# THE SYNTHESIS OF

# ASCIDIDEMIN

A thesis presented by

ROBERT THOMAS

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Hofmann Laboratory,
Chemistry Department,
Imperial College,
LONDON, SW7 2AY.

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**Abstract.**

The marine alkaloids based on the pyrido[k,l]acridine structure isolated to date are reviewed. Their sources are shown to include a wide range of simple animals from three Phyla. A biosynthetic pathway is described to assimilate the structural data, and by reference to this hypothesis two "anomalous" structures are discussed.

The varied and extremely interesting biological properties of these natural products are outlined. The anticancer activity of the alkaloids, a common feature of all those tested, is examined with reference to recent results on the mode of action of intercalating drugs.

The published syntheses of, and synthetic approaches to, these compounds are described.

A rapid and short synthesis of the marine alkaloid ascididemin is described in four steps from phenanthroline. This synthesis is designed around the azastilbene photocyclisation of a quinoneimine, and represents the first example of this reaction, which has rich potential for the rapid synthesis of polycyclic natural products from simple precursors.

A variety of reactions which has successfully replaced the azastilbene electrocyclisation is reviewed. These alternatives have been applied to the synthetic scheme, and have produced a number of interesting results.

An approach to the synthesis of amphimedine is described. This culminates in the synthesis of some highly reactive benzophenanthroline compounds.

Finally a number of model studies designed to complement the more standard acridine - 9 - aldehyde syntheses are described. The results gained have opened the field for further research into these important heterocyclic intermediates.

## ACKNOWLEDGMENTS.

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Finally, I thank my parents for their continued support throughout my education, and my wife Liz for her unfailing confidence and tolerance.

R. Th. 1990

*To Liz*

*With all my love.*

**Parturient montes, nascetur ridiculus mus.**

Horace.

CONTENTS PAGE

ABBREVIATIONS.....7

1 THE PYRIDOACRIDINE MARINE ALKALOIDS.....9

1.1 INTRODUCTION.....10

1.2 ISOLATION AND STRUCTURE DETERMINATION.....11

1.3 BIOLOGICAL ACTIVITY AND BIOSYNTHESIS.....17

1.3.1 Biological Activity.....17

1.3.2 Biosynthesis.....20

1.4 SYNTHETIC APPROACHES.....24

1.4.1 Amphimedine.....24

1.4.2 Ascididemin and 2-Bromoleptoclinidinone.....33

1.4.3 The Cystodytins.....34

1.5 SUMMARY.....37

2 THE SYNTHESIS OF ASCIDIDEMIN.....38

2.1 RETROSYNTHESIS.....39

2.2 RESULTS AND DISCUSSION.....45

2.3 CONCLUSION.....58

3 AN APPROACH TO AMPHIMEDINE.....59

3.1 RETROSYNTHESIS.....60

3.2 RESULTS AND DISCUSSION.....63

3.3 OTHER REACTIONS.....73

3.3.1 Introduction.....73

3.3.2 Reactions.....75

3.4 CONCLUSION.....80

4 EXPERIMENTAL SECTION.....81

4.1 GENERAL EXPERIMENTAL PROCEDURES.....82

4.1.1 Solvents and Reagents.....82

4.1.2 Chromatographic Procedures.....82

4.1.3 Spectroscopic Techniques.....83
4.1.4 Other Data and Instrumentation.....83
4.2 EXPERIMENTAL FOR CHAPTER 2.....84
4.3 EXPERIMENTAL FOR CHAPTER 3.....104
**5 REFERENCES.....122**
**6 APPENDIX A.....126**
A list of the pyridoacridine alkaloids.....126
**7 APPENDIX B.....132**
NMR SPECTRA.....131

## ABBREVIATIONS.

| | |
|---|---|
| Ac | acetyl |
| AIBN | azoisobutyronitrile |
| Ar | aryl |
| Asn | asparagine |
| Asp | aspartic acid |
| BOC | N - tert - butoxycarbonyl |
| CAN | cerium (IV) ammonium nitrate |
| Cys | cysteine |
| DBN | 1,5 - diazabicyclo [4.3.0] non - 5 - ene |
| DCC | 1,3 - dicyclohexylcarbodiimide |
| DCM | dichloromethane |
| DDQ | 2,3 - dichloro - 5,6 - dicyano - 1,4 - benzoquinone |
| DEAD | diethyl azodicarboxylate |
| DIPEA | diisopropylethylamine |
| DMAP | 4 - dimethylaminopyridine |
| DME | ethylene glycol dimethyl ether |
| DMF | N,N - dimethylformamide |
| DMF-DMA | N,N - dimethylformamide - dimethyl acetal |
| DMSO | dimethylsulphoxide |
| GABA | γ – aminobutyric acid |
| Gly | glycine |
| HMPA | hexamethylphosphoramide |
| $IC_{50}$ | the dose at which 50 % of a cell culture is killed |
| LDA | lithium diisopropylamide |
| NBS | N - bromosuccinimide |
| nOe | nuclear Overhauser effect |
| o-DCB | 1,2 - dichlorobenzene |
| Ph | phenyl |
| phen | 1,10-phenanthroline |
| PPA | polyphosphoric acid |
| pTs | p - toluenesulphonyl |
| Py | pyridine |
| TBDMS | tert - butyldimethylsilyl |

| | |
|---|---|
| Tf | trifluoromethanesulphonyl |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| Thr | threonine |
| TMSCl | trimethylsilyl chloride |

# CHAPTER ONE

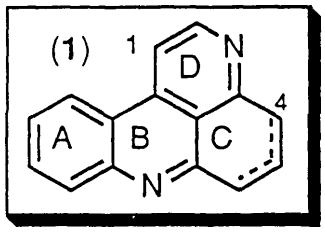
# THE PYRIDOACRIDINE MARINE ALKALOIDS.

## 1.1 INTRODUCTION.

Over the past decade the isolation and characterisation of marine alkaloids has been a steadily growing field, limited only by the high field NMR techniques available for their structure elucidation.

A prime example is calliactine, first isolated in 1940 [1], but characterised - and then only tentatively - in 1988.[2] The history of this compound also highlights another important facet of this field: despite startling advances in NMR techniques there is still a major role for total synthesis to play in structure elucidation of these materials.

To date the largest group of marine alkaloids characterised has been based on the pyrido [k,l] acridine skeleton (1). It is with the members of this group that this review will be concerned.

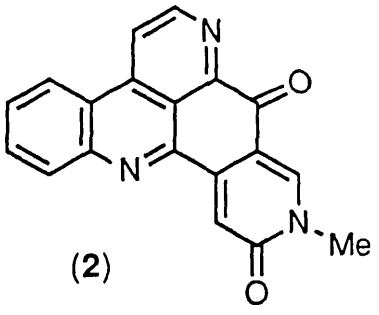



Despite their similarities, these alkaloids are found in a number of different marine animals: tunicates and ascidians from Phylum Chordata; sponges, from Phylum Porifera; and sea anemones from Phylum Cnidaria.

The review will briefly recall the isolation and structure elucidation of these pyridoacridines (Section 1.2), along with their considerable and diverse biological activities (1.3.1) and current thoughts about their biosynthesis (1.3.2). Also discussed in Section 1.3.2 will be the members of the group found to be anomalous with respect to this biosynthetic hypothesis. This is followed by synthetic approaches published to date in this field (1.4). Finally a summary (1.5) is included. For ease of reference, the alkaloid names, structures, and source species are gathered in Appendix A.

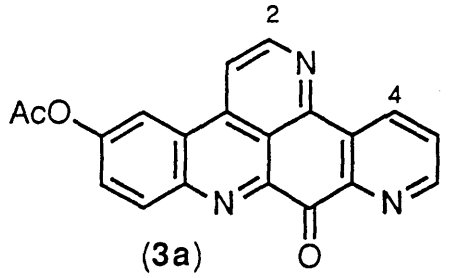
## 1.2 ISOLATION AND STRUCTURE DETERMINATION.

In 1983 Schmitz and coworkers [3] isolated a sparingly soluble yellow solid with cytotoxic properties from an *Amphimedon* sp. of sponge. Use of the elaborate INADEQUATE [4] NMR technique combined with other more common methods led to the unambiguous assignment of the structure of this material (**2**) which they named amphimedine.

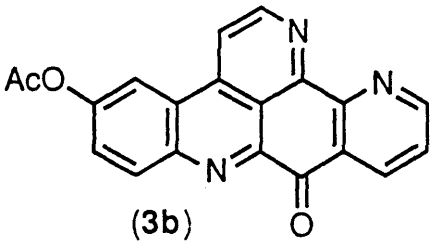


(**2**)

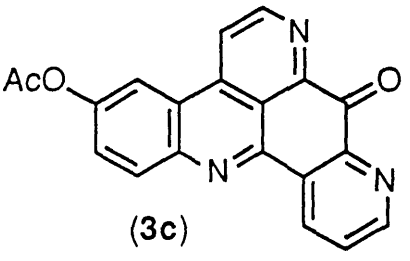
It was four years later that the next member of the group was confirmed. This alkaloid, called calliactine, had been eluding characterisation since its isolation by Lederer *et al* [1] in 1940. There were two reasons for this. Firstly the compound was extremely difficult to purify, and secondly all attempts at obtaining NMR spectra had been thwarted by the material's insolubility in most solvents. In 1987 Sodano *et al* [2] not only developed a simpler and superior method of isolating it from the sea anemone *Calliactis parasitica*, but also showed that the compound is soluble in methanol - acetic acid mixtures though it precipitates out in less than forty eight hours. For this reason $^{13}C$ NMR data were acquired on an aromatised derivative, neocalliactine acetate, which was found to be more soluble. A number of NMR techniques were employed from which a group of four structures (**3a-3d**) emerged as contenders. Of these Sodano chose (**3a**), implying (**4**) for calliactine itself. A criticism of this assignment appears in Section 1.3.2.



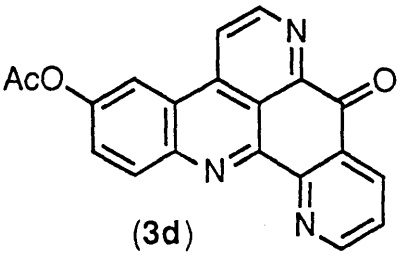
(**3a**)



(**3b**)

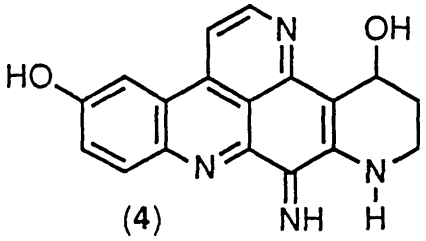


(**3c**)

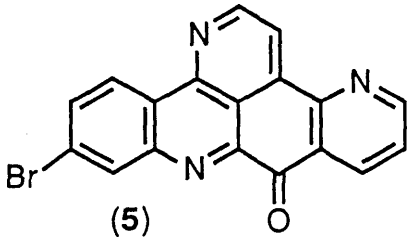


(**3d**)

In 1988 Schmitz [5] published the isolation and characterisation of 2-bromoleptoclinidinone (**5**). Another possible structure (**6**) was discounted because it contained the 1,10-phenanthroline substructure, and the alkaloid did not give a characteristic red chelate with iron (II) salts. This compound was isolated from a *Leptoclinides* sp. of ascidian.

