra: λ max EtOH: 250, 305, 340, 440nm; 20% EtOH/0.2M sulphuric acid: 260, 320, 370, 615nm; 20% EtOH/98% sulphuric acid: 260, 375nm. Mass spectrum: m/e 259, 257 (M^+). ($C_{14}H_{12}ClN_3$ requires M^+ 259, 257). The material in the middle fraction from the chromatography plate was subjected to counter-current distribution between 1M hydrochloric acid and benzene/light petroleum (1:1). The benzene/light petroleum ratio was progressively increased to 9:1. The material in the tubes nearest the solvent

front was 3-chlorobenzo[c]cinnoline (168mg, 18% recovery). The material in the tubes closer to the starting tube was 3-chloro-7-dimethylaminobenzo[c]cinnoline (274mg, 30%). This was recrystallized from chloroform/hexane and obtained as mustard yellow needles, m.p. 136.5-137.5° (Found: C, 65.1; H, 4.6; N, 16.1. $C_{14}H_{12}ClN_3$ requires C, 65.3; H, 4.7; N, 16.3%). N.m.r. spectrum: ∂ 3.3 (s, 6H, N-CH_3); 7.1 (dd, 1H, aromatic H); 7.5-7.8 (m, 3H, aromatic H); 8.3 (d, 1H, aromatic H); 8.5 (d, 1H, aromatic H). Ultraviolet-visible spectra: λ max EtOH: 250, 295, 315, 465nm; 20% EtOH/0.2M sulphuric acid: 255, 315, 365, 615nm; 20% EtOH/98% sulphuric acid: 260, 375nm. Mass spectrum: m/e 259, 257 (M^+). ($C_{14}H_{12}ClN_3$ requires M^+ 259, 257). The material in the tubes nearest the starting tube was 4-dimethylaminobenzo[c]cinnoline (179mg, 22%). This was recrystallized from chloroform/hexane and obtained as orange plates, m.p. and mixed m.p. 94.5-97° (lit.[55] 97.5-98°). The material (74mg) in the fraction of lowest Rf value obtained from the chromatogram was a mixture of several compounds and was not investigated further.

2.4 4-Chloro-7-dimethylaminobenzo[c]cinnoline

A solution of n-propyllithium (35ml, 0.27M) was prepared by the procedure described in 2.1. This was

added to a solution of dimethylamine (25ml) in ether. 4-Chlorobenzo[c]cinnoline (463mg) in benzene (40ml) was added at -20° over 5min. The ratio of lithium dimethylamide to 4-chlorobenzo[c]cinnoline was 4:1. The solution developed a dark green colouration which persisted until work-up. The cooling-bath was removed and the mixture stirred for another 5min. Water was added and after the usual working-up procedure the mixture was chromatographed on a column of alumina. The first fraction eluted with light petroleum/ether (19:1) was 4-chloro-7-dimethylaminobenzo[c]cinnoline (344mg, 62%). This was recrystallized from chloroform/hexane and obtained as dark orange-red needles, m.p. 152.5-154° (Found: C, 65.1; H, 4.6; N, 16.1. $C_{14}H_{12}ClN_3$ requires C, 65.3; H, 4.7; N, 16.3%). N.m.r. spectrum: ∂ 3.4(s, 6H, N-CH_3); 7.0 (dd, 1H, aromatic H); 7.4-7.9 (m, 4H, aromatic H); 8.3 (dd, 1H, aromatic H). Ultraviolet-visible spectra: λ max EtOH: 245, 320, 345, 465nm; 20% EtOH/0.2M sulphuric acid: 245, 325, 370, 630nm; 20% EtOH/98% sulphuric acid: 255, 265, 385nm. Mass spectrum: m/e 259, 257 (M^+). ($C_{14}H_{12}ClN_3$ requires M^+ 259, 257). The second fraction eluted from the column was 4-dimethylaminobenzo[c]cinnoline (125mg, 26%). There were no other compounds identified in the reaction mixture.

The reactions described in 2.5 and 2.6.1 were carried out in the apparatus shown in Fig.2. A similar procedure was followed in each case. The reactions were carried out under an atmosphere of dry nitrogen. Ether and benzene used were sodium-dried and distilled from lithium aluminium hydride immediately before use.

2.5 4,7-Bis(dimethylamino)benzo[c]cinnoline

Dimethylamine (ca. 15ml) was distilled from calcium hydride into flask B which contained ether (30ml). A portion of this solution (30ml) was transferred to flask D and to it was added a solution of n-butyllithium in hexane (10ml, 1.0M). When the formation of lithium dimethylamide was complete a solution of benzo[c]cinnoline (307mg) in benzene (40ml) was added over 2min. The solution developed a dark green colouration which persisted until work-up. The reaction mixture was stirred for 15hr. Water was added and after the usual working-up procedure the mixture was subjected to counter-current distribution between 0.5M hydrochloric acid and benzene. The material in the tubes nearest the solvent front was 4-dimethylaminobenzo[c]cinnoline. The material in the tubes nearest the starting tube was isolated and chromatographed on a column of alumina using benzene as eluant. The material in the

