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# Benzo[*c*]cinnoline Derivatives. VII* Reactions of Benzo[*c*]cinnoline and Chlorobenzo[*c*]cinnolines with Lithium Dimethylamide

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*Abstract*

The reactions of the four isomeric chlorobenzo[*c*]cinnolines and unsubstituted benzo[*c*]cinnoline with lithium dimethylamide in dimethylamine lead to the formation of complex product mixtures. Dimethylaminations occur as primary reactions at the 4- and 7-positions of the benzo[*c*]cinnoline nucleus; these involve displacement of hydrogen even when a chloro substituent is attached to another position in the same ring. Nucleophilic displacement of chloro substituents (in most instances as secondary reactions) appears to involve both direct (AE) substitution and EA cinesubstitution. With the 2-chloro compound 1,3-telesubstitution occurs as a primary reaction.

## Introduction

The reaction of 2-chlorobenzo[*c*]cinnoline with lithium dimethylamide in dimethylamine has been reported[1] as giving rise to two unexpected products, namely the 1,3-telesubstitution compound 4-dimethylaminobenzo[*c*]cinnoline (major product) and 2,4,7-tris(dimethylamino)benzo[*c*]cinnoline (minor product). In its reaction with dimethylamine alone, however, 2-chlorobenzo[*c*]cinnoline gives only the 2-dimethylamino compound.[2] The 1-, 3- and 4-chloro compounds with dimethylamine alone are likewise converted simply into the expected dimethylamino compounds with no sign of either 1,3-telesubstitution or 1,2-cinesubstitution.[3] Unsubstituted benzo[*c*]cinnoline has also been found[1] to react with lithium dimethylamide in dimethylamine giving 4-dimethylaminobenzo[*c*]cinnoline. In this case, however, the yield of the 4-dimethylamino compound was considerably higher than that obtained from the 2-chloro compound.

The reaction of 2-chlorobenzo[*c*]cinnoline with potassium amide[4] does not follow a parallel course to the reaction of the same compound with lithium dimethylamide, as 2-aminobenzo[*c*]cinnoline (85% yield) is the only detectable product. Moreover, the reactions of the 1-, 3- and 4-chloro compounds with potassium amide under similar conditions[4] result in varying degrees of 1,2-cinesubstitution; a small amount of 1,3-telesubstitution occurs in the case of the 4-chloro compound, yielding 2-aminobenzo[*c*]cinnoline.

* Part VI, *Aust. J. Chem.*, 1975, **28**, 2057.

[1] Lewis, G. E., and Reiss, J. A., *Aust. J. Chem.*, 1968, **21**, 1043.
[2] Lewis, G. E., and Reiss, J. A., *Aust. J. Chem.*, 1967, **20**, 1451.
[3] Lewis, G. E., and Reiss, J. A., *Aust. J. Chem.*, 1967, **20**, 2217.
[4] Lewis, G. E., Prager, R. H., and Ross, R. H. M., *Aust. J. Chem.*, 1975, **28**, 2057.

In view of these findings further studies were made of the reactions of the four isomeric chlorobenzo[*c*]cinnolines and of unsubstituted benzo[*c*]cinnoline with lithium dimethylamide in dimethylamine. The results as now reported have revealed additional anomalies, particularly in comparison with the reactions involving potassium amide.

**Results and Discussion**

It was found in the preliminary stages of the present studies that each of the four chlorobenzo[*c*]cinnolines, (1)–(4), gives a mixture of products on reaction with lithium dimethylamide in dimethylamine and that the composition of the product mixture in most cases varies markedly according to the time over which the reaction is allowed to run. Small-scale preparative experiments were carried out with each compound over different periods of reaction time; the individual compounds finally present in each reaction mixture were, as far as practicable, isolated and identified.

The samples of products, which were used both for elucidation of molecular structures and for subsequent preparation of standard reference mixtures for quantitative gas–liquid chromatographic analysis, were obtained as follows.

The 4-dimethylamino compound (6) and the 2-chloro-4-dimethylamino compound (13) were isolated from a short-period preparative scale reaction (*c.* 5 min) of the 2-chloro compound (2). The 2,4-bis(dimethylamino) compound (7) and the 2,4,7-tris-(dimethylamino) compound (9) were isolated from a longer-period reaction (*c.* 135 min) of the 2-chloro compound.

The 4,7-bis(dimethylamino) compound (8) was isolated from the reaction of benzo[*c*]cinnoline (5) over a 15 h period.

The 1-chloro-4-dimethylamino compound (10) and the 1-chloro-7-dimethylamino compound (11) were isolated from a short-period reaction (*c.* 10 min) of the 1-chloro compound (1). The 1-chloro-4,7-bis(dimethylamino) compound (12) was isolated from a reaction of the same starting compound run over a 5 h period.

Compounds (10) and (11) could not be separated completely in the working-up procedures; but sufficient partial separation was achieved by countercurrent distribution to enable workable quantities of the respective compounds to be isolated in a pure state from the opposite fringes adjoining the overlap zone.

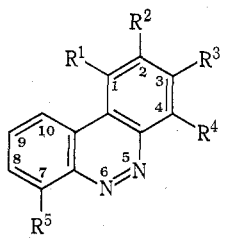
The 3-chloro-4-dimethylamino compound (15) and the 3-chloro-7-dimethylamino compound (16) were isolated from a reaction of the 3-chloro compound (3) run over a 15 min period. The 4-chloro-7-dimethylamino compound (17) was isolated in 62% yield from a reaction of the 4-chloro compound (4) run over a 10 min period. The 4-dimethylamino compound (6) was also isolated in 26% yield from this reaction.

The methods used for identification of the products, (6)–(13) and (15)–(17), are discussed under a separate heading below.

Following the preparative experiments it was shown by gas–liquid chromatography that the 4-dimethylamino compound (6) was also formed from the 3-chloro compound (3) in appreciable yield. Compound (8) was found also to arise from the 2-chloro compound (2), as well as from the unsubstituted compound (5), after long reaction times. Likewise, compounds (7) and (9) were found to arise in trace quantities from compounds (1) and (4), as well as in more substantial quantities from the 2-chloro compound.

Because of the complex variations in product composition the reactions of all the starting compounds, (1)–(5), were subsequently carried out under standard conditions

for the purpose of quantitatively monitoring the product mixtures at increasing time-intervals from the moment of commencement of reaction. Aliquots of reaction mixture were removed at intervals ranging from 0·1 min upwards; the product mixture present in each aliquot (after quenching with water) was analysed by gas–liquid chromatography with a column which had been calibrated with standard mixtures quantitatively prepared from the appropriately identified samples of the individual compounds obtained in the preparative experiments. The products (and yields) found to be present in the reaction mixtures obtained from the chlorobenzo[*c*]cinnolines at different reaction times are detailed in Tables 1–4.




| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ |
|---|---|---|---|---|---|
| (1) | Cl | H | H | H | H |
| (2) | H | Cl | H | H | H |
| (3) | H | H | Cl | H | H |
| (4) | H | H | H | Cl | H |
| (5) | H | H | H | H | H |
| (6) | H | H | H | $NMe_2$ | H |
| (7) | H | $NMe_2$ | H | $NMe_2$ | H |
| (8) | H | H | H | $NMe_2$ | $NMe_2$ |
| (9) | H | $NMe_2$ | H | $NMe_2$ | $NMe_2$ |

| | $R^1$ | $R^1$ | $R^3$ | $R^4$ | $R^5$ |
|---|---|---|---|---|---|
| (10) | Cl | H | H | $NMe_2$ | H |
| (11) | Cl | H | H | H | $HMe_2$ |
| (12) | Cl | H | H | $NMe_2$ | $NMe_2$ |
| (13) | H | Cl | H | $NMe_2$ | H |
| (14) | H | Cl | H | H | $NMe_2$ |
| (15) | H | H | Cl | $NMe_2$ | H |
| (16) | H | H | Cl | H | $NMe_2$ |
| (17) | H | H | H | Cl | $NMe_2$ |

As shown in Table 1, 1-chlorobenzo[*c*]cinnoline (1) reacted with a tenfold excess of lithium dimethylamide to the extent of 73% within 0·1 min to give a mixture of 1-chloro-4-dimethylaminobenzo[*c*]cinnoline (10) and the 1-chloro-7-dimethylamino compound (11), the combined yields of which amounted to 72% calculated on the basis of the quantity (73%) of starting material actually consumed. It was not possible to separate compounds (10) and (11) by the g.l.c. method of analysis; hence the individual yields could not be determined. However, in earlier preparative scale experiments an n.m.r. spectrum of a mixture of the two isomers indicated that the 1-chloro-4-dimethylamino compound had been formed in greater yield. The combined yields of compounds (10) and (11) decreased markedly with increased time of reaction. Eventually, small amounts of the 1-chloro-4,7-bis(dimethylamino) compound (12) and traces of the 2,4-bis(dimethylamino) compound (7) and of the 2,4,7-tris(dimethylamino) compound (9) were detected. At the same time the yield of intractable products appeared to increase.