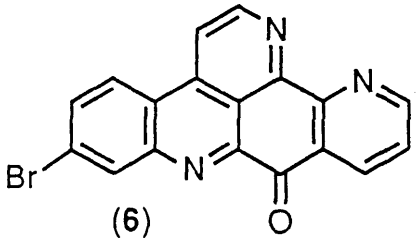


(4)

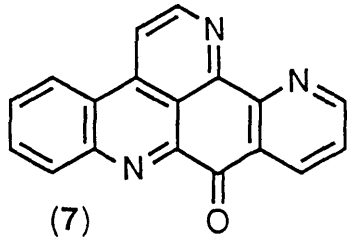


(5)

Two years later the structure was revised back to (**6**), [6] based on comparison with ascididemin (**7**), the debromo analogue of the Schmitz compound, which also did not complex iron (II) salts (this general feature of these compounds will be discussed in Section 1.3.2). Kobayashi *et al.*[7] had isolated ascididemin from the tunicate *Didemnum* sp. and unambiguously assigned its structure in 1988.



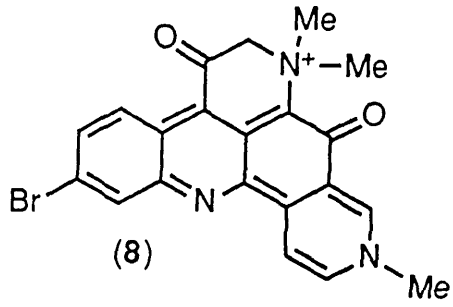
(6)



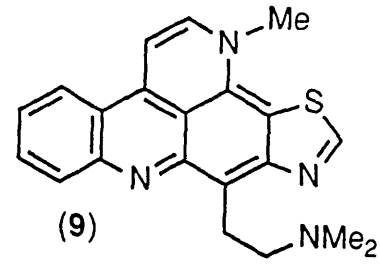
(7)

1988 was to see the publication of ten further alkaloids in quick succession: petrosamine [8] (**8**), with an amphimedine skeleton, from the sponge *Petrosia* sp.; dercitin [9] (**9**), a novel ring system containing a thiazole ring, from the sponge *Dercitus* sp.; segoline A (**10**), segoline B (**11**), isosegoline A (**12**), and nor-segoline (**13**),[10] all from the tunicate *Eudistoma* sp.; eilatin [10] (**14**), an intriguing heptacycle, shown to be nonplanar by X-ray crystallography, also from *Eudistoma* sp.; and cystodytins A (**15**), B (**16**) and C (**17**),[11] all from *Cystodytes dellechiajei*, a tunicate.

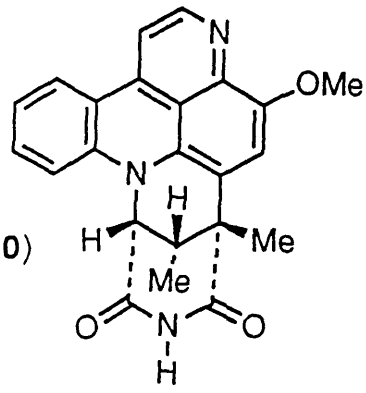
Shermilamine A [12] (**18**) appearing later in 1988 was followed by shermilamine B [13] (**19**) the following year. Both were isolated from the tunicate *Trididemnum* sp.


Me
O
N+–Me
O
Br
N
N
Me

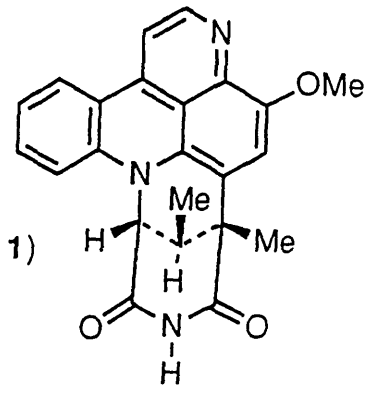
(8)


N
Me
S
N
N
NMe2

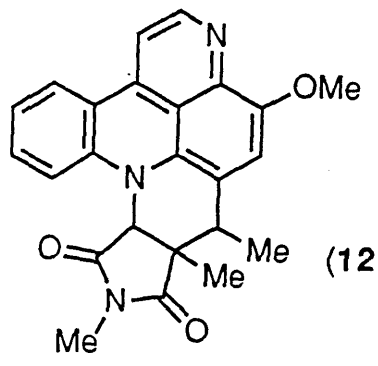
(9)


N
OMe
N
H
H
Me
Me
O
N
O
H

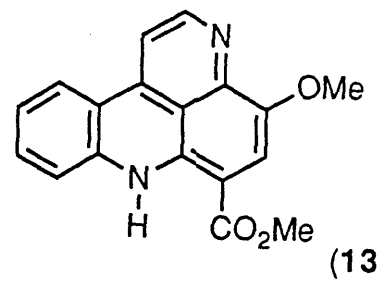
(10)


N
OMe
N
Me
H
Me
H
O
N
O
H

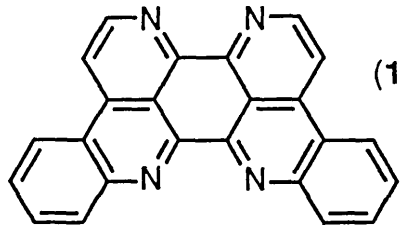
(11)


N
OMe
N
O
Me
Me
N
O
Me

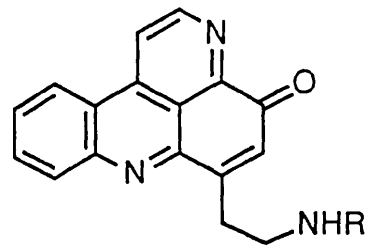
(12)

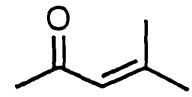

N
OMe
N
H
CO2Me

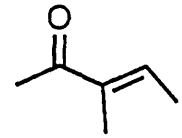
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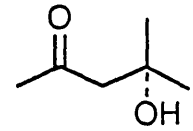


(14)

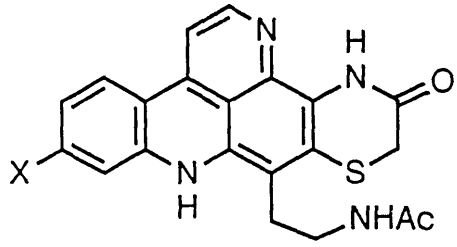


(15) R = 

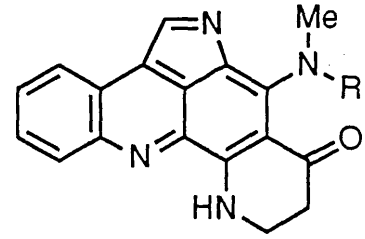
(16) R = 

(17) R = 

Plakinidine A (**20a**) and B (**21**),[14] isolated in 1989 from the sponge *Plakortis* sp. are included - despite lacking the pyrido-[k,l]-acridine substructure - because of their similarity to the group as a whole.

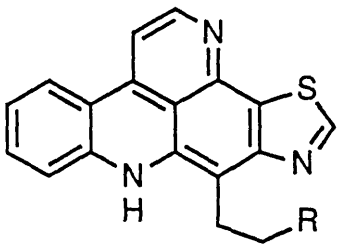


(**18**) X = Br
(**19**) X = H

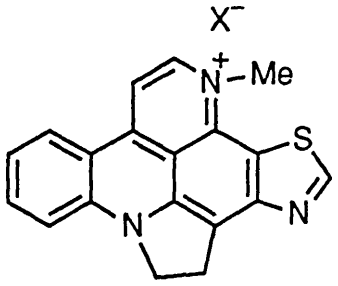


(**20a**) R = H
(**21**) R = $CH_3$

Late in 1989 came the publication of a group of dercitin analogues [15] - nordercitin (**22**), dercitamine (**23**), dercitamide (**24**), and cyclodercitin (**25**) - all isolated from *Dercitus* sp. and *Stellatta* sp. (also a sponge).

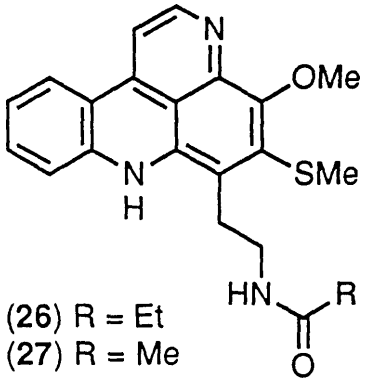


(22) R = $NMe_2$
(23) R = NHMe
(24) R = NHCOEt

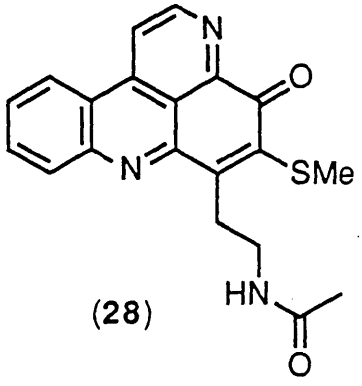


(25)

Varamine A (26) and B (27), isolated from the tunicate *Lissoclinum vareau*,[16] and diplamine (28) from the tunicate *Diplosoma* sp. [17] appeared in 1989. These three compounds are strikingly similar. If diplamine is viewed as a type of quinone monoimine then the varamines are the reduced (hydroquinoid) analogues.

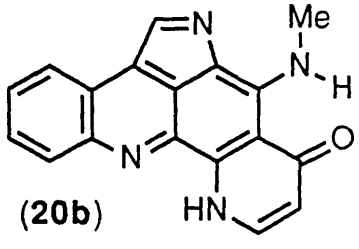


(26) R = Et
(27) R = Me



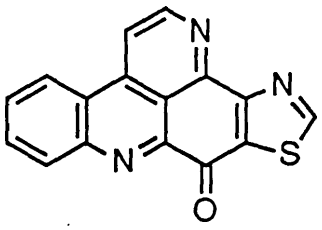
(28)

Ireland *et al.* published a further paper in 1990 concerning the plakinidine alkaloids (**20a** & **21**) which included a third member, plakinidine C, (**20b**) shown below. This was claimed not to be an artifact of isolation. However, the only evidence to support this conjecture was the fact that the analogous derivative of plakinidine B was not isolated. As well as the fact that plakinidine B is half as concentrated in the animal extracts as plakinidine A (which would imply a similar ratio between the artifacts - the concentration of plakinidine C is not provided), the structures (**20a**) and (**21**) may not be oxidised at the same rate as each other. The internal hydrogen bonding between the carbonyl and the secondary amine in (20a) may be a factor facilitating the ready oxidation of this compound to (**20b**).

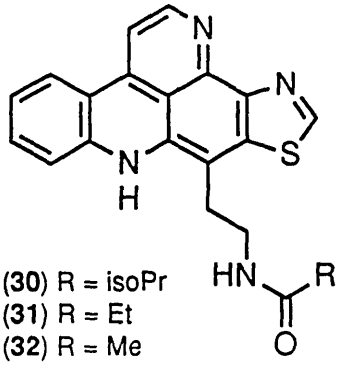


(**20b**)

Scheuer and Carroll isolated four new alkaloids from *Chelynotus semperi* , a type of mollusc in 1990.[54] The original source of the natural products was, however, an unidentified purple colonial tunicate on which the molluscs were feeding. The alkaloids, kaunoniamine A (**29**), B (**30**), C (**31**), and D (**32**) were found in both predator and prey.