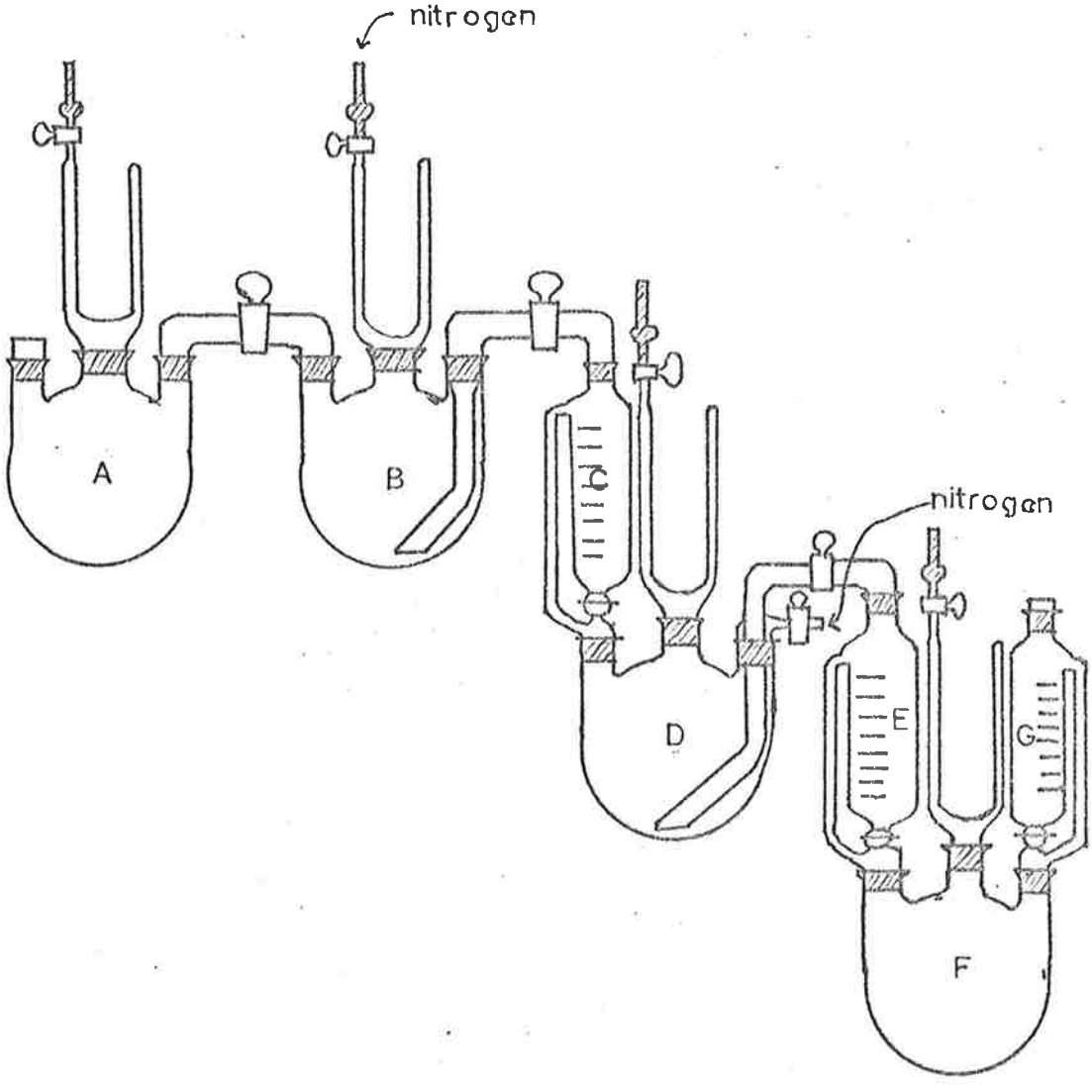

Fig. 2

first (orange) fraction was 4,7-bis(dimethylamino)benzo-[c]cinnoline (52mg, 12%). This was recrystallized from light petroleum, b.p. 60-80°, and obtained as yellow prisms, m.p. 94-95° (Found: C, 72.0; H, 6.7. $C_{16}H_{18}N_4$ requires C, 72.2; H, 6.8%). N.m.r. spectrum: δ 3.4 (s, 12H, N-CH_3); 7.2 (dd, 2H, aromatic H); 7.5-7.8 (t, 2H, aromatic H); 7.9-8.5 (dd, 2H, aromatic H). Mass spectrum: m/e 266 (M^+). ($C_{16}H_{18}N_4$ requires M^+ 266).

2.6.1 2,4-Bis(dimethylamino)benzo[c]cinnoline and 2,4,7-tris(dimethylamino)benzo[c]cinnoline

A solution of lithium dimethylamide in dimethylamine was made by adding a solution of n-butyllithium in hexane (37.5ml, 1M) to dimethylamine (15ml) in ether (22.5ml). A portion of this solution (50ml) was transferred to flask F. 2-Chlorobenzo[c]cinnoline (503mg) in benzene (60ml) was added at -10° over 15min. The reaction mixture was stirred at -10° for 1.5hr and then at room temperature for 0.5hr. Water was added and the mixture subjected to the usual working-up procedure. Chromatography of the mixture on a column of alumina was used to effect primary separation of 4-dimethylamino- and 2-chloro-4-dimethylaminobenzo[c]cinnoline from the more strongly adsorbed compounds. The remaining material was