The reaction of 2-chlorobenzo[*c*]cinnoline (2) with a 10-fold excess of lithium dimethylamide, as shown in Table 2, was complete within a matter of seconds. The products formed initially, namely the 4-dimethylamino compound (6) and 2-chloro-4-dimethylaminobenzo[*c*]cinnoline (13), accounted for over 90% of the totally consumed starting material. With increased reaction time the yields of compounds (6) and (13) fell as a result of subsequent reactions; this was accompanied by the appearance of

**Table 1. Yields of products from the reaction of 1-chlorobenzo[*c*]cinnoline (1) with a 10-fold excess of lithium dimethylamide in dimethylamine**

| Reaction time (min) | Extent of reaction (%) | Product yields (%)[A] (10) and (11)[B] | (12) | (7) | (9) |
|---|---|---|---|---|---|
| 0·1 | 73 | 72 | 0 | — | — |
| 20 | 88 | 60 | 0 | — | — |
| 120 | 95 | 40 | 3 | trace | trace |
| 450 | 100 | 25 | 15 | trace | trace |

[A] Based on the quantity of 1-chlorobenzo[*c*]cinnoline consumed (column 2).
[B] The individual yields of compounds (10) and (11) could not be determined (see text).

**Table 2. Yields of products from the reaction of 2-chlorobenzo[*c*]cinnoline (2) with a 10-fold excess of lithium dimethylamide in dimethylamine**

| Reaction time (min) | Extent of reaction (%) | Product yields (%) (6) | (13) | (8) | (7) | (9) |
|---|---|---|---|---|---|---|
| 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 3. Yields of products from the reaction of 3-chlorobenzo[*c*]cinnoline (3) with excess of lithium dimethylamide in dimethylamine**

| $LiNMe_2$ molar excess | Reaction time (min) | Extent of reaction (%) | Product yields[A] (6) | (15) | (16) |
|---|---|---|---|---|---|
| 10 | 0·1 | 69 | 7 | 51 | 30 |
| 10 | 60 | 77 | 6 | 44 | 29 |
| 10 | 120 | 78 | 7 | 48 | 33 |
| 20 | 0·1 | 66 | 12 | 52 | 30 |
| 20 | 20 | 94 | 15 | 30 | 21 |

[A] Based on the quantity of 3-chlorobenzo[*c*]cinnoline consumed (column 3).

**Table 4. Yields of products from the reaction of 4-chlorobenzo-[*c*]cinnoline (4) with a tenfold excess of lithium dimethylamide in dimethylamine**

| Reaction time (min) | Product yields (%)[A] (6) | (17) | (8) | (7) | (9) |
|---|---|---|---|---|---|
| 0·1 | —[B] | 19 | — | — | — |
| 25 | —[B] | 24 | — | — | — |
| 60 | —[B] | 8 | 9 | trace | trace |
| 120 | —[B] | 2 | 14 | trace | trace |

[A] Based on the total quantity of starting compound (4) employed.
[B] The yields of 4-dimethylaminobenzo[*c*]cinnoline could not be determined by g.l.c. analysis; but the compound was obtained in 26% yield in a preparative scale reaction of 4-chlorobenzo[*c*]cinnoline run over a 15 min period.

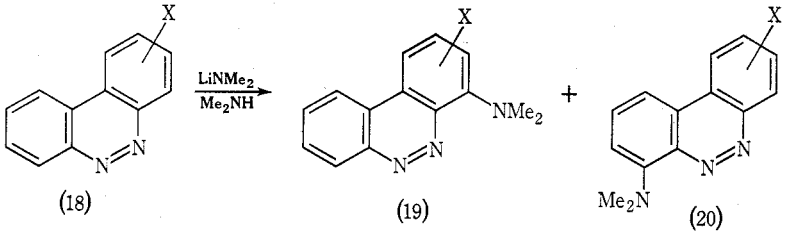
2,4-bis(dimethylamino)benzo[*c*]cinnoline (7), the 2,4,7-tris(dimethylamino) compound (9), and the 4,7-bis(dimethylamino) compound (8). There was no evidence that 2-chloro-7-dimethylaminobenzo[*c*]cinnoline (14) had been formed in this reaction, which was surprising in view of the formation of both 4- and 7-dimethylamino derivatives from 1-chloro- and from 3-chloro-benzo[*c*]cinnoline (see Tables 1 and 3).

As shown in Table 3, 3-chlorobenzo[*c*]cinnoline (3) reacted with a tenfold excess of lithium dimethylamide to give, in order of decreasing yield, the 3-chloro-4-dimethylamino compound (15), the 3-chloro-7-dimethylamino compound (16), and the 4-dimethylamino compound (6). In the reaction with a 20-fold excess of lithium dimethylamide the same products were formed, but the yield of 4-dimethylaminobenzo-[*c*]cinnoline increased in relation to the yields of the major co-products, (15) and (16).

Table 4 summarizes the results of the monitored reaction of 4-chlorobenzo[*c*]-cinnoline (4) with a tenfold excess of lithium dimethylamide. Although the 4-dimethylamino compound (6) was isolated in substantial yield in a preparative experiment starting with the 4-chloro compound, it could not be separated from unchanged 4-chlorobenzo[*c*]cinnoline by the g.l.c. analytical procedure in the case of the monitored reaction. The percentage yields of the other products given in Table 4 are therefore based on the total amount of starting material employed.

The monitored reaction of benzo[*c*]cinnoline (5) with a tenfold excess of lithium dimethylamide indicated that *c.* 70% of the compound had reacted within 0·1 min to give 4-dimethylaminobenzo[*c*]cinnoline (6) as the only detectable product in 95% yield (based on the quantity of benzo[*c*]cinnoline consumed). Essentially the same result was obtained after 60 min reaction time. In a preparative experiment, however, benzo[*c*]cinnoline was found to have given rise to the 4,7-bis(dimethylamino) compound (8) in 12% yield after reaction with lithium dimethylamide for 15 h.

The formation of the complex product mixtures in the reactions of the four chlorobenzo[*c*]cinnolines and benzo[*c*]cinnoline with lithium dimethylamide can be rationalized to a large degree in terms of 4- and 7-dimethylamination being primary reactions (Scheme 1; X = H or Cl in the 1-, 2-, 3- or 4-position) which are followed by secondary reactions of the products (19) and (20).




Scheme 1

The reactions of 2- and 3-chlorobenzo[*c*]cinnoline leading to the 4-dimethylamino compound (6) are however exceptional. Nevertheless, it is possible that both of these reactions involve the same types of intermediates as those participating in the reactions [(18) → (19)] (see discussion below).

The primary reactions summarized in Scheme 1 require displacement of an hydride ion from an aromatic nucleus in preference to a chloride ion, even when the chloro substituent is attached to the same ring as that vacated by the hydride ion. Although

not completely unprecedented,[5] this is surprising because a chloro substituent is normally regarded as a far better nucleofugal leaving group than hydrogen. Moreover, no comparable hydride-ion displacement was observed in the reactions of the chlorobenzo[*c*]cinnolines with potassium amide.[4] In addition, there is ample evidence[6–9] that halide ions are usually displaced in nucleophilic reactions of lithium dialkylamides with heterocyclic aryl halides.

It might reasonably be predicted that the order of susceptibility of the different ring-positions of the benzo[*c*]cinnoline nucleus towards nucleophilic attack would be the reverse of the order for electrophilic attack. Charge-density calculations made for the benzo[*c*]cinnoline nucleus by Longuet-Higgins and Coulson[10] and by Dewar and Maitlis[11] would then predict the order of susceptibility towards nucleophilic attack as: 2- > 4- > 3- > 1-position. Pullman's[12] calculations, however, would indicate the order as: 4- > 2- > 3- > 1-position. In either case, comparable reactivity at the 2- and the 4-position could be expected, in the absence of any complicating factors.

It is concluded therefore that there are special effects operating during the reactions of the benzo[*c*]cinnolines with lithium dimethylamide in dimethylamine which greatly facilitate nucleophilic attack and consequent hydride-ion displacement at the 4- and 7-positions.