(**29**)



(**30**) R = isoPr
(**31**) R = Et
(**32**) R = Me

Since the shell-fish (whose shells are covered in a fleshy mantle) are cryptic when feeding on its host tunicate, it seems that the pigments are concentrated by the predator for use as camouflage.

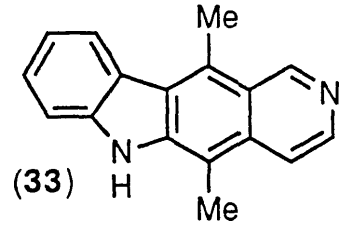
The similarity between these compounds and the dercitins [(**9**), (**22**) - (**24**)] is interesting, as is the fact that shermilamine B (**19**) was also found in these organisms.

## 1.3 BIOLOGICAL ACTIVITY AND BIOSYNTHESIS.

### 1.3.1 Biological Activity.

As a group these alkaloids show a number of general and very interesting properties. By far the most common is cytotoxicity. As well as this, many possess good to excellent antileukemic [for example ascididemin $IC_{50}$(L1210) 0.39 $\mu$g/ml][7] or anti-tumour [for example dercitin $IC_{50}$(P388) 0.05 $\mu$g/ml][9] activity. Examination of (**15** - **17**) and (**26** - **28**) reveals some simple structure - activity relationships. Activity against the L1210 leukemia cell line is unaffected by the oxidation level of the polycycle, that is whether the ring system is in the reduced (**26** - **27**)[16] or oxidised (iminoquinone) form (**28**).[17] However, the absence of the methylthio group in the cystodytins (**15** - **17**) reduces their potency tenfold.[11] The reason for this must remain a mystery until detailed mechanistic studies into the mode of action of these alkaloids are carried out.

It has been suggested [17] that these compounds intercalate with DNA, and in view of their structural similarity to the extensively studied acridines this would appear to be a reasonable assumption. This property and recent work on the mechanism of cytotoxicity of drugs of this class highlight a number of intriguing facts.



(**33**)

Primarily, intercalation, though inhibiting *in vitro* DNA polymerases and DNA dependent RNA polymerases [18] does not cause cell death for this reason. [19] Also, though DNA binding is a prerequisite for activity among the intercalators there is only a slight correlation between DNA binding affinities and cytotoxicity. [20] From this information it may be deduced that although DNA is involved in the activity of these drugs, there is another factor involved. In the ellipticine series [for example ellipticine (**33**)], and more recently with other intercalators, the additional factor has been shown to involve topoisomerase II. This enzyme catalyses the passage of a double strand of DNA across

another, increasing the linkage number by two. In the case of circular DNA the result is to supercoil the DNA loop. This activity is shown schematically in Diagram 1.

The intercalators appear to stabilise one of two intermediate DNA-topoisomerase complexes leading to hidden single or double DNA strand breaks. These may be revealed using Proteinase K (Diagram 1). Though this process can be reversed by removal of the drug, it is thought to be the cause of cell death by a mechanism as yet unknown. [21]

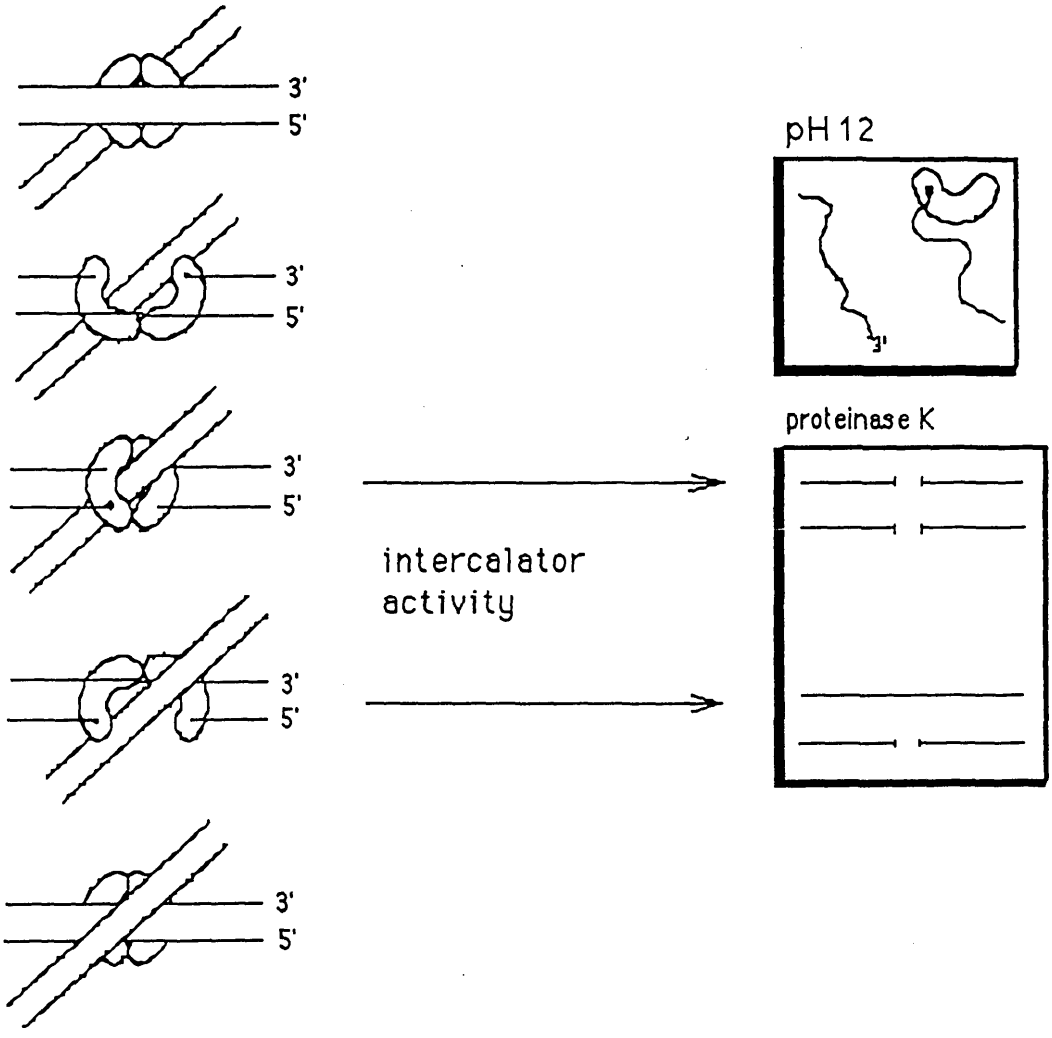



**Diagram 1** showing the mechanism of action of topoisomerase II. The parallel lines represent the DNA double strands being acted on by the enzyme (split doughnut shape). On the right is shown the unmasking of strand breaks by adding Proteinase K to the intercalator-stabilised complexes, and also the destruction of the stabilised complexes by high pH.

The intercalators so far studied have been shown to produce DNA strand breaks at characteristic and specific sites, and furthermore the more selective antineoplastic agents have been shown to produce these breaks within protooncogenes - now known to be linked to tumour proliferation. [22] Since these genes are considerably amplified in tumour cells it would be reasonable to suppose that the selectivity of the drugs is directly related to this activity.

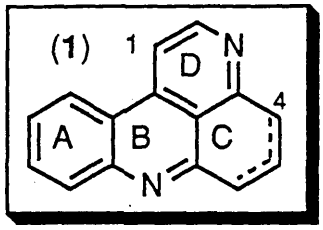
The compounds discussed in this review are important because they form a novel group of compounds which are very likely intercalators. Thus their study may be able to shed more light on structure - activity relationships and the mechanism of topoisomerase - mediated cytotoxicity of DNA binding drugs.

The alkaloids show toxicity to a wide range of organisms (including parasites[14] and microbes[17]), but it was not stated whether this is specific or a function of their cytotoxicity. Dercitin was shown to inhibit viral activity in a number of model systems such as A-59 murine coronavirus.[17] In this case cytotoxicity was negligible for total inhibition of the virus at a concentration of 1 $\mu$g/well. Other less common properties include immunosuppression by the dercitin group,[14,15] reverse transcriptase inactivation by the plakinidines,[14] and potent calcium-releasing activity in sarcoplasmic reticulum by ascididemin[7] and the cystodytins.[11]

It can be seen from this summary that these drugs warrant considerable biological testing to reveal the full scope of useful properties which may be only hinted at by the present studies. Implicit in this statement is the fact that versatile and efficient syntheses are required to assist the development of therapeutic analogues.

### 1.3.2 Biosynthesis.

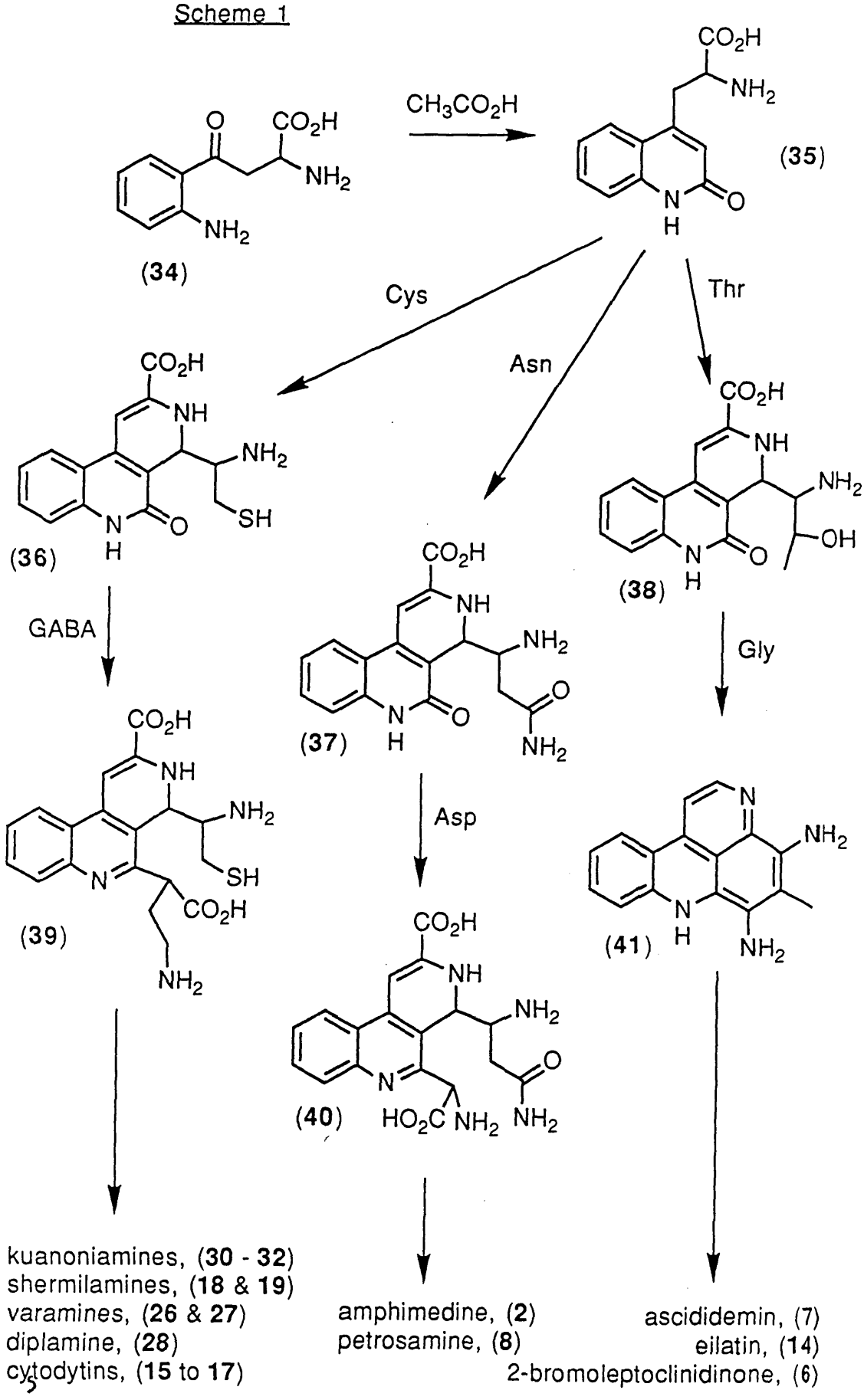
On examination of the structures of these compounds it is notable that almost all the structural diversity in the group is found on the C ring of the pyridoacridine substructure (1). It will also be seen that this substructure is always substituted by nitrogen or oxygen in the 4 - position (with the notable exception of the dercitin family and the tentatively assigned calliactine).