subjected to counter-current distribution between 0.01M hydrochloric acid and benzene. The material in the tubes nearest the solvent front was 4-dimethylaminobenzo[c]-cinnoline. The material in the tubes nearest the starting tube was isolated and subjected to counter-current distribution between 0.001M hydrochloric acid and benzene. Two overlapping bands were obtained. The material in the tubes nearest the solvent front was 2,4,7-tris(dimethylamino)benzo[c]cinnoline. This was recrystallized from light petroleum, b.p. 60-80°, and obtained as dark orange needles, m.p. 151.5-152.5° (lit.[57] 148-150°). A sample of 2,4,7-tris(dimethylamino)benzo[c]cinnoline from other workers[57] which had been purified by counter-current distribution between 0.001M hydrochloric acid and benzene showed m.p. and mixed m.p. 145-148° with this sample. Both samples showed the same retention time when analysed by gas-liquid chromatography using column C. The material in the tubes nearest the starting tube was 2,4-bis(dimethylamino)benzo[c]cinnoline. This was recrystallized from light petroleum, b.p. 60-80°, and obtained as orange needles, m.p. 163-165° (Found: C, 72.2; H, 6.9. $C_{16}H_{18}N_4$ requires C, 72.2; H, 6.8%). N.m.r. spectrum: δ 3.2 (s, 6H, N-CH_3); 3.4 (s, 6H, N-CH_3); 6.6 (s, 1H, aromatic H); 7.0 (s, 1H, aromatic H); 7.7-7.9 (m,

2H, aromatic H); 8.4-8.7 (m, 2H, aromatic H). Mass spectrum: m/e 266 (M^+). ($C_{16}H_{18}N_4$ requires M^+ 266). The material in the tubes between the two isolated fractions was a mixture of the two compounds.

2.6.2 2,4-Bis(dimethylamino)benzo[c]cinnoline from 2,4-dichlorobenzo[c]cinnoline

2,4-Dichlorobenzo[c]cinnoline (66mg) in dimethylamine (ca. 1ml) was heated in a sealed tube at 165° for 3hr. The reaction mixture was chromatographed on a plate of silica developing with ether/light petroleum/dimethoxyethane (3:3:1). The material in the major fraction was recrystallized from light petroleum, b.p. 60-80°, to give 2,4-bis(dimethylamino)benzo[c]cinnoline as orange needles, m.p. 156-162°.

2.7 1-Chloro-4,7-bis(dimethylamino)benzo[c]cinnoline

A solution of lithium dimethylamide in dimethylamine was made by adding a solution of n-butyllithium in hexane (20ml, 1M) to dimethylamine (10ml) in ether (40ml). When the formation of lithium dimethylamide was complete a portion of this solution (40ml) was removed for another reaction. To the remaining solution was added 1-chlorobenzo[c]cinnoline (480mg) in benzene (40ml). The mixture

was stirred for 2hr and then water was added. Analysis of the mixture by thin layer chromatography showed that the major product was a mixture of 1-chloro-4-dimethylamino- and 1-chloro-7-dimethylaminobenzo[c]cinnolines. The mixture was redissolved in benzene (40ml) and added to a fresh solution of lithium dimethylamide in dimethylamine. This was prepared by adding a solution of n-butyllithium in hexane (10ml, 1M) to dimethylamine (10ml) in ether (20ml). A portion of this solution (20ml) was used in the above reaction. The mixture was stirred for 5hr and then water was added. After the usual working-up procedure the mixture was subjected to counter-current distribution between 0.05M hydrochloric acid and benzene. The material in the tubes nearest the solvent front was a mixture of 1-chloro-4-dimethylamino- and 1-chloro-7-dimethylaminobenzo[c]cinnolines. The material in the tubes nearest the starting tube was 1-chloro-4,7-bis(dimethylamino)benzo[c]cinnoline (25mg, 4%). This was recrystallized from light petroleum, b.p. 60-80°, and obtained as blood-red needles, m.p. 91.5-93.5° (Found: C, 64.1; H, 5.7; N, 18.7. $C_{14}H_{17}ClN_4$ requires C, 63.9; H, 5.7; N, 18.6%). N.m.r. spectrum: ∂ 3.4 (s, 12H, $N-CH_3$); 7.3-7.4 (m, 2H, aromatic H); 7.7-7.9 (m, 2H, aromatic H); 9.0-9.2 (m, 1H, aromatic H). Mass spectrum:

m/e 302, 300 (M^+). ($C_{14}H_{17}ClN_4$ requires M^+ 302, 300).

3. Monitored reactions of the Chlorobenzo[c]cinnolines and Benzo[c]cinnoline with Lithium dimethylamide in dimethylamine

All reactions were carried out in the apparatus shown in Fig. 2. All reactions were carried out in an atmosphere of dry nitrogen. Ether and benzene were sodium-dried and distilled from lithium aluminium hydride immediately before use. Quantitative analyses by gas-liquid chromatography were carried out using column C. Yields are based on unrecovered starting material. The same procedure was followed in all reactions and the reaction of 1-chlorobenzo[c]cinnoline is typical.

3.1 Reaction of 1-chlorobenzo[c]cinnoline with lithium dimethylamide in dimethylamine

A solution of lithium dimethylamide in dimethylamine was made by adding a solution of n-butyllithium in hexane (30ml, 1M) to a solution of dimethylamine (10ml) in ether (20ml). A portion of this solution (20ml) was transferred to flask F. 1-Chlorobenzo[c]cinnoline (193mg) in benzene (30ml) was added at reflux temperature over 2min. An aliquot (5ml) was taken from the reaction mixture im-

mediately after the addition of 1-chlorobenzo[c]cinnoline was complete. Further aliquots (each 5ml) were taken at reaction times of 5, 20, 65 and 120min. The reaction mixture was stirred for 7.6hr and then water was added. As each aliquot was taken it was quenched with water. Each aliquot and the final reaction mixture were subjected to the usual working-up procedure. 2,3,6,-Trimethylnaphthalene was added as internal standard and the mixtures were analysed by gas-liquid chromatography (column C). The results of the reactions are given in Tables 7 to 11.