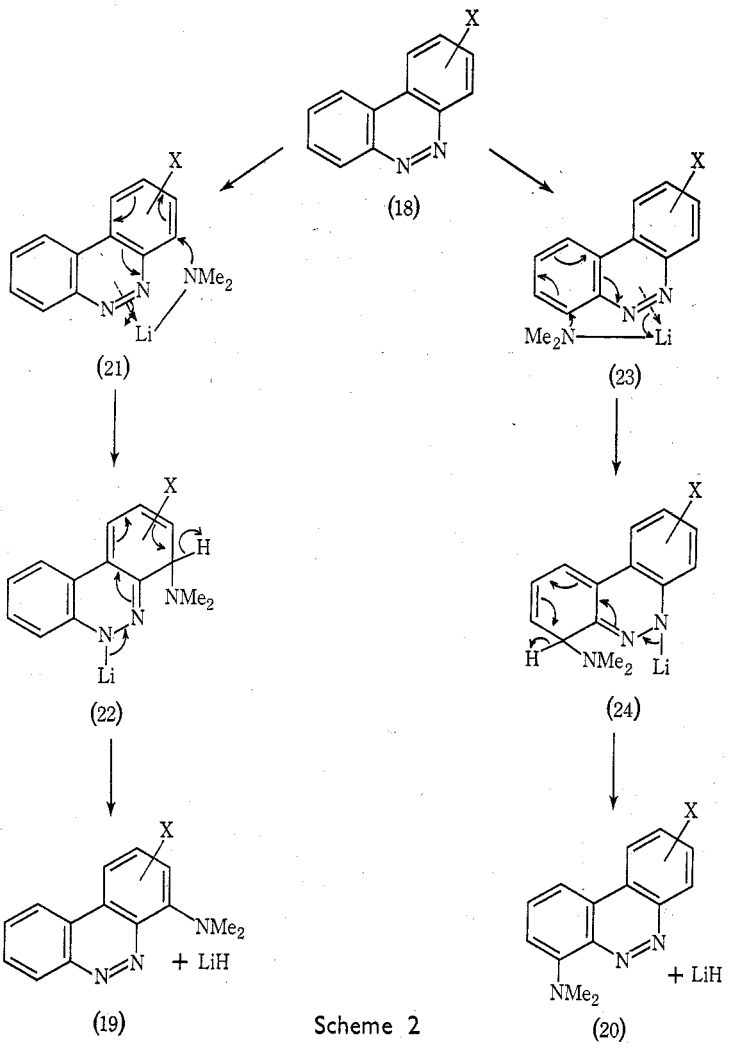
On the assumption that lithium dimethylamide under the reaction conditions employed is probably associated (cf. the aggregation of lithium cyclohexylamide as ion-pairs in solution in cyclohexylamine[13–15]) and that a complex is formed between lithium dimethylamide and each benzo[*c*]cinnoline derivative at the 5,6-diaza linkage, a mechanism can be postulated (see Scheme 2) to account for the 4- and 7-dimethylaminations in Scheme 1.

Essential features of the mechanism proposed in Scheme 2 are: (*a*) the formation of a $\pi$-complex which could adopt the alternative conformations, (21) and (23), whereby the dimethylamino group could be held in reasonable proximity to the 4- or the 7-position; (*b*) transformation of the $\pi$-complex into the $\sigma$-complexes (22) and (24), in which the dimethylamino group becomes attached to the 4- and to the 7-position respectively; and (*c*) loss of lithium hydride (or its mechanistic equivalent) to yield the 4- and 7-substituted products (19) and (20), either during the course of the reaction or at the termination stage when the reaction mixture is quenched with water.

The formation of such complexes would account also for the colorations observed during the reactions of benzo[*c*]cinnoline and its chloro derivatives with lithium dimethylamide. In each case, a transient deep red-purple coloration occurs immediately the reactants are mixed; this is quickly replaced by an intense dark green colour, which persists until the reaction is terminated. The red-purple colour is thought to be

[5] Gilman, H., and Spatz, S. M., *J. Amer. Chem. Soc.*, 1944, **66**, 621.
[6] Kauffmann, T., and Boettcher, F. P., *Chem. Ber.*, 1962, **95**, 1528.
[7] Kauffmann, T., Boettcher, F. P., and Hansen, J., *Justus Liebigs Ann. Chem.*, 1962, **659**, 102.
[8] Kauffmann, T., Hansen, J., and Wirthwein, R., *Justus Liebigs Ann. Chem.*, 1964, **680**, 31.
[9] Kauffmann, T., *Angew. Chem., Int. Ed. Engl.*, 1965, **4**, 543.
[10] Longuet-Higgins, H. C., and Coulson, C. A., *J. Chem. Soc.*, 1949, 971.
[11] Dewar, M. J. S., and Maitlis, P. M., *J. Chem. Soc.*, 1957, 2521.
[12] Pullman, A., *Rev. Sci.*, 1948, **86**, 219 (*Chem. Abstr.*, 1959, **43**, 2095b).
[13] Streitwieser, A., Caldwell, R. A., Granger, M. R., and Laughton, P. M., *J. Phys. Chem.*, 1964, **68**, 2916.
[14] Streitwieser, A., and Padget, W. M., *J. Phys. Chem.*, 1964, **68**, 2919.
[15] Streitwieser, A., Padget, W. M., and Schwager, I., *J. Phys. Chem.*, 1964, **68**, 2922.

due to $\pi$-complexes, (21) or (23), and the green colour to $\sigma$-complexes, (22) and (24), or other complexes such as (22a) referred to below. It may be noted that the benzo-[*c*]cinnoline–dilithium adduct described by Wittig[16] is dark green. During preliminary investigations of these reactions, in which very small quantities of lithium dimethyl-amide were employed in relation to the quantity of substrate, only the red-purple coloration was observed. Only starting material was recovered from such reactions.

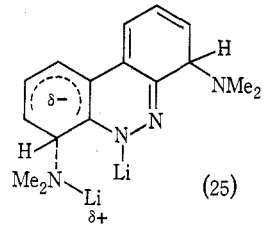



Scheme 2

It is considered that the conversion of the $\sigma$-complex intermediates (22) and (24) into the corresponding products (19) and (20), through elimination of lithium hydride, must occur to a significant extent during the course of reaction so as to allow for the observed secondary reactions, e.g. the formation of 4,7-bis(dimethylamino)benzo[*c*]-cinnoline (8) from the 4-dimethylamino compound (6). Secondary substitution in a

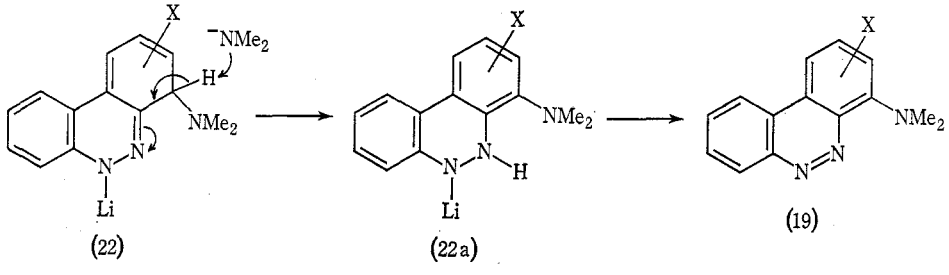
[16] Wittig, G., Jesaitis, M. A., and Glos, M., *Justus Liebigs Ann. Chem.*, 1952, **577**, 1.

$\sigma$-complex *per se*, e.g. (22), would seem to be unlikely on the grounds that the transition state, e.g. (25), for such a reaction could not be stabilized by delocalization of the negative charge to a ring-nitrogen atom.




(25)

In view of the formation of dihydroaromatics in the addition reactions of butyllithium to pyridine, quinoline, isoquinoline and acridine,[17] the rapid loss of lithium hydride during the reactions of lithium dimethylamide with benzo[*c*]cinnoline derivatives might appear questionable. It is suggested, however, that the driving force for such facile loss of lithium hydride could arise from the rearrangement of the initially formed $\sigma$-complex (22) (under the strong basic conditions employed) into (22a) (see Scheme 3), with considerable gain in resonance stabilization and subsequent restoration of the total aromatic system through loss of lithium hydride.




(22) (22a) (19)

Scheme 3

Although the mechanism proposed in Scheme 2 is consistent with predominant 4- and 7-dimethylamination, this does not preclude the possibility that coordination between lithium dimethylamide and a benzo[*c*]cinnoline molecule at the diaza linkage may activate other ring positions (notably the 2- and 9-positions) towards attack by another molecule (or aggregate of molecules) of lithium dimethylamide.

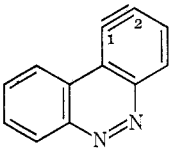
The fact that the corresponding displacement of hydride ions from the 4- and 7-positions of halogenobenzo[*c*]cinnolines in the reactions with potassium amide[4] did not occur can be attributed to the greater degree of dissociation of potassium amide.[18]

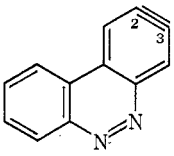
The loss of a chloro substituent in secondary reactions of the primary products (19 and 20; X = Cl) can be attributed to nucleophilic displacement by a dimethylamino group, either through direct addition–elimination (AE substitution) or through an elimination–addition (EA) mechanism involving a substituted 1,2-aryne intermediate.