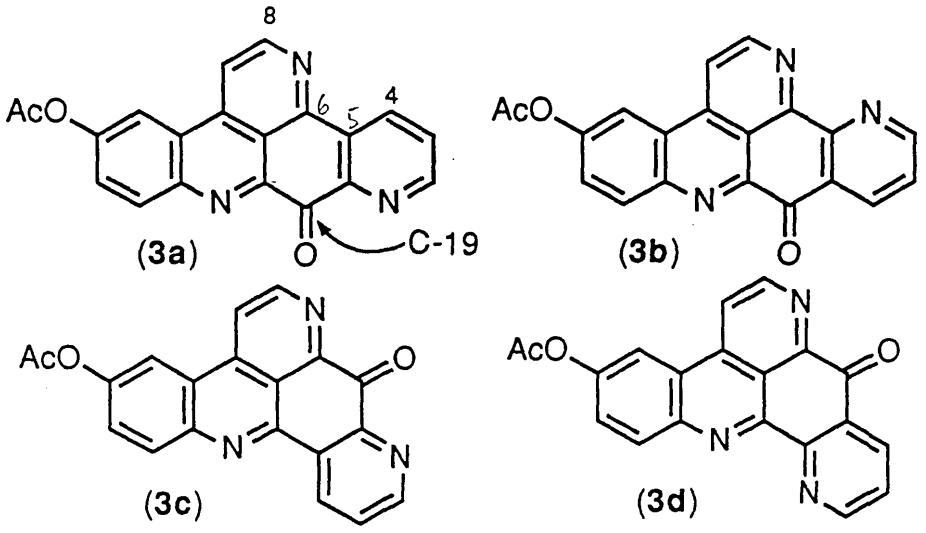

The close similarities between the members of this group suggest strongly that they are biosynthetically related. However, as stated in the introduction, their marine sources span three phyla. This amount of differentiation usually brings with it far greater secondary metabolite diversity than is seen in this group of alkaloids. It is for this reason that the suggestion has been made that these alkaloids are the work of symbionts,[8] and it may be that these anabolise some simple intermediate common to all the host animals.

It is known that animals, unlike plants, base their quinoline syntheses on kynurenine (34), an oxidation product of tryptophan. It is on this material that the biosynthesis is thought to be based (Scheme 1).[23] There are a limited number of structures not covered by the scheme. In particular, the dercitin group, whose assignment is irrefutable, bear a thiazole ring which appears to contradict the biosynthetic hypothesis. The varamines (**26**, **27**), diplamine (**28**), shermilamines (**18** - **19**), and particularly the kaunoniamines (**29** - **32**) which show a striking similarity to the dercitins but for the regioisomerism of the sulphur and nitrogen, are all tunicate / ascidian metabolites, whereas the dercitins are isolated from sponges. This fact may be the key to the apparent anomaly.

Scheme 1


CH3CO2H
(34)
(35)
Cys
Asn
Thr
(36)
(37)
(38)
GABA
Asp
Gly
(39)
(40)
(41)
kuanoniamines, (30 - 32)
shermilamines, (18 & 19)
varamines, (26 & 27)
diplamine, (28)
cytodytins, (15 to 17)
amphimedine, (2)
petrosamine, (8)
ascididemin, (7)
eilatin, (14)
2-bromoleptoclinidinone, (6)

The other anomaly in the group is calliactine.[2] It is worth examining the proposed structure of calliactine in greater detail. A combination of NMR, IR and MS techniques lead the authors to suggest four possible structures for neocalliactine acetate (**3a** to **3d**), a fully aromatic degradation product of calliactine. Further evidence was then sought.




(i) C-19 was shown to be a doublet ($\underline{J}$ = 3.8 Hz) coupled to H-4 (by $^{1}H$ - $^{13}C$ long range correlations with 5 Hz as $\underline{J}$ value, and by an H-4 irradiated $^{13}C$ - gated spectrum). Both ascididemin (**7**) and 2-bromoleptoclinidinone (**6**) showed cross peaks corresponding to analogous couplings, with J values of the order of 3 Hz. This evidence points to (**3b**) or (**3d**) for neocalliactine acetate.

(ii) Conflicting evidence came from selected nOe data. Irradiating H-4 in an nOe difference spectrum showed enhancement of H-8 as well as the obvious enhancement of H-3. Of the structures proposed, (**3a**) presents the shortest interatomic distance between these protons, though even this is of the order of 4.2 Å (from Dreiding models). In support of this conjecture 6-methoxy-1,7-phenanthroline was examined. nOe enhancement was found on irradiation of the analogous protons.

(iii) On examination of the structures proposed, it may be seen that (**3b**) and (**3d**) contain the 1,10-phenanthroline substructure. Since no chelation of iron (II) by neocalliactine acetate was observed these structures were discounted by the authors. However it is now well known that this group of natural products do not chelate iron (II) despite the presence (where applicable) of the phenanthroline nitrogens. This property is also found in the case of 1,10-phenanthroline-5,6-quinone. It is suggested that inductive

electron withdrawal from the phenanthroline nitrogens reduces the interaction between the lone pairs of electrons thus making the phenanthroline a weaker chelating group. It is worth noting that the UV spectra of these compounds show that complex interactions still occur with transition metal cations.

The evidence given is thus found to be conflicting. If the biosynthetic hypothesis bears any validity (**3b**) would be the structure of choice and synthetic activities in this direction would be prudent.§

Finally, it must be noted that calliactine is anomalous not only by right of its structure, but also because it is the only member of the pyridoacridine group to have been isolated from a sea anemone. The incongruities of this compound suggest that it is at the very least a distant biosynthetic relation to the others (if it is related at all).

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§ It is worth noting in passing that, with the exception of carbon atoms nearest the ring substituents, $^{13}C$ shifts for (**3**), (**6**), and (**7**) are almost identical. In the case of a completely delocalised aromatic system this suggests that the ring systems are identical.

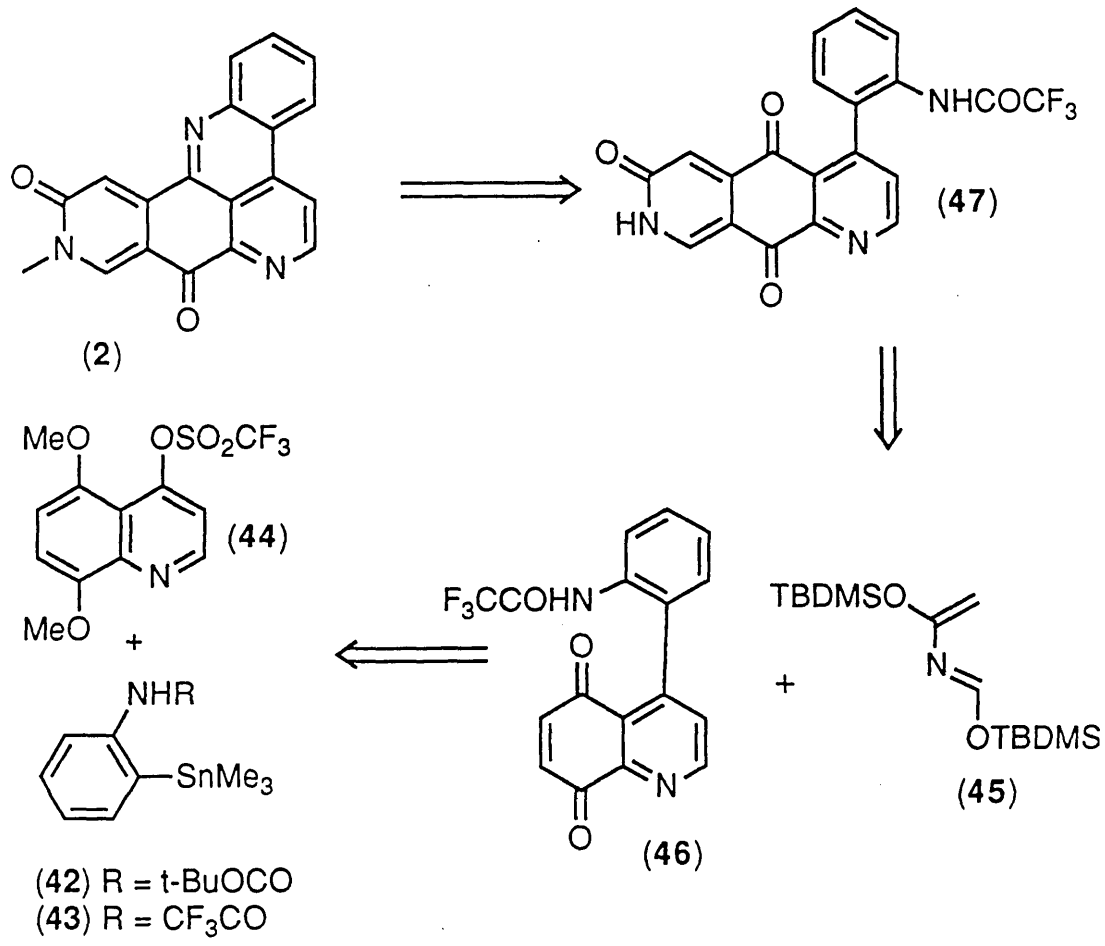
## 1.4 SYNTHETIC APPROACHES.

### 1.4.1 Amphimedine.

As befits the senior member of the group, most synthetic work published to date has been on this pentacycle.