TABLE 7

Reaction of 1-chlorobenzo[c]cinnoline with lithium dimethylamide in dimethylamine

Molar Ratio $LiNMe_2$	Reactn time (min)	% Reactn	Yields (%) Mixture of 1-Cl-4-NMe_2 1-Cl-7-NMe_2	1-Cl 4,7 bis(NMe_2)	2,4(bis) NMe_2	2,4,7(tris) NMe_2
10	0.1	73	72	0	-	-
	20	88	60	0	-	-
	120	95	40	3	trace	trace
	450	100	25	15	trace	trace

TABLE 8

Reaction of 2-chlorobenzo[c]cinnoline with lithium dimethylamide in dimethylamine

Molar Ratio $LiNMe_2$	Reactn time (min)	% Reactn	Yields (%) 4-NMe_2	2-Cl 4-NMe_2	4,7(bis) NMe_2	2,4(bis) NMe_2	2,4,7(tris) NMe_2
10	0.1	100	53	40	-	-	-
	5	100	47	29	-	4	-
	10	100	43	21	-	11	4
	45	100	35	15	-	21	6
	120	100	42	2	7	31	12

TABLE 9

Reactions of 3-chlorobenzo[c]cinnoline with lithium dimethylamide in dimethylamine

Molar Ratio $LiNMe_2$	Reactn time (min)	% Reactn	Yields (%) 4-NMe_2	3-Cl-4-NMe_2	3-Cl-7-NMe_2
10	0.1	69	7	51	30
	60	77	6	44	29
	120	78	7	48	33
20	0.1	66	12	52	30
	20	94	15	30	21

TABLE 10

Reaction of 4-chlorobenzo[c]cinnoline with lithium dimethylamide in dimethylamine

Molar Ratio $LiNMe_2$	Reactn time (min)	% Reactn	Yields (%)* 4-NMe_2	4-Cl 7-NMe_2	4,7 (bis) NMe_2	2,4 (bis) NMe_2	2,4,7 (tris) NMe_2
10	0.1	not known	not known	19	-	-	-
	25			24	-	-	-
	60			8	9	trace	trace
	120			2	14	trace	trace

TABLE 11

Reaction of benzo[c]cinnoline with lithium dimethylamide in dimethylamine

Molar Ratio $LiNMe_2$	Reactn time (min)	% Reactn	Yields (%) 4-NMe_2
10	0.1	69	97
	60	68	85

* Based on total starting material.

Reaction of Benzo[c]cinnoline with Lithium Piperidide in Piperidine

This reaction was carried out using part of the apparatus shown in Fig. 2. Dimethoxyethane was sodium dried and distilled from lithium aluminium hydride immediately before use.

A solution of n-butyllithium in hexane (15ml, 2M) was added to ether (10ml). This was added to a solution of piperidine (10ml) in ether (10ml) contained in flask D. When the formation of lithium piperidide was complete 20ml of this solution was transferred to flask F. A solution of benzo[c]cinnoline (498mg) in dimethoxyethane (15ml) was added over 5min at room temperature. The mixture was stirred for a further 10min then water was added. After the usual working-up procedure the mixture was subjected to counter-current distribution between 0.5M hydrochloric acid and benzene/hexane (1:1). The material in the tubes closest to the solvent front was benzo[c]cinnoline (298mg, 60% recovery). The organic solvent was changed to benzene/chloroform (9:1) and the counter-current distribution continued.

The material in the tubes nearest the solvent front was 4-piperidinobenzo[c]cinnoline (230mg, 79% based on unrecovered starting material). This was recrystallized

from light petroleum, b.p. 60-80°, and obtained as orange needles, m.p. 142.5-144° (Found: C, 77.8; H, 6.5. $C_{17}H_{17}N_3$ requires C, 77.5; H, 6.5%). N.m.r. spectrum: δ 1.5-2.2 (m, 6H, aliphatic-CH_2-); 3.5-3.7 (m, 4H, aliphatic N-CH_2-); 7.3 (dd, 1H, aromatic H); 7.3-8.1 (m, 4H, aromatic H); 8.5-8.6 (m, 2H, aromatic H). Ultra-violet-visible spectra: λ max EtOH: 240, 290, 340, 430nm; 20% EtOH/0.2M sulphuric acid: 250, 315, 360nm; 20% EtOH/ 98% sulphuric acid: 250, 370nm. Mass spectrum: m/e 263 (M^+). ($C_{17}H_{17}N_3$ requires M^+ 263). The material in the tubes nearest the starting tube was 4,7-bis(piperidino)-benzo[c]cinnoline (28mg, 7%). This was recrystallized from light petroleum, b.p. 60-80°, and obtained as orange needles, m.p. 110-112.5°. The compound could not be obtained sufficiently pure for accurate analysis. N.m.r. spectrum: δ 1.5-2.2 (m, 12H, aliphatic -CH_2-); 3.3-3.7 (m, 8H, aliphatic N-CH_2-); 7.2-7.6 (dd, 2H, aromatic H); 7.5-7.7 (t, 2H, aromatic H); 7.8-8.1 (dd, 2H, aromatic H). Mass spectrum: m/e 346 (M^+). ($C_{22}H_{26}N_4$ requires M^+ 346).