Of the possible 1,2-arynes, (26), (27) and (28), derivable from 1-, 2-, 3- and 4-halogenobenzo[*c*]cinnolines, (26) and (28) are expected to arise in preference to (27)

[17] Ziegler, K., and Zeiser, H., *Justus Liebigs Ann. Chem.*, 1931, **485**, 174.
[18] Caruso, J. A., Takemoto, J. H., and Lagowski, J. J., *Spectrosc. Lett.*, 1968, **1**, 311.

from 2- and 3-halogenobenzo[c]cinnolines, respectively.[4] In some of the secondary reactions of (19) and of (20), dimethylamino-substituted arynes could be involved.


(26)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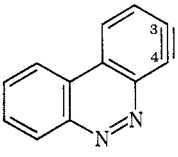
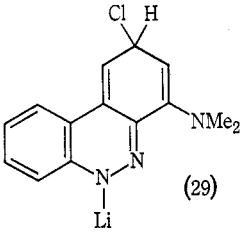
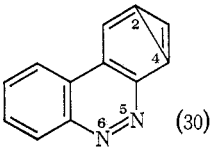

(28)

The initial formation of 1-chloro-4-dimethylaminobenzo[c]cinnoline (10) and the isomeric 1-chloro-7-dimethylamino compound (11) as the major products from 1-chlorobenzo[c]cinnoline (Table 1) is consistent with the mechanism proposed in Scheme 2. The 1-chloro-4,7-bis(dimethylamino) compound (12), which appeared in appreciable yields after longer reaction times, undoubtedly arises through subsequent dimethylamination of the primary products (10) and (11), the latter in all probability being formed in the free state during the course of reaction through elimination of lithium hydride from the precursory $\sigma$-complexes. Trace amounts of other products from 1-chlorobenzo[c]cinnoline were also observed after longer reaction times. One of these, the 2,4-bis(dimethylamino) compound (7), was probably formed from compound (10) by replacement of the chloro substituent in an EA (cinesubstitution) reaction, via 4-dimethylamino-1,2-dehydrobenzo[c]cinnoline, with the incoming dimethylamino group becoming attached exclusively to the 2-position. Support for this proposal comes from the fact that 1-chlorobenzo[c]cinnoline reacts with potassium amide in ammonia giving 2-aminobenzo[c]cinnoline exclusively.[4] Another trace product, the 2,4,7-tris(dimethylamino)compound (9), could have been formed through 7-dimethylamination of compound (7) or through EA displacement of the 1-chloro substituent in compound (12), with the incoming dimethylamino group again becoming attached exclusively to the 2-position.

The major product detected in the early stages of the monitored reaction of 2-chlorobenzo[c]cinnoline (2) was the previously reported[1] 1,3-telesubstitution compound (6). One mechanism already suggested[1] for this interconversion involves essentially the transformation of the $\sigma$-complex (22; X = 2-Cl) into another intermediate (29), which latter should then yield the 4-dimethylamino compound (6) on loss of lithium chloride.


(29)


(30)

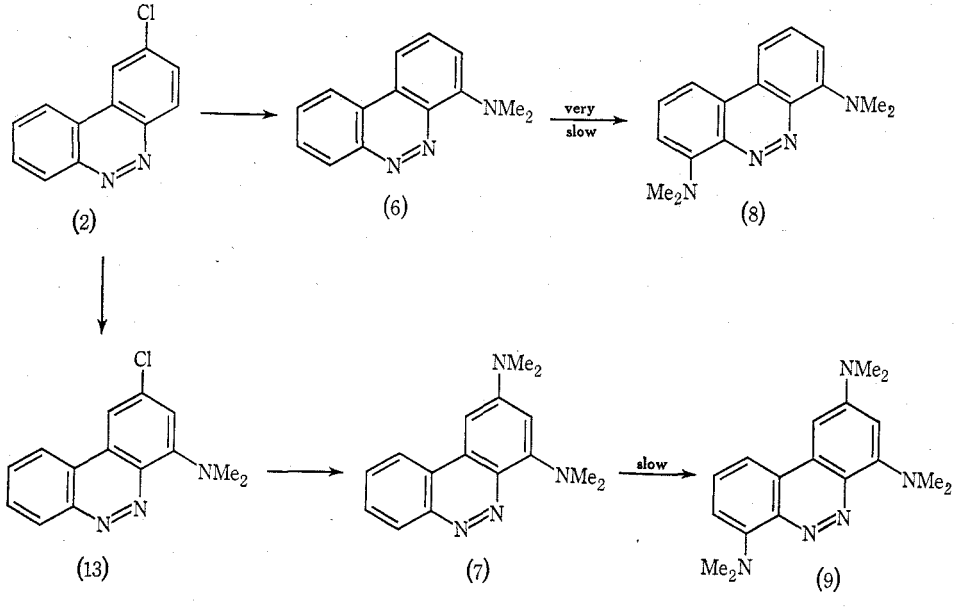
The suggested rearrangement of (22; X = 2-Cl) into (29) may be compared with the rearrangement [(22) → (22a)] shown in Scheme 3; but the driving force for rearrangement leading to (29) is attributed to the greater stability of the *p*-quinonoid structure (29) over the *o*-quinonoid structure (22).

A possible alternative mechanism of the EA type, involving participation of 2,4-dehydrobenzo[*c*]cinnoline (30) as an intermediate, must be considered (cf. the formation of 2-aminobenzo[*c*]cinnoline from 4-chlorobenzo[*c*]cinnoline[4]). Intermediate (30) would formally be capable of undergoing dimethylamination at the 2- and the 4-position; but the 4-position could well be favoured if the incoming dimethylamino group were to come from a molecule of lithium dimethylamide already complexed in associated form with the diaza linkage.

The formation of 2-chloro-4-dimethylaminobenzo[*c*]cinnoline (13), which was the other main product from 2-chlorobenzo[*c*]cinnoline, is mechanistically in accordance with Scheme 2. With increased reaction time (see Table 2) the yields of the 2-chloro-4-dimethylamino compound (13) dropped very markedly, while the yields of the 2,4-bis(dimethylamino) compound (7) and the 2,4,7-tris(dimethylamino) compound (9) increased. It would seem from the sequence of appearance of these compounds that compound (7) arises from compound (13) via AE or EA substitution of the 2-chloro substituent by a dimethylamino group, and that the 2,4-bis(dimethylamino) compound (7) is in turn dimethylaminated at the 7-position, in accordance with Scheme 2, to give the 2,4,7-tris(dimethylamino) compound (9).

The decrease in yield of the 4-dimethylamino compound (6) with increased reaction time was not so marked; apparently it corresponded to the belated formation (in small yield) of the 4,7-bis(dimethylamino) compound (8). The conversion of compound (6) into compound (8) is also in accordance with Scheme 2.

The sequence of formation of products from 2-chlorobenzo[*c*]cinnoline is summarized in Scheme 4.



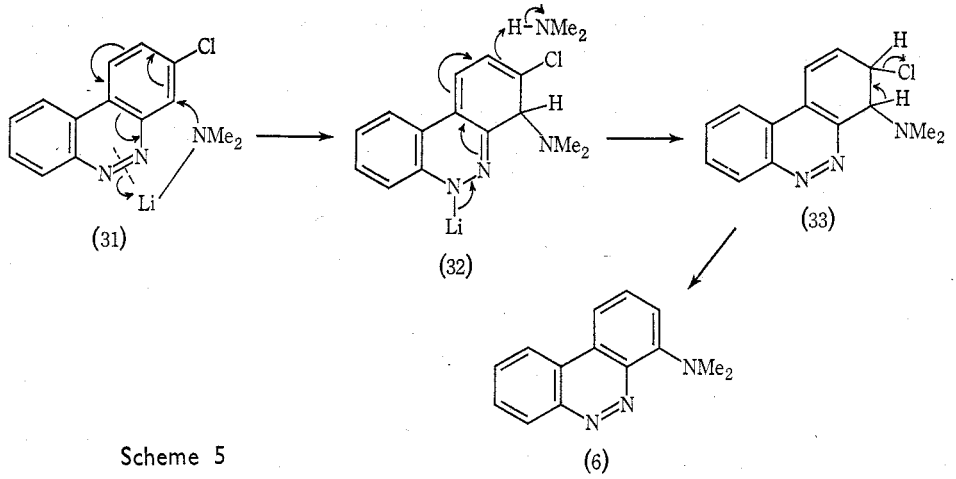

Scheme 4

In the earlier study[1] of the reaction of 2-chlorobenzo[*c*]cinnoline with lithium dimethylamide a reaction time of at least 2 h was used. Besides the 4-dimethylamino compound (6) only the 2,4,7-tris(dimethylamino) compound (9) was isolated. From

Table 2 it is clear why the 2-chloro-4-dimethylamino compound (13) was not detected in the earlier study. The failure to detect the 2,4-bis(dimethylamino) compound, however, is now attributed to the inevitable co-elution of compounds (7) and (9) in the column-chromatographic separation of the reaction products and the subsequent loss of compound (7) in the successive recrystallizations used for purification of compound (9). The present studies have shown that compounds (7) and (9) cannot be separated even by thin-layer chromatography with a variety of solvents, although countercurrent distribution is effective.