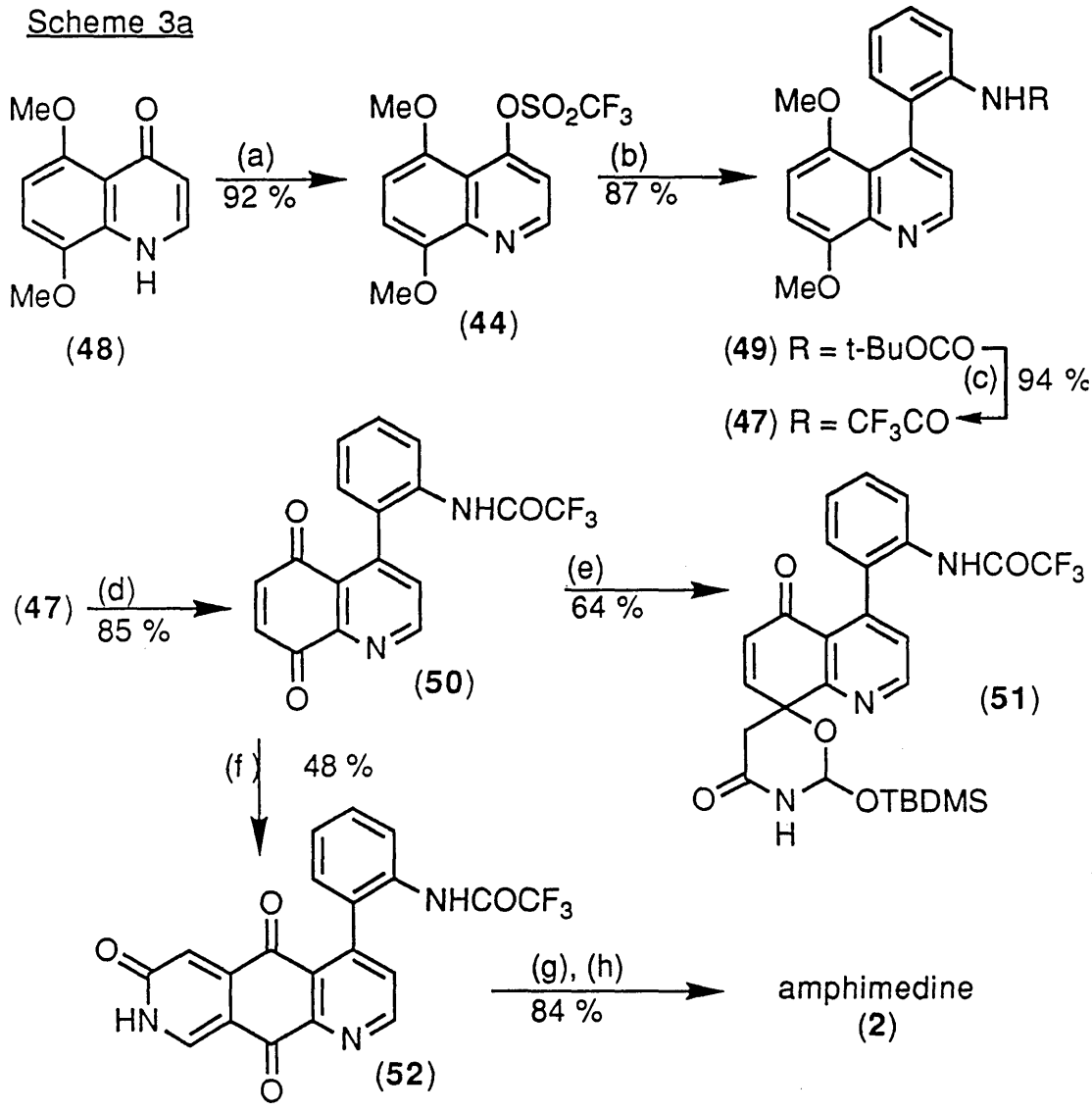
In 1988 Echavarren and Stille [24] published the first total synthesis of amphimedine (Scheme 3a). This was based on an elegant series of disconnections hinged on palladium cross coupling of aryl triflates with organostannanes developed in Stille's group (Scheme 2). The synthesis of the intermediate (**50**) was readily achieved. However, the switching of the aniline protecting group, an unplanned extra step, was required for a number of reasons.

Scheme 2



Firstly, the trifluoroacetate protected anilinostannane was derived from the BOC analogue in a poor conversion sequence hampered by extensive destannylation. The coupling reaction of the trifluoroacetate was also more sluggish and lower yielding than that of the BOC analogue due to deactivating electron withdrawal by the trifluoroacetate. The reason for the switch back to trifluoroacetate prior to oxidation to the quinone (**52**) was that preferential oxidation of the aniline ring occurred when it was protected with a BOC group.

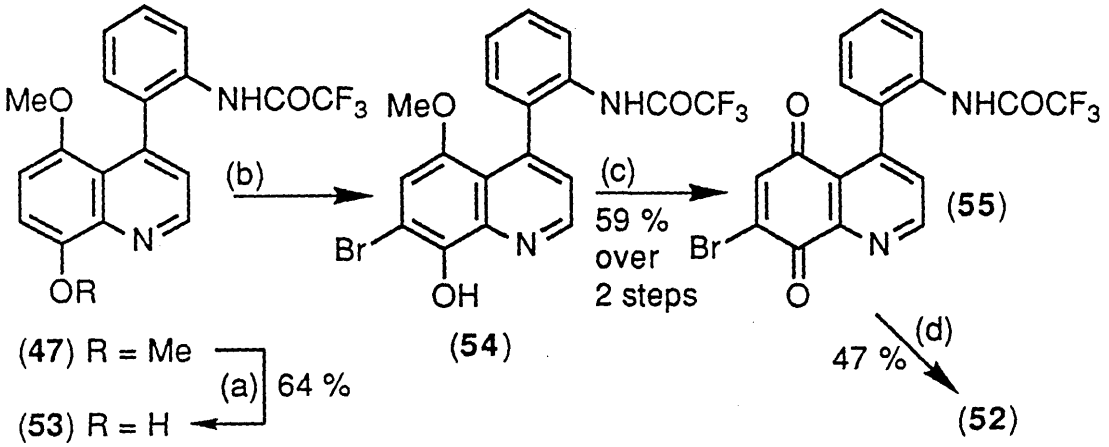
Scheme 3a




(a) $pTs_2O$, 2,6-lutidine, DMAP, $CH_2Cl_2$ , 0-23 °C 30 min, 23 °C 1 h. (b) (**42**), $Pd(PPh_3)_4$, LiCl, 1,4-dioxane, 100 °C 5 - 7 h. (c) (i) TFA 23 °C 1h; (ii) TFAA, DIPEA, THF, 0 °C 30 min. (d) CAN, $CH_3CN$ - $H_2O$, 23 °C 15 min. (e) (i) (**45**), dry acid free $CHCl_3$, 23 °C 6 h; (ii) MeOH, 23 °C 30 min. (f) (i) (**45**), THF, 23 °C 6 h; (ii) pyridinium hydrofluoride. (g) 1:1 6M HCl - THF, 70 - 80 °C 3 h. (h) $Me_2SO_4$, $K_2CO_3$, DMF, 23 °C 3 h.

Reaction of the intermediate (**50**) with Ghosez's diene (**45**) under standard conditions (chloroform, ambient temperature) produced a novel and unprecedented cycloadduct (**51**), that of Diels-Alder reaction with a carbonyl of the quinone. Replacement of chloroform with THF gave the expected product (**52**). This regioisomer would be expected on the basis of the electronics of the quinone, but to confirm this supposition the Diels-Alder reaction was repeated on the bromoquinone (**54**) (Scheme 3b). This gave the same product, vindicating the assumed regiochemistry. Deprotection of the aniline and methylation of the amide readily gave amphimedine in an overall yield of 26 %.

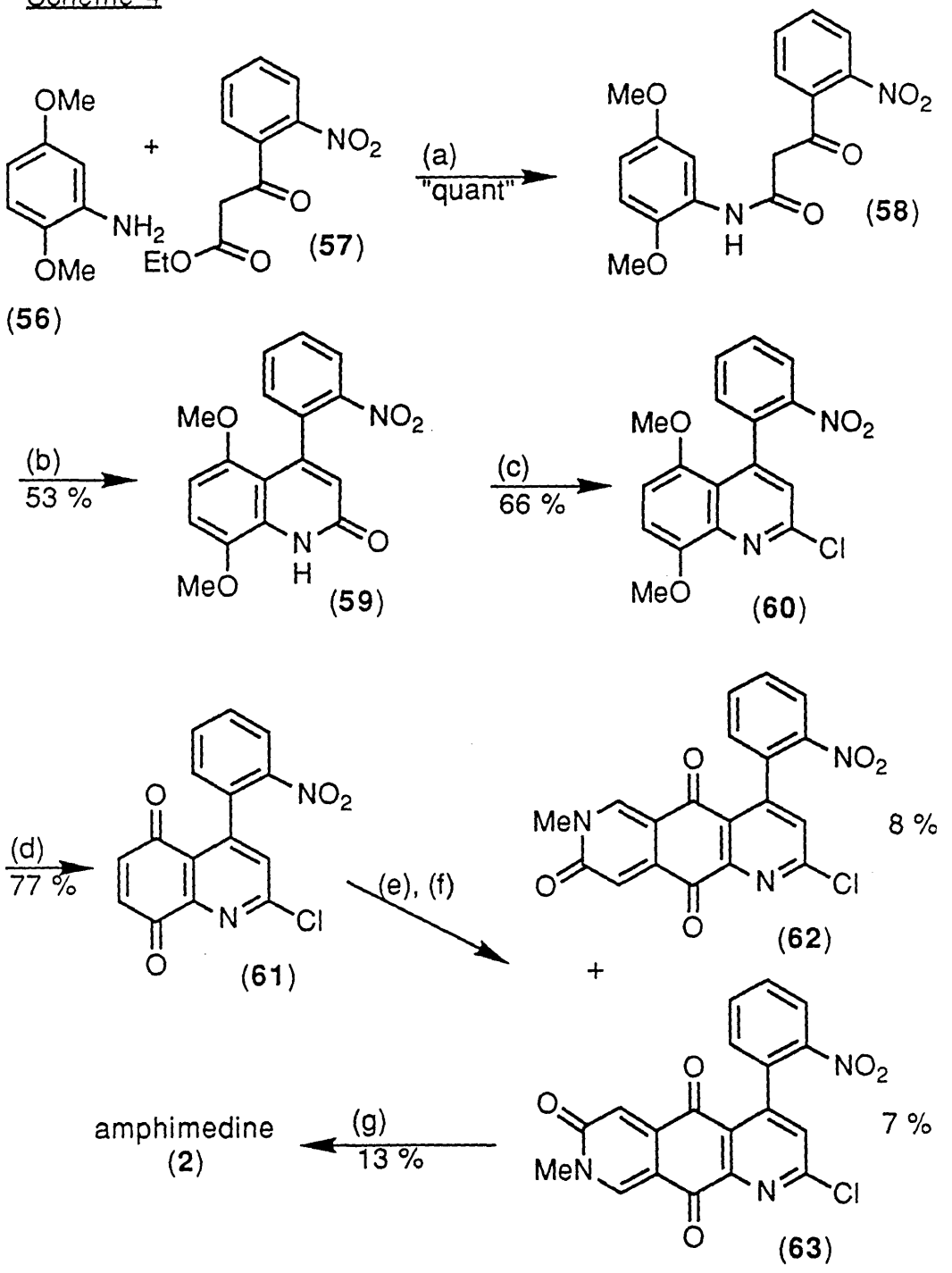
Scheme 3b




(a) LiI, 2,6-lutidine, 140-145 °C. (b) $Br_2$, HOAc, $CHCl_3$. (c) CAN, $CH_3CN$-$H_2O$, 0°C 15 min. (d) (**45**), THF, 23 °C 21 h.