PART II

REACTIONS OF THE HALOGENOBENZO[c]CINNOLINES WITH POTASSIUM AMIDE IN AMMONIA

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1. Starting materials

1.1 Iodoazobenzenes

2-, 3- and 4-Iodoazobenzene were prepared from nitrosobenzene and the appropriate iodoaniline by the method of Badger, Drewer and Lewis.[110] Yields and melting points were consistent with literature values.

1.2 Halogenobenzo[c]cinnolines

2-, 3- and 4-Iodobenzo[c]cinnolines were prepared by the photochemical cyclization of the appropriate iodoazobenzene in 11M sulphuric acid using the method of Badger, Drewer and Lewis.[110] Yields and melting points were consistent with literature values. 1-, 2-, 3- and 4-chlorobenzo[c]cinnolines were available from earlier work.

2. Products

2.1.1 1-Aminobenzo[c]cinnoline

This was prepared by the method of Barton and Cockett.[52]

a) 1-Nitrobenzo[c]cinnoline

This was prepared from benzo[c]cinnoline in 48% yield.

b) 1-Aminobenzo[c]cinnoline

This was prepared from 1-nitrobenzo[c]cinnoline in 96% yield and was obtained as orange-red plates, m.p. 167.5-170° (lit.[52] 167-168°).

2.1.2 Unsuccessful attempt to prepare 1-aminobenzo[c]-cinnoline from 1-chlorobenzo[c]cinnoline

A mixture of 1-chlorobenzo[c]cinnoline (30mg), anhydrous ammonia (2ml), 95% ethanol (2ml) and copper sulphate (a few crystals) was heated in a stainless steel bomb at 270° for 2hr. Thin layer chromatographic analysis of the reaction mixture showed that mainly starting material along with small amounts of other products were present. This method was abandoned in favour of the one mentioned above.

2.2 2-Aminobenzo[c]cinnoline

a) Benzo[c]cinnoline-N-oxide

This was prepared in 74% yield from 2,2'-dinitrobiphenyl by the method of King and King.[115]

b) 2-Nitrobenzo[c]cinnoline-N-oxide

This was prepared in 37% yield from benzo[c]-cinnoline-N-oxide by the method of King and King[115] and was obtained as a lemon-coloured powder, m.p. 274-279° (lit.[115] 274-276°).

c) 2-Aminobenzo[c]cinnoline

This was prepared in 69% yield from 2-nitro-benzo[c]cinnoline-N-oxide by the method of Barton and Cockett[52] and was obtained as olive-green needles, m.p. 243.5-244.5° (lit.[52] 244-245°).

2.3.1 3-Aminobenzo[c]cinnoline

This was prepared by the method of Badger, Joshua and Lewis.[116]

a) 3-Nitroazobenzene

This was prepared in 72% yield from 3-nitro-aniline and nitrosobenzene and was obtained as orange needles, m.p. 94-97° (lit.[116] 96°).

b) 3-Aminoazobenzene

This was prepared in 38% yield from 3-nitroazobenzene and was obtained as orange-red needles, m.p. 66.5-68° (lit.[116] 68°).

c) 3-Aminobenzo[c]cinnoline

This was prepared in 6% yield from 3-aminoazobenzene and was obtained as red-brown needles, m.p. 161-163° (lit.[116] 163°).

2.3.2 Unsuccessful attempts to prepare 3-aminobenzo[c]cinnoline

2.3.2.1 From 2,4,2'-trinitrobiphenyl

a) 2,4,2'-Trinitrobiphenyl was prepared in 33% yield from 2,2'-dinitrobiphenyl by the method of Gull and Turner[117] and was obtained as cream needles, m.p. 145-151° (lit.[117] 150-151°).

b) Attempts to reduce 2,4,2'-trinitrobiphenyl to 3-aminobenzo[c]cinnoline with W-7 Raney nickel[118] and hydrazine hydrate by the method of Moore and Furst[119] failed. Hydrazine hydrate was used in molar ratios of 4:1, 6:1 and much higher ratios, but in each case investigation of the products by thin layer chromatography indicated that no 3-aminobenzo[c]cinnoline had been formed.

2.3.2.2 From 2,2'-diamino-4-nitrobiphenyl

a) 2,2'-Diaminobiphenyl was prepared in 74% yield from 2,2'-dinitrobiphenyl by the method of Lloyd and McDougall.[120]

b) 2,2'-Diamino-4-nitrobiphenyl was prepared from 2,2'-diaminobiphenyl by the method of Barton and Cockett[52] and distilled as an orange-red oil, b.p. 190-200°/0.35mm (lit.[52] 190-200°/0.35mm).

c)i) Attempts to convert 2,2'-diamino-4-nitrobiphenyl into 3-nitrobenzo[c]cinnoline-N-oxide with 80% w/v hydrogen peroxide by the method of Corbett and Holt[102] gave a complex mixture of products, and the method was abandoned.

ii) Attempts to convert 2,2'-diamino-4-nitrobiphenyl into 3-nitrobenzo[c]cinnoline with phenyliodosodiacetate by the method of Barton and Cockett[52] also gave a complex mixture of products, and the method was abandoned.