The formation of 3-chloro-4-dimethylaminobenzo[*c*]cinnoline (15) and the 3-chloro-7-dimethylamino compound (16) as the main products from the reaction of the 3-chloro compound (3) (see Table 3) is in accordance with Scheme 1 and the mechanism proposed in Scheme 2. The fact that neither the yields of the main products, (15) and (16), nor the yields of the minor product, 4-dimethylaminobenzo[*c*]cinnoline (6), varied markedly with time of reaction suggests that compound (6) arose directly from the starting material (3).

One possible mechanism for the conversion of 3-chlorobenzo[*c*]cinnoline (3) into the 4-dimethylamino compound (6) is shown in Scheme 5, commencing with the $\pi$-complex (31), which corresponds to structure (21) in Scheme 2. The mechanism in Scheme 5 is comparable with that suggested for the formation of compound (6) from 2-chlorobenzo[*c*]cinnoline (see above).




Scheme 5

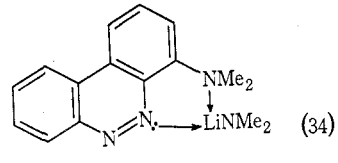
Another possible mechanism could be the EA type involving 3,4-dehydrobenzo[*c*]-cinnoline (28) as an intermediate, generated through dehydrochlorination of compound (3). Formally the dehydro intermediate (28) could yield 3-dimethylaminobenzo[*c*]-cinnoline as well as the 4-dimethylamino compound (6). There is evidence[4] that (28) as an intermediate in reactions with potassium amide gives considerably higher yields of 3-aminobenzo[*c*]cinnoline than of the 4-amino compound. This was interpreted[4] as being in accordance with rules advanced by Roberts[19] for substituent effects in arynes. However, if lithium dimethylamide in associated form is complexed with the

[19] Roberts, J. D., Vaughan, C. W., Carlsmith, L. A., and Semenow, D. A., *J. Amer. Chem. Soc.*, 1956, **78**, 611.

5,6-diaza linkage of intermediate (28) selective formation of the 4-dimethylamino compound (6) from such an intermediate can be rationalized.

The main products formed from 4-chlorobenzo[*c*]cinnoline (4) after short reaction times (see Table 4) were 4-dimethylaminobenzo[*c*]cinnoline (6) and the 4-chloro-7-dimethylamino compound (17). Compound (6) would appear to have arisen through direct AE nucleophilic substitution of the chloro substituent in (4). The formation of compound (17), on the other hand, is in accordance with Scheme 1 and the mechanism suggested in Scheme 2. The formation of the 4,7-bis(dimethylamino) compound (8), which appeared after long periods of reaction, can be attributed to direct AE nucleophilic substitution of the chloro substituent in compound (17), the rise in yield of compound (8) with increased reaction time corresponding fairly closely to the fall in yield of compound (17). This does not preclude the possibility, however, that a small amount of compound (8) may have been formed from the 4-dimethylamino compound (6) through direct dimethylamination at the 7-position. The formation of compounds (7) and (9) after long reaction times suggests that the 4-dimethylamino compound (6) and the 4,7-bis(dimethylamino) compound (8) are both subject to very slow dimethylamination at the 2-position. However, only traces of (7) and (9) were detected, even after 2 h reaction time. It is therefore clear that the extent of displacement of an hydride ion from the 2-position in the presence of lithium dimethylamide is practically insignificant.

In earlier work[1] it was shown that 4-dimethylaminobenzo[*c*]cinnoline (6) reacts only very slowly with lithium dimethylamide, far more slowly in fact than does benzo[*c*]cinnoline. The variations in the composition of product-mixtures shown in Tables 2 and 3 constitute further evidence for the low reactivity of the 4-dimethylamino compound. It seems likely that compound (6) forms a relatively strong complex with lithium compounds, possibly of the type corresponding to structure (34), thus retarding formation of the $\pi$-complex necessary for initiating subsequent dimethylamination at the 7-position.



(34)

Similar considerations apply (see Table 1) to the 1-chloro-4-dimethylamino compound (10) and the 1-chloro-7-dimethylamino isomer (11).

**Structural Identification of Products**

With few exceptions the structural identification of the products isolated in the present work was made solely on the basis of microanalytical data, mass spectrometric determinations of molecular weights, and n.m.r. spectral data.

The 4-dimethylamino compound (6) and the 2,4,7-tris(dimethylamino) compound (9) were unambiguously identified in earlier work.[1] The structure of 2,4-bis(dimethylamino)benzo[*c*]cinnoline (7) as a new compound was confirmed (see below) through an independent synthesis involving conversion of 2,4-dichloroazobenzene into 2,4-dichlorobenzo[*c*]cinnoline by the method[20] of photochemical cyclodehydrogenation

[20] Badger, G. M., Drewer, R. J., and Lewis, G. E., *Aust. J. Chem.*, 1964, **17**, 1036.

and reaction of the latter compound with dimethylamine under previously described[3] conditions. Supporting evidence for the structure of 3-chloro-4-dimethylaminobenzo-[*c*]cinnoline (15) came from the fact that this compound was also obtained through photochemical cyclodehydrogenation of 2,3-dichloroazobenzene to 3,4-dichlorobenzo-[*c*]cinnoline and reaction of the latter with dimethylamine, the preferential displacement of the 4-chlorosubstituent being in accordance with the evidence presented above (see also refs[10–12]) concerning the greater susceptibility of the 4-position (over the 3-position) towards nucleophilic attack.

There were four basic considerations in applying n.m.r. spectral data to the determination of substitution patterns in the benzo[*c*]cinnoline derivatives obtained in the present work. These are summarized as follows.

Firstly, the n.m.r. spectrum of unsubstituted benzo[*c*]cinnoline[21] shows multiplets at: $\delta$ 8·6, 2H (4- and 7-positions); 8·2, 2H (1- and 10-positions); and 7·7, 4H (2-, 3-, 8- and 9-positions).

Secondly, the chemical shifts of the protons in dimethylamino substituents in a benzo[*c*]cinnoline nucleus give some information as to the ring-positions of these substituents. Signals arising from the *N*-methyl protons in 2- and 3-dimethylamino-benzo[*c*]cinnoline occur at $\delta$ 3·1, whereas the corresponding signals from the 1-dimethylamino compound and the 4-dimethylamino compound are shifted upfield (to $\delta$ 2·8) and downfield (to $\delta$ 3·35), respectively.[3] Accordingly, the integrated n.m.r. spectrum of 2,4,7-tris(dimethylamino)benzo[*c*]cinnoline (9)[1] shows a singlet at $\delta$ 3·1, 6H (2-$NMe_2$) and another singlet at $\delta$ 3·3, 12H (4-$NMe_2$ and 7-$NMe_2$), while the remainder of the spectrum shows peaks in the $\delta$ 6·8–7·9 range which account for the ring-protons at the 1-, 3-, 8-, 9- and 10-positions.

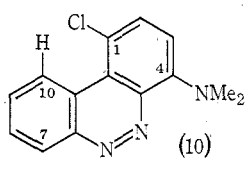
Thirdly, it is known[22] that a dimethylamino group in an aromatic ring causes considerable upfield shifts in the resonance of protons *ortho* or *para* to it. It was found in the n.m.r. spectra of the dimethylamino-substituted benzo[*c*]cinnolines that the signal from the proton *ortho* to the dimethylamino group was shifted upfield sufficiently to be separated from the signals of the remaining protons attached to the aromatic rings. It was then possible on the basis of the splitting pattern in the upfield resonance to elucidate whether there was a chloro substituent in the same ring, and, if so, in which position.

Fourthly, although a chloro substituent has relatively little effect on proton chemical shifts within a single aromatic ring,[22] a 1-chloro substituent in the benzo[*c*]cinnoline nucleus causes a marked downfield shift in the resonance of a proton attached to the 10-position. In 1-chlorobenzo[*c*]cinnoline the signal from the 10-proton appears at $\delta$ 9·7, which is markedly downfield from the region where the peaks for the other ring-protons appear. Such *peri* effects, or 'through space' interactions, in polycyclic compounds are well known.[23] The extent of the observed downfield shift, as modified by the effects of other substituents, was important for distinguishing between 1-chloro-4-dimethylaminobenzo[*c*]cinnoline (10) and 1-chloro-7-dimethylaminobenzo[*c*]cinnoline (11).

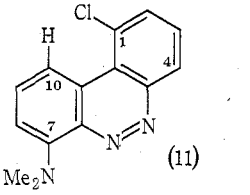
The signal from the proton at the 10-position in the 1-chloro-4-dimethylamino compound (10) occurs at $\delta$ 9·6, whereas in the spectrum of the 1-chloro-7-dimethyl-

[21] Bennett, R. P., *Inorg. Chem.*, 1970, **9**, 2184.
[22] Spiesecke, H., and Schneider, W. G., *J. Chem. Phys.*, 1961, **35**, 731.
[23] Jackman, L. M., and Sternhell, S., 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry' (Pergamon Press: Oxford 1969).

amino compound (11), the 10-position of which is subjected to a *para* upfield shift due to the dimethylamino group in the 7-position, the corresponding signal occurs at $\delta$ 9·0.