1988 also saw the publication of Kubo and Nakahara's [25] synthesis. Their disconnections were almost identical to Stille's but, lacking the cross coupling methodology, they were forced to rely on older annulation methods to produce the intermediate (**59**) (Scheme 4). Chlorination of the quinolone followed by oxidation to the quinone and then a troublesome Diels-Alder reaction with Ghosez's diene (**45**) led to a low yield of the two regioisomeric adducts, which were methylated *in situ* to assist separation. This was followed by catalytic hydrogenation, which yielded amphimedine in one step (0.25 % overall).

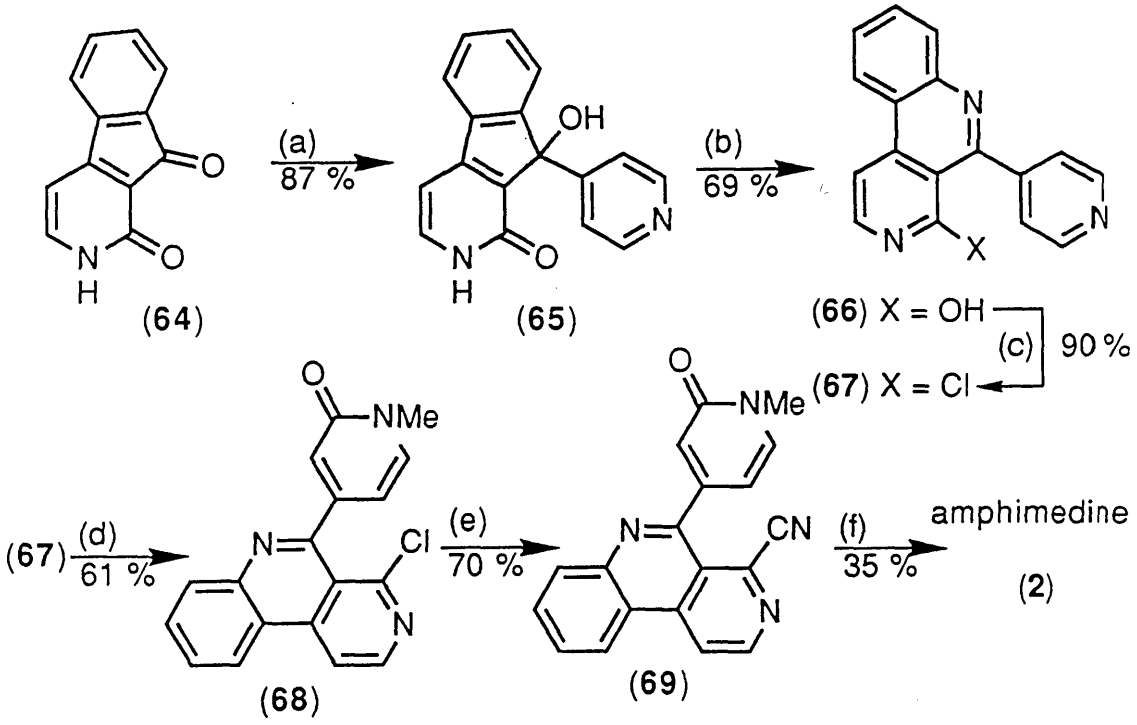
Scheme 4




(a) PhMe, catalytic Py, 140 °C 6 h. (b) 80 % $H_2SO_4$, 75 °C 30 min. (c) $PCl_5/POCl_3$, 70 °C 45 min. (d) CAN, $CH_3CN$-$H_2O$, 0 °C 15 min. (e) (i) (**45**), $CHCl_3$, 35 °C 8 h; (ii) $H^+$. (f) $CH_3I$, $K_2CO_3$, tris[2-(2-methoxyethoxy)ethyl]amine, DMF, 25 °C 1 h. (g) $H_2$, 10 % Pd/C, $Et_3N$, MeOH, 25 °C 20 h.

A year after Kubo's synthesis Prager and Tsopelas [26] produced a novel route to the molecule involving an azide mediated ring expansion (Scheme 5). Protection of the amide functionality in (**64**) followed by addition of 4-lithiopyridine to the fluorenone carbonyl yielded (**65**).Azido-dehydroxylation was followed by synchronous nitrogen elimination and aryl migration to give (**66**) in one step. Previous work by Prager [27] had shown that the most electron rich aryl group migrates, as was found to be the case in this reaction. Chlorodehydroxylation of the quinolone was followed by methylation and oxidation to (**68**). Finally cyano-dechlorination and acid catalysed cyclisation gave amphimedine in an overall yield of 8 %.

Scheme 5

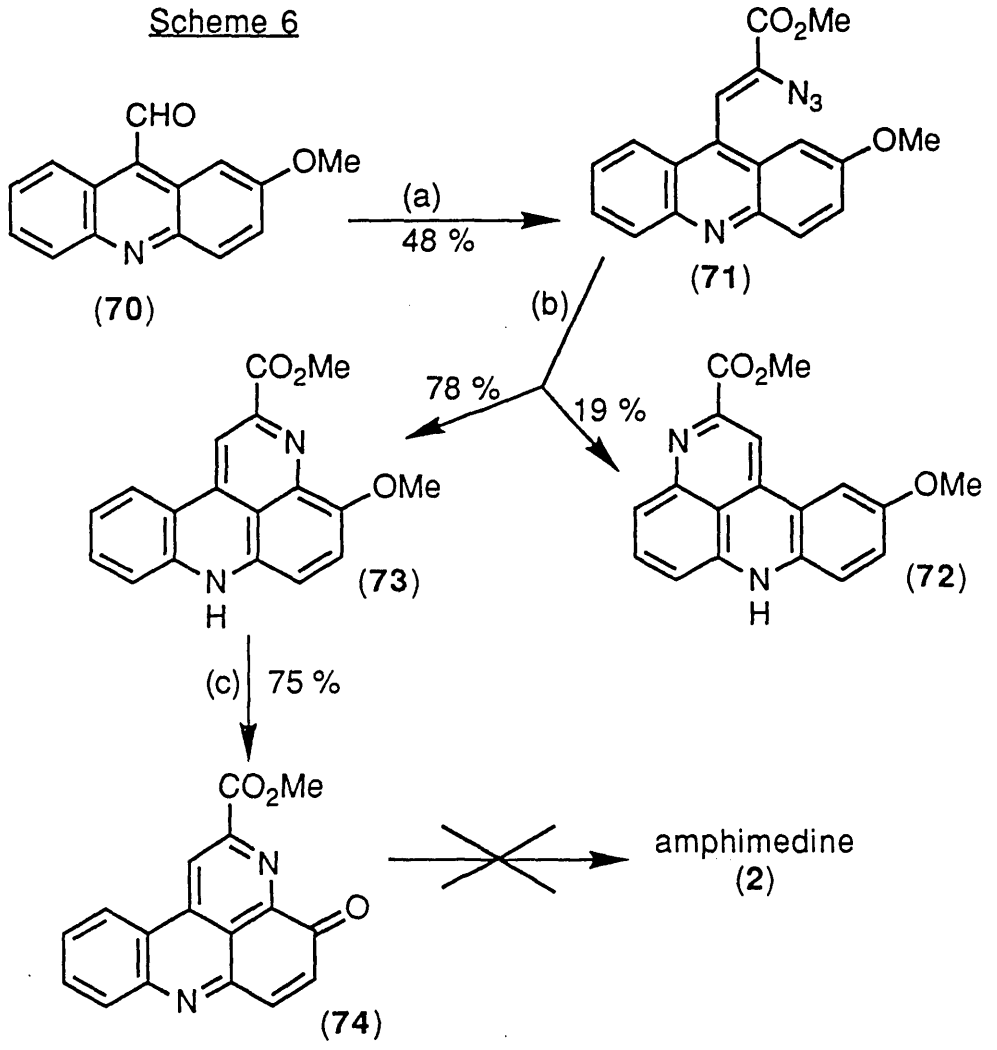



(a) (i) TMSCl, $Et_3N$, THF, 60 °C 60 min; (ii) 4-bromopyridine, BuLi, - 40 to 20 °C 2 h. (b) $NaN_3$, PPA, 45 °C 20 h. (c) $PCl_5$, DMF (cat.) in $POCl_3$, 180 °C 20 h. (d) (i) $MeOSO_2F$, 1.3 equiv.,20 °C 40 min; (ii) KOH, $K_3Fe(CN)_6$, 2 equiv., 20 °C 10 h. (e) CuCN, DMSO, 150 °C 4 h. (f) PPA, 90 °C 5 h.

Prior to these three syntheses Moody and Rees[28] had published a study towards amphimedine (Scheme 6). Starting from the readily available acridine aldehyde (**70**), condensation with methyl azidoacetate followed by azide decomposition yielded the intermediate tetracycle in what is now a well known annulation procedure. Oxidation of

this tetracycle to the iminoquinone (**74**) was readily achieved. However this material resisted all attempts to effect a Diels-Alder reaction with Ghosez's diene (**45**). There appear to be two reasons for this. Firstly the compound is extremely insoluble. This can be counteracted by transesterification to give the isopropyl ester. Lack of reactivity of this analogue is thought to be due to unfavourable frontier orbital energetics resulting from the considerable delocalisation through the aromatic polycycle.