2.3.2.3 From 3-chlorobenzo[c]cinnoline

Several attempts were made to prepare 3-aminobenzo[c]cinnoline by heating 3-chlorobenzo[c]cinnoline and ammonia with and without traces of copper sulphate in a sealed tube. Only small amounts of the desired product as well as starting material and tars were observed in each case, and the method was abandoned. In a typical reaction

3-chlorobenzo[c]cinnoline (198mg), anhydrous ammonia (3ml), 95% ethanol (1ml) and copper sulphate (a few crystals) were heated in a sealed tube at 160° for 6hr. Analysis of the reaction mixture by thin layer chromatography showed the presence of a trace of 3-aminobenzo[c]cinnoline, some starting material and a large amount of tarry material.

2.4 4-Aminobenzo[c]cinnoline

4-Chlorobenzo[c]cinnoline (258mg), anhydrous ammonia (4ml), 95% ethanol (4ml) and copper sulphate (a few crystals) were heated in a sealed tube at 190° for 20hr. The reaction mixture was chromatographed on a plate of silica to give two main bands. The band with highest Rf value contained starting material (14mg). The material in the other band was subjected to counter-current distribution between 1M hydrochloric acid and light petroleum. Three fractions were obtained. The fastest fraction contained starting material (63mg) which, combined with that obtained from chromatography, gave a 30% recovery. The second fastest fraction contained benzo[c]cinnoline (81mg, 54%, based on unrecovered starting material). The slowest fraction contained 4-aminobenzo[c]cinnoline (52mg, 32%). On recrystallization from ethanol/water this was obtained as golden plates, m.p. 204.5-205.5° (lit.[52] 206-207°).

3. Apparatus

The reactions of the chloro- and iodobenzo[c]-cinnolines with potassium amide in ammonia were carried out in the apparatus shown in Fig. 2. Before use the apparatus was flame-dried while being flushed with dry nitrogen. Commercial anhydrous ammonia was distilled from the cylinder into flask A. The ammonia was dried by the addition of sodium metal and distilled into flask B. A known volume was transferred by nitrogen pressure *via* the graduated dropping funnel C into flask D, which contained dimethoxyethane. A known weight of potassium metal and a few crystals of ferric nitrate were added and the mixture was stirred until formation of potassium amide was complete. A known volume of the potassium amide solution was transferred by nitrogen pressure into flask F through the graduated dropping funnel E. A solution of the halogenobenzo[c]cinnoline in dimethoxyethane was then added from dropping funnel G.

4. Reactions of Halogenobenzo[c]cinnolines with Potassium amide in ammonia

All reactions were carried out in an atmosphere of dry nitrogen. Benzene and ether were sodium-dried. Dimethoxyethane was sodium-dried and distilled from lithium aluminium hydride immediately before use. Quantitative

analyses by gas-liquid chromatography were carried out using column A or B. A 20:1 excess of potassium amide to halogenobenzo[c]cinnoline was used in each reaction. No starting material was recovered in these reactions. Therefore yields are absolute. A similar procedure was followed in each reaction and the reaction of 3-iodobenzo[c]cinnoline with potassium amide in ammonia is typical.

4.1 Reaction of 3-Iodobenzo[c]cinnoline with Potassium amide in ammonia

A solution of potassium amide in ammonia was made by adding ammonia (180ml) to potassium (1.05g) and dimethoxyethane (15ml) in flask D of the apparatus shown in Fig.2. A portion (38ml) of this solution was transferred to flask F and to it was added, over 7min, a solution of 3-iodobenzo[c]cinnoline (50mg) in dimethoxyethane (15ml). An aqua colour developed immediately and deepened as the reaction proceeded. The reaction mixture was stirred for a total of 15min and was then rendered inactive by the addition of water. The mixture was extracted with chloroform; and the chloroform layer was then washed, dried over anhydrous magnesium sulphate, and evaporated to dryness. The residue was run through a column of alumina to remove grease residues and tars. 2,2'-Dinitrobiphenyl (7.04mg)

was added as standard; and the mixture was dissolved in methanol (5ml) and subjected to analysis by gas-liquid chromatography. The results of the reactions are given in Tables 12 and 13 below. In these tables "addition time" refers to the length of time during which the solution of halogenobenzo[c]cinnoline in dimethoxyethane was added to the solution of potassium amide in ammonia.

TABLE 12

Reactions of chlorobenzo[c]cinnolines with potassium amide in ammonia

Chloro-compd.	Addition time (min)	Total Reactn time (min)	Colour of Reactn Mixture	Yields (%) 1-NH_2	2-NH_2	3-NH_2	4-NH_2	Total
1-Cl	10	25	Orange	0	100	0	0	100
2-Cl	10	25	Orange	0	85	0	0	85
3-Cl a)	10	25	Green	0	0	40	15	55
3-Cl b)	10	25	Green	0	0	35	15	50
4-Cl	10	25	Green	0	5	20	3	30

TABLE 13

Reactions of iodobenzo[c]cinnolines with potassium amide in ammonia

Iodo-compd.	Addition time (min)	Total Reactn time (min)	Colour of Reactn Mixture	Percentage yields 1-NH_2	2-NH_2	3-NH_2	4-NH_2	Total
2-I	5	15	Orange	0	95	0	0	95
3-I	7	14	Aqua	0	0	90	1-2	90
4-I	5	15	Aqua	0	0	80	5	85

5. Product stability studies

The behaviour of the four isomeric aminobenzo[c]cinnolines with potassium amide in ammonia was studied under the same conditions as those used for the reactions with the halogenobenzo[c]cinnolines. Analysis of the reaction mixtures by thin layer chromatography and by gas-liquid chromatography showed that in each case no reaction had taken place.