(10)



(11)

The foregoing basic considerations apply to the interpretation of the n.m.r. spectral data presented in the Experimental section as evidence for the assigned molecular structures.

## Experimental

### (*a*) General

Melting points (uncorrected) were determined on a Reichert hot-stage microscope. Microanalyses were carried out by the Australian Microanalytical Service. Mass spectra were determined with an Hitachi Perkin–Elmer RMU-6D spectrometer at 70 eV. Nuclear magnetic resonance spectra were determined with a Varian DP-60 or T-60 spectrometer at 60 MHz in deuterochloroform solutions with tetramethylsilane as internal standard. The n.m.r. data are reported in the following sequence: chemical shifts ($\delta$) in p.p.m. relative to tetramethylsilane; multiplicity: s (singlet), d (doublet), dd (doublet of doublets), m (multiplet); coupling constants ($J$) in Hz; proton count; and assignments (in parentheses). Alumina (Spence) was used for column chromatography. Merck silica gel G was used for thin-layer (0·25 mm) and preparative thick-layer (2 mm) chromatography. Separations of compounds by countercurrent distribution were carried out with a Quickfit automatic (50-tube) apparatus with stationary and moving phases of 25 ml each. Quantitative gas–liquid chromatographic analyses were carried out with a Perkin–Elmer 881 gas chromatograph fitted with a Perkin–Elmer 194 B printing integrator. The light petroleum used had a boiling range of 40–60°, unless stated otherwise.

### (*b*) Starting Materials

*Benzo*[c]*cinnoline*

This was prepared by photochemical cyclodehydrogenation of azobenzene.[24]

*Chlorobenzo*[c]*cinnolines*

Samples of the four isomers were available from earlier work.[3,4]

*2,4-Dichlorobenzo*[c]*cinnoline*

2,4-Dichloroazobenzene was prepared by the method described by Stieglitz and Graham.[25] On photochemical cyclodehydrogenation[20] this was converted into *2,4-dichlorobenzo*[c]*cinnoline* in 8% yield, which gave yellow needles, m.p. 236–237°, when recrystallized from ethanol (Found: C, 58·0; H, 2·5; N, 11·1; *m/e* 250, 248 $M^+$. $C_{12}H_{16}Cl_2N_2$ requires C, 57·8; H, 2·4; N, 11·3%; *m/e* 250, 248 $M^+$).

*3,4-Dichlorobenzo*[c]*cinnoline*

2,3-Dichloroazobenzene was prepared by the method of Stieglitz and Graham[25] from 2,3-dichloroaniline and nitrosobenzene; this was obtained in 19% yield as orange needles, m.p. 73·5–74·5°, when recrystallized from benzene (Found: C, 57·7; H, 3·2; N, 11·0; *m/e* 252, 250 $M^+$.

[24] Lewis, G. E., *J. Org. Chem.*, 1960, **25**, 2193.
[25] Stieglitz, J., and Graham, H. T., *J. Amer. Chem. Soc.*, 1916, **38**, 1748.

Calc. for $C_{12}H_{18}Cl_2N_2$: C, 57·4; H, 3·2; N, 11·2; *m/e* 252, 250 $M^+$). 2,3-Dichloroazobenzene was then photochemically cyclodehydrogenated[20] to give *3,4-dichlorobenzo*[c]*xinnoline* in 14% yield which formed olive-green needles, m.p. 268–269°, when recrystallized from benzene and ethanol (Found: C, 57·8; H, 2·4; N, 11·1; *m/e* 250, 248 $M^+$. $C_{12}H_{16}Cl_2N_2$ requires C, 57·8; H, 2·4; N, 11·3%; *m/e* 250, 248 $M^+$).

*Lithium Dimethylamide*

In each instance lithium dimethylamide was generated *in situ*. For some of the preparative reactions (see, for example, the preparation and isolation of 1-chloro-4-dimethylamino- and 1-chloro-7-dimethylamino-benzo[*c*]cinnoline below) the method of generation involved preparation of a solution of propyllithium in ether through the reaction of an ethereal solution of propyl bromide with metallic lithium and subsequent reaction of the propyllithium with anhydrous dimethylamine. For other preparative reactions, and for the monitored reactions, stock solutions of butyllithium in hexane were used, which had been prepared according to the method of Gilman and Morton.[26] The solutions were stored under nitrogen and analysed by a double-titration technique[27] immediately before use.

**(*c*) Isolation and Identification of Dimethylamination Products**

The reactions described in this section were carried out in an atmosphere of dry nitrogen. All ether and benzene used was first dried over sodium wire.

*1-Chloro-4-dimethylaminobenzo*[c]*cinnoline* (*10*) *and 1-Chloro-7-dimethylaminobenzo*[c]*cinnoline* (*11*)

A solution of propyllithium was prepared by adding propyl bromide (5·92 g) in ether (30 ml) to lithium (1·2 g) in ether (15 ml) at −10° over 30 min. The mixture was stirred for a further 1 h at room temperature. The propyllithium solution (35 ml, 0·85M) was added to anhydrous dimethylamine (*c.* 25 ml) in ether (10 ml) at −10° over 5 min. The mixture was stirred for a further 30 min at room temperature. 1-Chlorobenzo[*c*]cinnoline (469 mg) in benzene (30 ml) was added to the lithium dimethylamide at −10° over 5 min, the molar ratio of lithium dimethylamide to 1-chlorobenzo[*c*]cinnoline finally being 13 : 1. Upon addition of the chlorobenzo[*c*]cinnoline the reaction mixture turned an intense red-purple colour; this gave way within *c.* 0·5 min to a dark green colour. The mixture was stirred for a further 5 min at room temperature, and water was then added. The quenched reaction mixture was extracted with chloroform; the extract was washed with water and dried ($MgSO_4$). The solvent was then removed; the residue was chromatographed on a thick-layer silica gel plate, development being effected with a mixture of ether, light petroleum and benzene (3 : 3 : 1). The material in the upper fraction was isolated and subjected to countercurrent distribution between hydrochloric acid (0·05M) and a mixture of benzene and light petroleum (3 : 17). The material in the tubes nearest the solvent front was identified as unchanged 1-chlorobenzo[*c*]cinnoline (69 mg, 15% recovery). The material (369 mg) in the tubes closer to the starting tube proved to be a mixture of 1-chloro-4-dimethylamino- and 1-chloro-7-dimethylamino-benzo[*c*]cinnoline. These two compounds could not be completely separated from each other but were contained in a band which had been separated from starting material and other products. Through isolation of the contents of several tubes at both ends of the band pure samples of the two compounds were obtained. From this band, the tubes nearest the solvent front contained *1-chloro-7-dimethylaminobenzo*[c]*cinnoline* (11), which was isolated and recrystallized from chloroform/hexane to give orange-red needles, m.p. 122°–123·5° (Found: C, 65·4; H, 4·8; N, 16·1; *m/e* 259, 257 $M^+$. $C_{14}H_{12}ClN_3$ requires C, 65·3; H, 4·7; N, 16·3%; *m/e* 259, 257 $M^+$). The n.m.r. spectrum showed peaks at: $\delta$ 3·3, s, 6H (7-$NMe_2$); 7·2, dd, *J* 8 and *J* 1·5, 1H (H8; 8,9-*ortho*-coupling and 8,10-*meta*-coupling); 7·4–7·8, m, 3H (H2, H3, H9); 8·6, dd, J 7 and *J* 2·5, 1H (H4; 3,4-*ortho*-coupling and 2,4-*meta*-coupling); 9·0, dd, *J* 8 and *J* 1·5, 1H (H10; 9,10-*ortho*-coupling and 8,10-*meta*-coupling). From the same band, the tubes nearest the starting tube contained *1-chloro-4-dimethylaminobenzo*[c]*cinnoline* (10), which was isolated and recrystallized from chloroform/hexane to give red needles, m.p. 100–101·5° (Found: C, 65·4; H, 5·0; N, 16·5; *m/e* 259, 257 $M^+$. $C_{14}H_{12}ClN_3$ requires C, 65·3; H, 4·7; N, 16·3%; *m/e* 259

[26] Gilman, H., and Morton, J. W., *Org. React.*, 1954, **8**, 259.
[27] Gilman, H., and Haubein, A. H., *J. Amer. Chem. Soc.*, 1944, **66**, 1515.