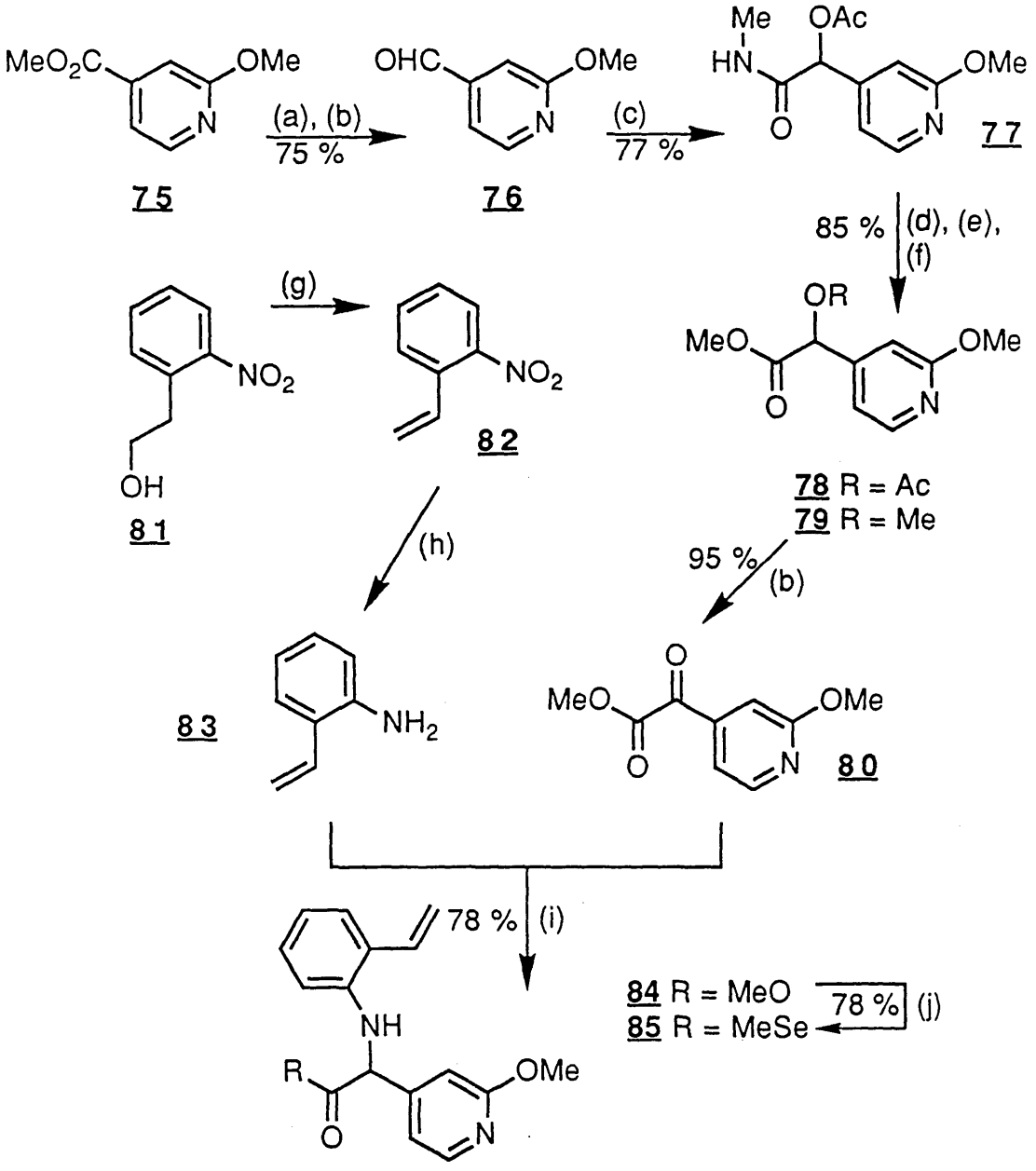
Scheme 6




(a) $MeO_2CCH_2N_3$, NaOMe, MeOH, -10 to 0 °C. (b) xylene, 140 °C. (c) $MnO_2$, 35 % $H_2SO_4$.

A second study towards amphimedine was published in 1989 by Weinreb *et al* [29] involving an interesting intramolecular Kondrat'eva reaction.[33] This reaction involves the Diels - Alder reaction of an oxazole with an alkene to give, after aromatisation, a pyridine ring. The intermediate (**85**) was synthesised using standard techniques (shown in Scheme 7), and then converted into the oxazole (**86**) utilizing the Kozikowski modification[34] of the Schöllkopf oxazole synthesis.[35]

Scheme 7

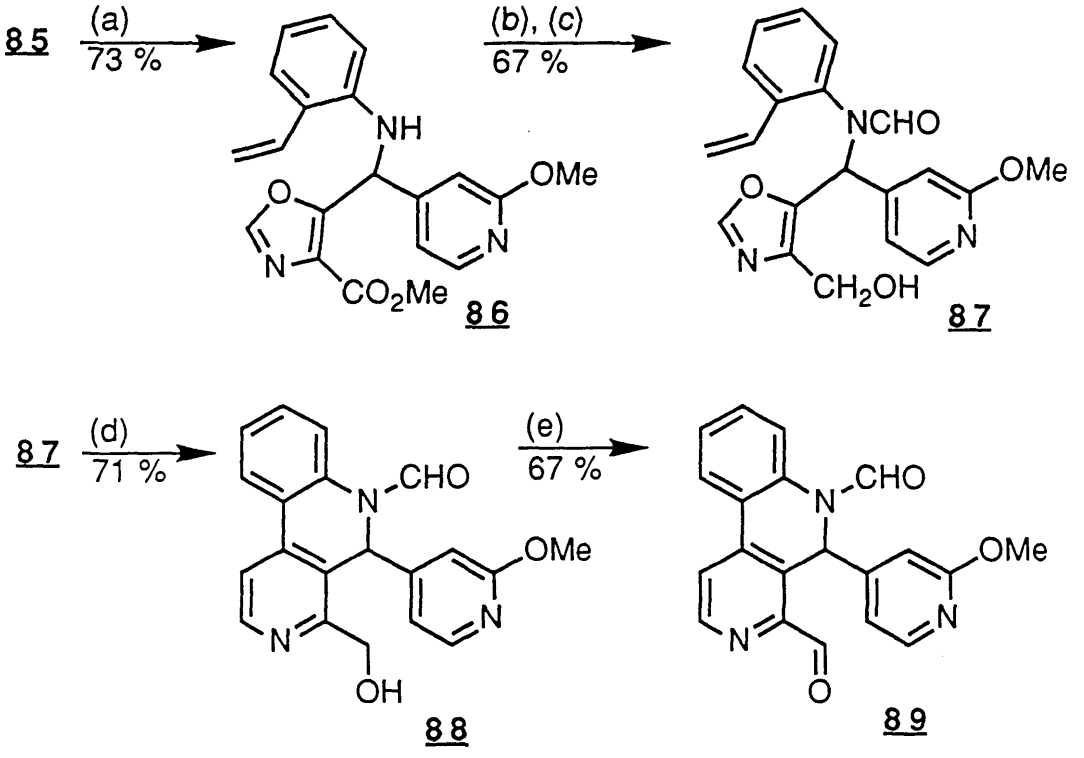



(a) $Ca(BH_4)_2$, THF, room temperature. (b) $CrO_3$ / Py, $CH_2Cl_2$, room temperature. (c) MeNC, MeOH, AcOH, 60 - 65 °C. (d) $NaNO_2$, $Ac_2O$, AcOH, 0 °C. (e) $Na_2CO_3$, $CCl_4$, reflux. (f) NaOMe, MeOH, 0 °C. (g) MsCl / DBU, THF, 83 °C. (h) Fe, AcOH, EtOH, 60 °C. (i) (1) pTsOH, PhMe, 90 °C; (2) $NaCNBH_3$, MeOH, AcOH. (j) $Me_2AlSeMe$, PhMe.

This oxazole (**86**), with an ester functionality on the 4-position of the oxazole was reduced to the hydroxymethyl compound and protected at the free amino site to give the intermediate (**87**). Earlier model studies had shown that the ester (**93**) underwent decarboxylation whilst cyclising, but that the silylated alcohol reacted as required.

Kondrat'eva had also found that electron - withdrawing groups at C-4 of the oxazole prevented reaction (this suggests that decarboxylation occurs prior to cyclisation). For these reasons the ester in (**86**) was reduced prior to cyclisation. The Kondrat'eva reaction on the unprotected alcohol (**87**) then produced the required naphthyridine (**88**) in 71 % yield (shown in Scheme 8).

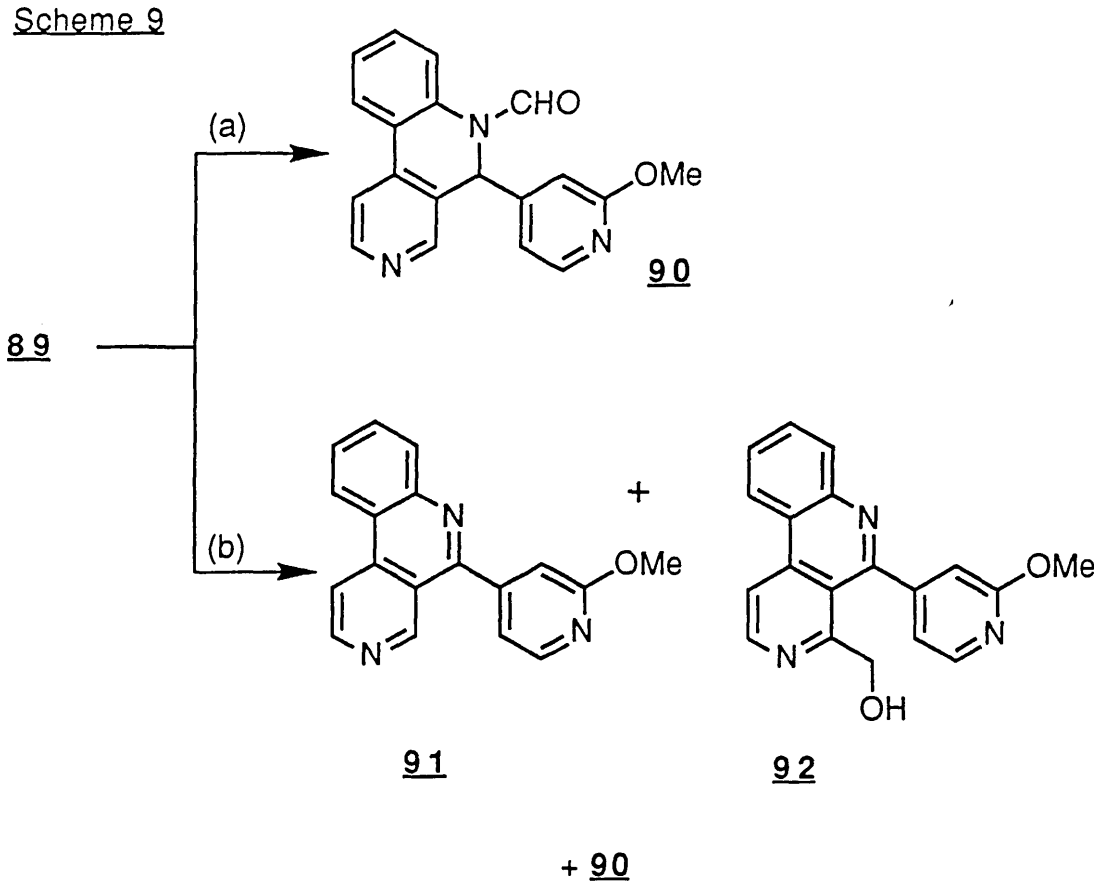
Scheme 8




(a) $CNCH_2CO_2Me$, $Et_3N$, $Cu_2O$, THF. (b) $Ca(BH_4)_2$, THF, MeOH. (c) $Ac_2O$, $HCO_2H$, THF, room temperature. (d) *o* - DCB, DBN, 150 °C. (e) $MnO_2$, $CHCl_3$, room temperature.

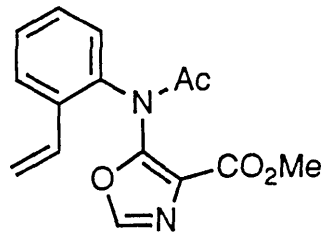
Manganese dioxide oxidation of this alcohol to (**89**) led to a system which Weinreb hoped would photoenolise and then undergo a Diels - Alder reaction to give (**94**) from which amphimedine would be readily accessible.

Scheme 9

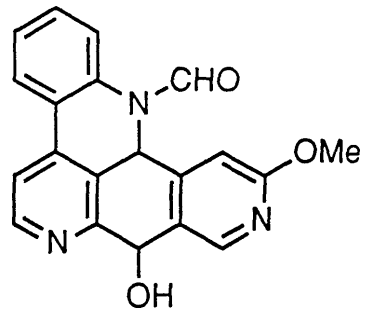



(a) hν, $Me_2CO$ or PhH. (b) hν, DME.

Unfortunately, despite the use of a variety of solvents no cyclised products could be isolated. Various products isolated on two particular runs were described without yields and are shown in Scheme 9.