6. Reaction of 3-Chlorobenzo[c]cinnoline with potassium amide in ammonia (in which apparatus shown in Fig.2 was not used)

Ammonia (80ml) was introduced into a 250ml

2-necked flask and dried with sodium metal. The ammonia was distilled *via* a glass U-tube into another 250ml, 2-necked flask containing dimethoxyethane (20ml). The flask was fitted with a soda-lime drying tube, ammonia condenser and a magnetic stirrer. Potassium metal (220mg) and ferric nitrate (a few crystals) were added, and the mixture was stirred. When the formation of potassium amide was complete, a solution of 3-chlorobenzo[c]cinnoline (55mg) in dimethoxyethane (20ml) was added over 30min. A dark green coloration developed. The mixture was stirred for another 15min and then water (40ml) was added and the mixture subjected to the usual working-up procedure. Azobenzene (4.3mg) was added as an internal standard and the mixture was analysed by gas-liquid chromatography. The results of the reaction are given in Table 14 below.

TABLE 14

Reaction of 3-chlorobenzo[c]cinnoline with potassium amide in ammonia

Molar Ratio KNH_2	Addition time (min)	Total Reaction time (min)	% Reactn	Benzo c - cinn.	3-NH_2	4-NH_2	Total
20	30	45	100	28	31	28	87

PART III

FURTHER AROMATIC NUCLEOPHILIC SUBSTITUTION REACTIONS

Some of the work dealt with in Part III of Results and Discussion has already been described in earlier Experimental sections.

1. Starting materials

1.1 2,3-Dichloroazobenzene

This was prepared in 19% yield from 2,3-dichloroaniline and nitrosobenzene by the method of Stieglitz.[111] It was recrystallized from benzene and obtained as orange needles, m.p. 73.5-74.5° (Found: C, 57.7; H, 3.2; N, 11.0. $C_{12}H_{18}Cl_2N_2$ requires C, 57.4; H, 3.2; N, 11.2%). Mass spectrum: m/e 252, 250 (M^+). ($C_{12}H_{18}Cl_2N_2$ requires M^+ 252, 250).

1.2 3,4-Dichlorobenzo[c]cinnoline

This was prepared in 14% yield from 2,3-dichloroazobenzene by the method of Lewis.[112] It was recrystallized from benzene and ethanol to give olive-green needles, m.p.

268-269° (Found: C, 57.8; H, 2.4; N, 11.1. $C_{12}H_{16}Cl_2N_2$ requires C, 57.8; H, 2.4; N, 11.3%). Mass spectrum: m/e 250, 248 (M^+). $C_{12}H_{16}Cl_2N_2$ requires M^+ 250, 248.

1.3 6-Chlorophthalazine

This was prepared by the method of Favini and Simonetta.[121]

1.3.1 3,4-Dimethylchlorobenzene

This was prepared in 60% yield from 3,4-dimethylaniline by the method of Lyon and Mann.[122]

1.3.2 ∝,∝,∝',∝'-Tetrabromo-3,4-dimethylchlorobenzene

This was prepared in 50% yield from 3,4-dimethylchlorobenzene by the method of Bill and Tarbell.[123] N.m.r. spectrum: ∂ 6.8 (s, 1H, aliphatic $CHBr_2$); 6.9 (s, 1H, aliphatic $CHBr_2$); 7.1-7.3 (dd, 1H, aromatic H); 7.4-7.6 (m, 2H, aromatic H).

1.3.3 4-Chloro-o-phthalaldehyde

This was prepared in 55% yield from , , ', '-tetrabromo-3,4-dimethylchlorobenzene by the method of Bill and Tarbell.[123] N.m.r. spectrum: ∂ 7.6-8.0 (m, 3H, aromatic H); 10.3 (s, 1H, aliphatic CH=O); 10.4 (s, 1H, aliphatic CH=O).

1.3.4 6-Chlorophthalazine

This was prepared in 40% yield from 4-chloro-o-phthalaldehyde and was obtained as a brown powder, m.p. 134-135.5° (lit.[121] 132°). N.m.r. spectrum: ∂ 7.9-8.1 (m, 3H, aromatic H); 9.5 (s, 2H, aromatic H [heterocyclic ring]).

1.4 4-Chlorocinnoline

This was prepared by the method of Leonard and Boyd.[124]

1.4.1 4-Hydroxycinnoline

This was prepared in 20% yield from o-amino-acetophenone. It was sublimed at 170° and recrystallized from ethanol to give white crystals of 4-hydroxycinnoline, m.p. 231-233° (lit.[124] 232-233°).

1.4.2 4-Chlorocinnoline

This was prepared in 80% yield from 4-hydroxy-cinnoline and was recrystallized from light petroleum, b.p. 60-80° to give yellow-brown needles, m.p. 74.5-76° (lit.[124] 75-76°).