257 $M^+$). The n.m.r. spectrum showed peaks at: $\delta$ 3·3, s, 6H (4-$NMe_2$); 7·0, d, $J$ 8, 1H (H3; 2,3-*ortho*-coupling); 7·6, d, $J$ 8, 1H (H2; 2,3-*ortho*-coupling); 7·7–7·9, m, 2H (H8, H9); 8·3–8·7, m, 1H (H7); 9·5–9·7, m, 1H (H10). Other products formed in the reaction of 1-chlorobenzo[*c*]-cinnoline with lithium dimethylamide were not present in sufficient quantities to warrant further investigation.

*1-Chloro-4,7-bis(dimethylamino)benzo*[c]*cinnoline* (*12*)

A solution of lithium dimethylamide in dimethylamine was prepared by adding a solution of butyllithium in hexane (20 ml, 1M) to a solution of dimethylamine (10 ml) in ether (40 ml). When the formation of lithium dimethylamide was complete, a portion (30 ml) was added to a solution of 1-chlorobenzo[*c*]cinnoline (480 mg) in benzene (40 ml). The mixture was stirred for 5 h and then quenched with water. The product was extracted with chloroform, the extract was washed with water and dried, and the residue, after removal of the solvent and chromatography on a thick-layer silica gel plate (ether/light petroleum/benzene; 3 : 3 : 1), was subjected to countercurrent distribution between hydrochloric acid (0·05M) and benzene. The material in the tubes nearest the solvent front proved to be a mixture of 1-chloro-4-dimethylaminobenzo[*c*]cinnoline and the 1-chloro-7-dimethylamino compound. The tubes nearest the starting tube contained *1-chloro-4,7-bis(dimethylamino)-benzo*[c]*cinnoline* (12) (25 mg, 4%), which was isolated and recrystallized from light petroleum (b.p. 60–80°) to give red needles, m.p. 91·5–93·5° (Found: C, 64·1; H, 5·7; N, 18·7; *m/e* 302, 300 $M^+$. $C_{14}H_{17}ClN_4$ requires C, 63·9; H, 5·7; N, 18·6%; *m/e* 302, 300 $M^+$). The n.m.r. spectrum showed peaks at: $\delta$ 3·4, s, 12H (4-$NMe_2$ and 7-$NMe_2$); 7·1–7·4, m, 2H (H3, H8); 7·6–7·8, m, 2H (H2, H9); 9·0–9·2, m, 1H (H10).

*4-Dimethylaminobenzo*[c]*cinnoline* (*6*) *and 2-Chloro-4-dimethylaminobenzo*[c]*cinnoline* (*13*)

A solution of propyllithium in ether (35 ml, 0·61M) was prepared by the procedure described above; this was added to a solution of dimethylamine (*c.* 25 ml) in ether. A solution of 2-chlorobenzo[*c*]-cinnoline (389 mg) in benzene (50 ml) was added to the lithium dimethylamide (cooled to −30°) over 2·5 min. The cooling bath was then removed; the mixture was stirred for a further 2 min period before water was added. The ratio of lithium dimethylamide to 2-chlorobenzo[*c*]cinnoline was 10 : 1. The mixture developed a dark green colour which persisted until the reaction was quenched with water. After the usual working-up procedure the extracted product-mixture was chromatographed on a thick-layer silica gel plate (development with ether/light petroleum/benzene; 3 : 3 : 1). The material in the two fractions with the highest $R_F$ values was isolated and subjected to countercurrent distribution between sulphuric acid (0·1M) and benzene/light petroleum (1 : 4). The material in the tubes nearest the solvent front was 2-chlorobenzo[c]cinnoline (37 mg, 9% recovery). Tubes nearer the starting tube contained *2-chloro-4-dimethylaminobenzo*[c]*cinnoline* (13) (234 mg, 56%) which was isolated and recrystallized from chloroform/hexane to give orange-yellow needles, m.p. 146·5–148·5° (Found: C, 65·3; H, 4·7; N, 16·2; *m/e* 259, 257 $M^+$. $C_{14}H_{12}ClN_3$ requires C, 65·3; H, 4·7; N, 16·3%; *m/e* 259, 257 $M^+$). The n.m.r. spectrum showed peaks at: $\delta$ 3·3, s, 6H (4-$NMe_2$); 6·9, d, $J$ 2, 1H (H3; 1,3-*meta*-coupling); 7·6–7·8, m, 3H (H1, H8, H9); 8·2–8·6, m, 2H (H7, H10). The material in the tubes nearest the starting tube was 4-dimethylaminobenzo[*c*]cinnoline (6) (175 mg, 48%). This was recrystallized from chloroform/hexane to give orange-yellow plates (m.p. 93–96°) and shown to be identical (mixed m.p., n.m.r. spectrum) with an authentic sample.[3]

*2,4-Bis(dimethylamino)benzo*[c]*cinnoline* (*7*) *and 2,4,7-Tris(dimethylamino)benzo*[c]*cinnoline* (*9*)

A solution of lithium dimethylamide in dimethylamine was prepared by adding a solution of butyllithium in hexane (35 ml, 1M) to dimethylamine (15 ml) in ether (22·5 ml). To a portion (50 ml) of this solution, which was maintained at −10°, was added a solution of 2-chlorobenzo[*c*]-cinnoline (503 mg) in benzene (60 ml) over 15 min. The mixture was stirred at −10° for 1·5 h and then at room temperature for 0·5 h. Water was then added; the mixture was subjected to the usual working-up procedure. Chromatography on a column of alumina effected primary separation of 4-dimethylamino- and 2-chloro-4-dimethylamino-benzo[*c*]cinnoline from the more strongly adsorbed components of the product-mixture. The latter were subjected to countercurrent distribution between hydrochloric acid (0·01M) 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 again to countercurrent distribution between hydrochloric acid (0·001M) 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 (9) which, after isolation and recrystallization from light petroleum (b.p. 60–80°), was obtained as orange-red needles, m.p. 151·5–152·5°. This was shown to be identical (mixed m.p., comparative g.l.c., n.m.r. spectrum) with an authentic sample.[1] The material in the tubes nearest the starting tube was *2,4-bis(dimethylamino)benzo*[c]*cinnoline* (7), which on recrystallization from light petroleum (b.p. 60–80°) gave orange needles, m.p. 163–165° (Found: C, 72·2; H, 6·9; *m/e* 266 $M^+$. $C_{16}H_{18}N_4$ requires C, 72·2; H, 6·8%; *m/e* 266 $M^+$). The n.m.r. spectrum showed peaks at: $\delta$ 3·2, s, 6H (2-$NMe_2$); 3·4, s, 6H (4-$NMe_2$); 6·6, d, *J* 2, 1H (H3; 1,3-*meta*-coupling); 7·0, d, *J* 2, 1H (H1; 1,3-*meta*-coupling); 7·7–7·9, m, 2H (H8, H9); 8·3–8·7, m, 2H (H7, H10). The identity of this compound was confirmed by independent synthesis from 2,4-dichlorobenzo[c]cinnoline (for preparation see above). 2,4-Dichlorobenzo[c]cinnoline (66 mg) in dimethylamine (*c.* 1 ml) was heated in a sealed tube at 165° for 3 h (cf. Lewis and Reiss[3]). The reaction mixture was chromatographed on a thick-layer silica gel plate and developed with ether/light petroleum/dimethoxyethane (3 : 3 : 1). 2,4-Bis(dimethylamino)benzo[c]cinnoline, which constituted the major chromatographic fraction, was isolated and recrystallized from light petroleum (b.p. 60–80°) to give orange needles which were identical (mixed m.p., n.m.r. spectrum) with those described above.

*4,7-Bis(dimethylamino)benzo*[c]*cinnoline* (*8*)

A solution of lithium dimethylamide in dimethylamine was prepared from dry dimethylamine (*c.* 15 ml) in ether (30 ml) and a solution of butyllithium in hexane (10 ml, 1·0M). When the formation of lithium dimethylamide was complete, a solution of benzo[c]cinnoline (307 mg) in benzene (40 ml) was added over 2 min. A dark green coloration developed, and this persisted until the reaction was finally quenched. The reaction mixture was stirred for 15 h before being quenched with water. Following the usual working-up procedure, the product-mixture was subjected to countercurrent distribution between hydrochloric acid (0·5M) 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, with benzene being used as the eluent. The first (orange) fraction contained *4,7-bis(dimethylamino)benzo*[c]*cinnoline* (8) (52 mg, 12%) which 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; *m/e* 266 $M^+$. $C_{16}H_{18}N_4$ requires C, 72·2; H, 6·8%; *m/e* 266 $M^+$). The n.m.r. spectrum showed peaks at: $\delta$ 3·4, s, 12H (4-$NMe_2$ and 7-$NMe_2$); 7·2, dd, *J* 8 and *J* 2, 2H (H3, H8; 2,3- and 8,9-*ortho*-coupling; 1,3- and 8,10-*meta*-coupling); 7·3–7·7, m, 2H (H2, H9); 7·9, dd, *J* 8 and *J* 2, 2H (H1, H10; 1,2- and 9,10-*ortho*-coupling; 1,3- and 8,10-*meta*-coupling).

*3-Chloro-4-dimethylaminobenzo*[c]*cinnoline* (*15*) *and 3-Chloro-7-dimethylaminobenzo*[c]*cinnoline* (*16*)

A solution of propyllithium (35 ml, 0·65M) was prepared as described above. This was added to a solution of dimethylamine (*c.* 25 ml) in ether. The resulting lithium dimethylamide was maintained at −10°; 3-chlorobenzo[c]cinnoline (936 mg) in benzene (85 ml) was added over 5 min. The ratio of lithium dimethylamide to 3-chlorobenzo[c]cinnoline was 5 : 1. A dark green coloration persisted until the reaction was eventually quenched with water. After 5 min at −10°, the mixture was allowed to warm to room temperature while being stirred for a further 10 min. Water was then added; and after the usual working-up procedure the product mixture was chromatographed on a thick-layer silica gel plate, development being carried out with ether/light petroleum/benzene (3 : 3 : 1). Three fractions (A, B and C) were obtained. The material from the fraction of highest $R_F$ value (A) was subjected to countercurrent distribution between hydrochloric acid (0·5M) and hexane. Only *3-chloro-4-dimethylaminobenzo*[c]*cinnoline* (15) was present (212 mg, 23%); this was recrystallized from chloroform/hexane to give yellow needles, m.p. 130–131·5° (Found: C, 65·4; H, 4·5; N, 16·2; *m/e* 259, 257 $M^+$. $C_{14}H_{12}ClN_3$ requires C, 65·3; H, 4·7; N, 16·3%; *m/e* 259, 257 $M^+$). The n.m.r. spectrum showed peaks at: $\delta$ 3·3, s, 6H (4-$NMe_2$); 7·6–8·1, m, 4H (H1, H2, H8, H9); 8·3–8·7, m, 2H (H7, H10). The same compound was obtained when 3,4-dichlorobenzo[c]cinnoline (29 mg) and dimethylamine (3 ml) were heated together in a sealed tube at 150° for 2 h, followed by chromatography of the product on a thick-layer silica gel plate. The compound (20 mg, 67%) formed yellow needles, m.p. 130–131°, and was identical (mixed m.p., n.m.r. spectrum) with that obtained from 3-chlorobenzo[c]cinnoline and lithium dimethylamide. The material in the second chromatographic fraction (B) was subjected to countercurrent distribution between hydrochloric acid (1M) 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 (168 mg, 18% recovery). The material in the tubes closer to the starting tube was *3-chloro-7-dimethylaminobenzo*[c]-*cinnoline* (16) (274 mg, 30%), which when recrystallized from chloroform/hexane formed yellow needles, m.p. 136·5–137·5° (Found: C, 65·1; H, 4·6; N, 16·1; *m/e* 259, 257 $M^+$. $C_{14}H_{12}ClN_3$ requires C, 65·3; H, 4·7; N, 16·3%; *m/e* 259, 257 $M^+$). The n.m.r. spectrum showed peaks at: $\delta$ 3·3, s, 6H (7-$NMe_2$); 7·1, dd, *J* 7 and *J* 2, 1H (H8; 8,9-*ortho*-coupling and 8,10-*meta*-coupling); 7·5–7·8, m, 3H (H2, H9, H10); 8·3, d, *J* 8·5, 1H (H1; 1,2-*ortho*-coupling); 8·5, d, *J* 2, 1H (H4; 2,4-*meta*-coupling). The material in the tubes nearest the starting tube was 4-dimethylaminobenzo[*c*]-cinnoline (179 mg, 22%). This was recrystallized from chloroform/hexane to give orange-yellow plates (m.p. 94–97°) and shown to be identical (mixed m.p., n.m.r. spectrum) with an authentic sample.[3] The material (74 mg) in the third chromatographic fraction (C) was found to be a mixture of several compounds and was not investigated further.

*4-Chloro-7-dimethylaminobenzo*[c]*cinnoline* (*17*)

A solution of propyllithium (35 ml, 0·27M) was prepared by the procedure described above. To this was added a solution of dimethylamine (25 ml) in ether. 4-Chlorobenzo[*c*]cinnoline (463 mg) in benzene (40 ml) was added over 5 min to the lithium dimethylamide, which was maintained at −20°. The ratio of lithium dimethylamide to 4-chlorobenzo[*c*]cinnoline was 4 : 1. As in other cases, a dark green coloration persisted throughout the reaction. After the addition, the reaction mixture was allowed to warm to room temperature, while being stirred for another 5 min. After the reaction had been quenched with water and the mixture subjected to the usual working-up procedure, the extract was chromatographed on a column of alumina. The first fraction was eluted with light petroleum/ether (19 : 1); this yielded *4-chloro-7-dimethylaminobenzo*[c]*cinnoline* (17) (344 mg, 62%), which on recrystallization from chloroform/hexane afforded orange-red needles, m.p. 152·5–154° (Found: C, 65·1; H, 4·6; N, 16·1; *m/e* 259, 257 $M^+$. $C_{14}H_{12}ClN_3$ requires C, 65·3; H, 4·7; N, 16·3%; *m/e* 259, 257 $M^+$). The n.m.r. spectrum showed peaks at: $\delta$ 3·4, s, 6H (7-$NMe_2$); 7·0, dd, *J* 7 and *J* 2, 1H (H8; 8,9-*ortho*-coupling and 8,10-*meta*-coupling); 7·4–7·9, m, 4H (H2, H3, H9, H10); 8·3, dd, *J* 8 and *J* 2 (H1; 1,2-*ortho*-coupling and 1,3-*meta*-coupling). The second chromatographic fraction yielded 4-dimethylaminobenzo[*c*]cinnoline (125 mg, 26%), which was identified, as in the previous cases, by direct comparison with an authentic sample.[3]

**(*d*) Monitored Reactions**

All the monitored reactions of the chlorobenzo[*c*]cinnolines and benzo[*c*]cinnoline with lithium dimethylamide in dimethylamine were carried out in an atmosphere of dry nitrogen in apparatus (previously illustrated[4]) incorporating four three-necked flasks (A, B, D, and F) connected in series, each flask having an inlet/outlet for the introduction or release of nitrogen. All solvents such as ether, benzene, and hexane were dried over sodium wire and distilled from lithium aluminium hydride immediately before use. Dimethylamine in flask A was in each case distilled from calcium hydride through a closable inlet into flask B (containing ether as solvent) from where a measured quantity of the resulting ethereal solution of dimethylamine could be transferred by nitrogen under pressure through an interconnecting graduated dropping funnel (labelled C in Fig. 1 of ref.[4]) into flask D which contained a solution of butyllithium in hexane[26] of known strength[27] and volume. When the formation of lithium dimethylamide in flask D was complete a measured quantity of the solution was transferred by nitrogen under pressure through an interconnecting graduated dropping funnel (labelled E in Fig. 1 of ref.[4]) into flask F, into which a solution of the benzo[*c*]cinnoline in benzene was added through a terminal graduated dropping funnel (labelled G in Fig. 1 of ref.[4]). The reaction mixture in flask F was stirred continuously.

As a typical example, the monitored reaction of 1-chlorobenzo[*c*]cinnoline was carried out as follows. A solution of lithium dimethylamide in dimethylamine was prepared by transferring a solution of dimethylamine (10 ml) in ether (20 ml) from flask B into flask D, which contained a solution of butyllithium in hexane (30 ml, 1M). A portion (20 ml) of the lithium dimethylamide solution was then transferred into flask F; a solution of 1-chlorobenzo[*c*]cinnoline (193 mg) in benzene (30 ml) was added over 2 min, the mixture being continuously stirred. An aliquot (5 ml) of the reaction mixture was removed immediately after the addition of the 1-chlorobenzo[*c*]cinnoline was complete; further aliquots (each 5 ml) were removed at increasing time intervals (see Table 1). Water was added

to each aliquot immediately upon removal in order to quench the reaction. The remainder of the reaction mixture was stirred for a total time of 7·5 h before being deactivated with water. The product mixture in each aliquot and in the remaining deactivated reaction mixture was extracted with chloroform. Each chloroform extract was washed with water, dried (anhydrous $MgSO_4$), passed through a short column of alumina to remove any residual grease and tars, and finally evaporated to dryness. The residue in each case was dissolved in methanol, containing 2,3,6-trimethylnaphthalene as an internal standard, and subjected to gas–liquid chromatographic analysis. The g.l.c. analyses were carried out with a silanized glass-tubing column (5 ft by 0·125 in) containing 3% silicon GE XE-60 (82–001565) on Varaport-30 (100–120 mesh), nitrogen being used as carrier gas (flow rate: 30 ml/min). The identification and estimation of product components were then made in relation to calibration graphs constructed by analysing accurately prepared mixtures of the internal standard (2,3,6-trimethylnaphthalene) and authentic samples of the products described in section (*c*) above.

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