2. Reaction of 3,4-dichlorobenzo[c]cinnoline with dimethylamine

A mixture of 3,4-dichlorobenzo[c]cinnoline (29mg) and dimethylamine (3ml) was heated in a sealed Pyrex tube at 150° for 2hr. The mixture was chromatographed on a plate of silica to give 3-chloro-4-dimethylaminobenzo[c]-cinnoline (20mg, 67%) as yellow needles, m.p., mixed m.p. 130-131°.

3. Reactions of the Chlorobenzo[c]cinnolines with piperidine

3.1 1- and 3-Chlorobenzo[c]cinnolines

The procedure followed was the same for each chlorobenzo[c]cinnoline.

A mixture of the chlorobenzo[c]cinnoline (3mg) and piperidine (1ml) was heated under reflux for 5hr. Analysis of the reaction mixture by thin layer chromatography showed that only starting material was present.

3.2 2-Chlorobenzo[c]cinnoline

A mixture of 2-chlorobenzo[c]cinnoline (51mg) and piperidine (6ml) was heated under reflux for 5hr. At the end of this time piperidine was removed and the residue was chromatographed on a plate of silica, developing with

ether/benzene (3:1). Isolation of the two major bands on the plate gave 2-chlorobenzo[c]cinnoline (42mg, 82%) and 2-piperidinobenzo[c]cinnoline (6.5mg, 10%). The latter compound was recrystallized from ethanol and obtained as orange-yellow needles, which showed two melting points, one at 126-128° and one at 134.5-135.5°. (Found: C, 77.9; H, 6.5. $C_{17}H_{17}N_3$ requires C, 77.6; H, 6.5%). N.m.r. spectrum: δ 1.5-2.6 (m, 6H, aliphatic CH_2); 3.3-4.3 (m, 4H, aliphatic N-CH_2); 7.3-7.9 (m, 4H, aromatic H); 8.3-8.7 (m, 3H, aromatic H). Ultraviolet-visible spectra: λmax EtOH: 250, 265, 315, 400nm; 20% EtOH/0.2M sulphuric acid: 240, 275, 325, 340, 480nm; 20% EtOH/98% sulphuric acid: 245, 355, 400nm. Mass spectrum: m/e 263 (M^+). ($C_{17}H_{17}N_3$ requires M^+ 263).

3.3 4-Chlorobenzo[c]cinnoline

A mixture of 4-chlorobenzo[c]cinnoline (27mg) and piperidine (3ml) was heated under reflux for 5hr. At the end of this time piperidine was removed and the residue was chromatographed on a plate of silica, developing with benzene. Isolation of the first major band gave 4-chlorobenzo[c]cinnoline (10mg, 42%) which was recrystallized from ethanol to give yellow needles, m.p., mixed m.p., 192-193° (lit.[110] 191-192°). The second major band from the plate

contained 4-piperidinobenzo[c]cinnoline (17mg, 54%) which was recrystallized from ethanol to give orange prisms, m.p., mixed m.p. 138-141°.

4. Attempted reaction of 6-Chlorophthalazine with lithium dimethylamide in dimethylamine

This reaction was attempted several times but in each case only starting material was obtained. A typical procedure was as follows.

A solution of lithium dimethylamide was made by adding a mixture of lithium (210mg) and n-butylbromide (2.01g) in ether to dimethylamine (15ml). A solution of 6-chlorophthalazine (55mg) in dimethoxyethane (20ml) was added over 15min and the mixture was stirred for a further 15min. No immediate colouration was observed but the reaction mixture had turned a dark brown after 10min. After a reaction time of 30min, water was added and the mixture was extracted with chloroform. The solvent was removed and the residue purified by chromatography on a short column of alumina. Investigation of the eluted substance by thin layer chromatography indicated that only starting material was present. N.m.r. spectrum: δ 7.9-8.1 (m, 3H, aromatic H); 9.5 (s, 2H, aromatic H [heterocyclic ring]).

5. Reaction of 4-Chlorocinnoline with piperidine

A solution of 4-chlorocinnoline (40mg) in piperidine (0.2ml) was warmed on a water bath for 1min. Piperidine was removed to give a cream solid, believed to be 4-piperidinocinnoline, which recrystallized from chloroform/benzene/light petroleum as white needles (21mg, 36% after recrystallization), m.p. 245-247°. Mass spectrum: m/e 213 (M^+). ($C_{13}H_{15}N_3$ requires M^+ 213).

6. Reaction of 4-Chlorocinnoline with lithium piperidide in piperidine

This reaction was carried out several times and a typical procedure was as follows.

A solution of lithium piperidide in piperidine was prepared from a solution of n-butyllithium in hexane (8ml, 0.8M) and piperidine (5ml). 4-Chlorocinnoline (105mg) in dimethoxyethane (10ml) was added over 1min at 20°C. The mixture turned a dark mauve-blue colour on addition of the cinnoline. After 10min, water (5ml) was added and the mixture extracted with chloroform and the solvent removed to give a dark brown residue. Investigation of this by thin layer chromatography showed that the mixture consisted of two major components, neither of which was starting material. One of these components showed the same Rf value as that of the compound obtained in the reaction of

4-chlorocinnoline with piperidine, thought to be 4-piperidinocinnoline. The residue was chromatographed on a plate of silica developing with ether/X4/benzene (1:1:1). The two major bands were removed and chromatographed on plates of silica developing with ether/light petroleum (1:1). Only small amounts of oils were obtained from each plate and these could not be identified.

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