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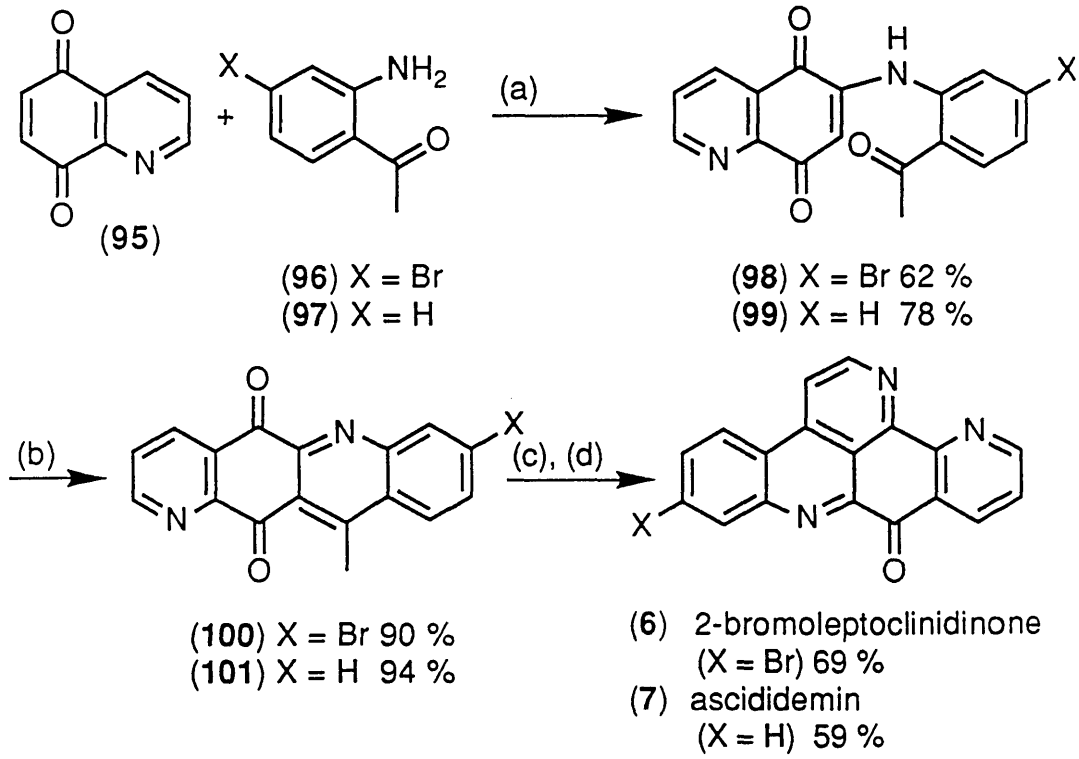



94

### 1.4.2 Ascididemin and 2-Bromoleptoclinidinone.

In 1990 Franz Bracher produced the first synthesis of ascididemin [30] and 2-bromoleptoclinidinone. [31] These syntheses are almost identical and will be discussed together (Scheme 10). Central to both is the regioselective amination of quinoline-5,8-quinone (**95**) in the presence of cerium (III). Thus amination with 2-aminoacetophenone (**97**) or the 4-bromo analogue (**96**) as required, followed by cyclodehydration, gave the intermediate tetracycles (**100**) and (**101**). Condensation with dimethylformamide-diethyl acetal and subsequent cyclisation with ammonium chloride in acetic acid in a rapid one-pot annulation procedure produced 2-bromoleptoclinidinone and ascididemin (38 % and 43 % yield respectively from the quinolinequinone).

Scheme10

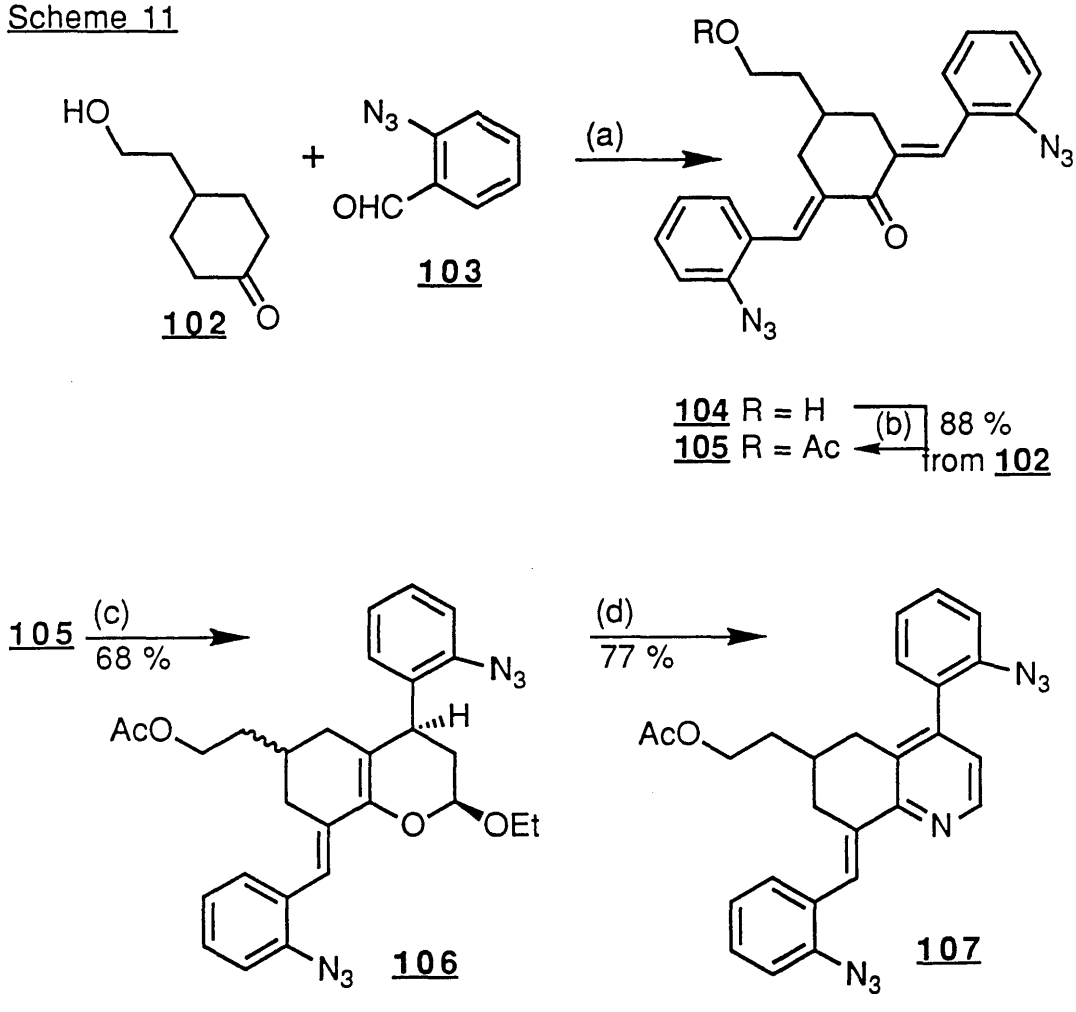



(a) $CeCl_3.7H_2O$, EtOH, 20 °C 16 h. (b) conc. $H_2SO_4$—AcOH (1:10), reflux 10 min. (c) $HC(OEt)_2NMe_2$, DMF, 120 °C 1 h. (d) $NH_4Cl$, AcOH, reflux 1 h.

### 1.4.3 The Cystodytins.

In 1989 Ciufolini and Byrne [32] published the first synthesis of the cystodytin framework. Though they approached within a few steps of the fully functionalised cystodytin A they did not publish a complete synthesis. The synthesis is centered around a modification of the Knoevenagel - Stobbe pyridine synthesis developed in their group (Scheme 11).

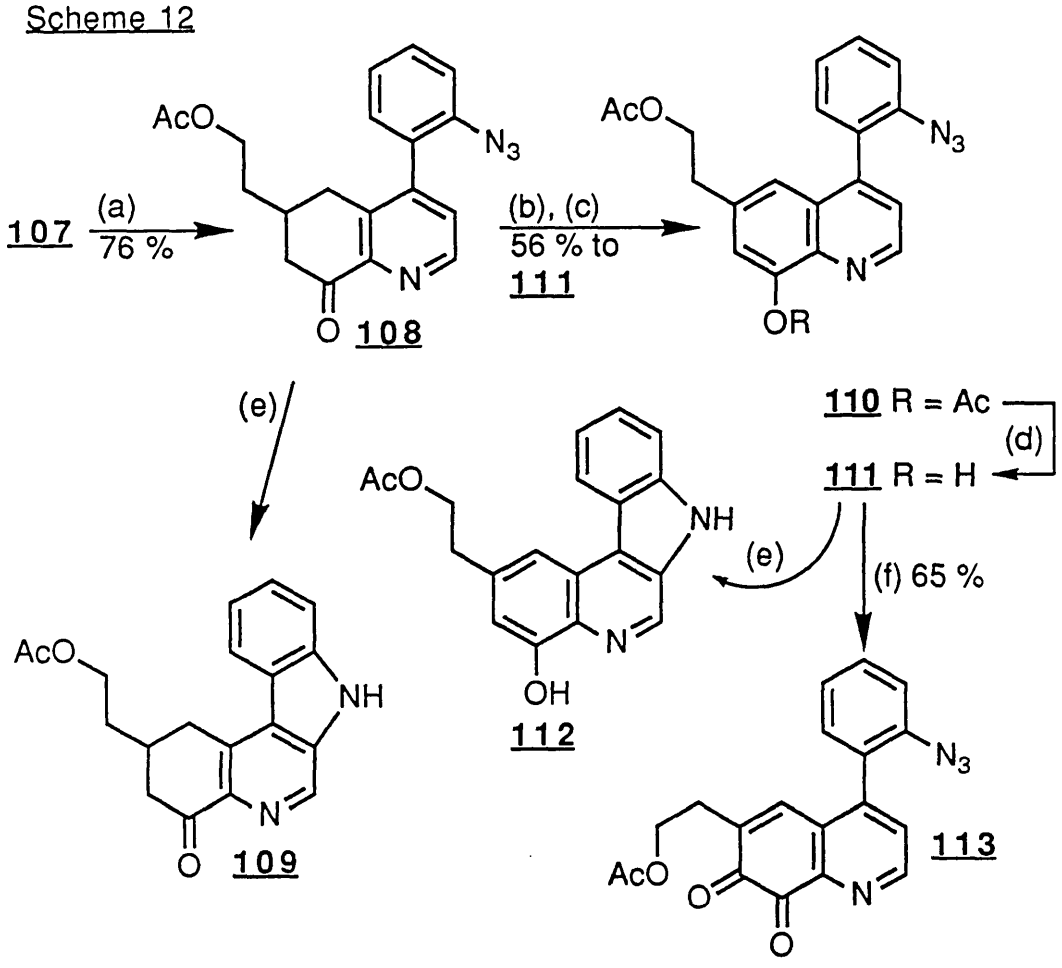
Scheme 11




(a) 10 % aq. NaOH, EtOH, 0°C. (b) $Ac_2O$, Py. (c) $CH_2$=CHOEt, $(CH_2Cl)_2$, $Yb(fod)_3$, reflux. (d) $HONH_3^+Cl^-$, MeCN, reflux.

Thus, double aldol condensation of (**102**) with (**103**) gave (**104**) which was acylated to give the symmetrical conjugated enone (**105**). This material, in contrast to aliphatic enones, reacted readily with ethyl vinyl ether to give what appeared to be only the cis-ethoxydihydropyran (**106**). This intermediate, a latent 1,5-dicarbonyl compound, was cleanly converted into the pyridine (**107**) using hydroxylamine hydrochloride.

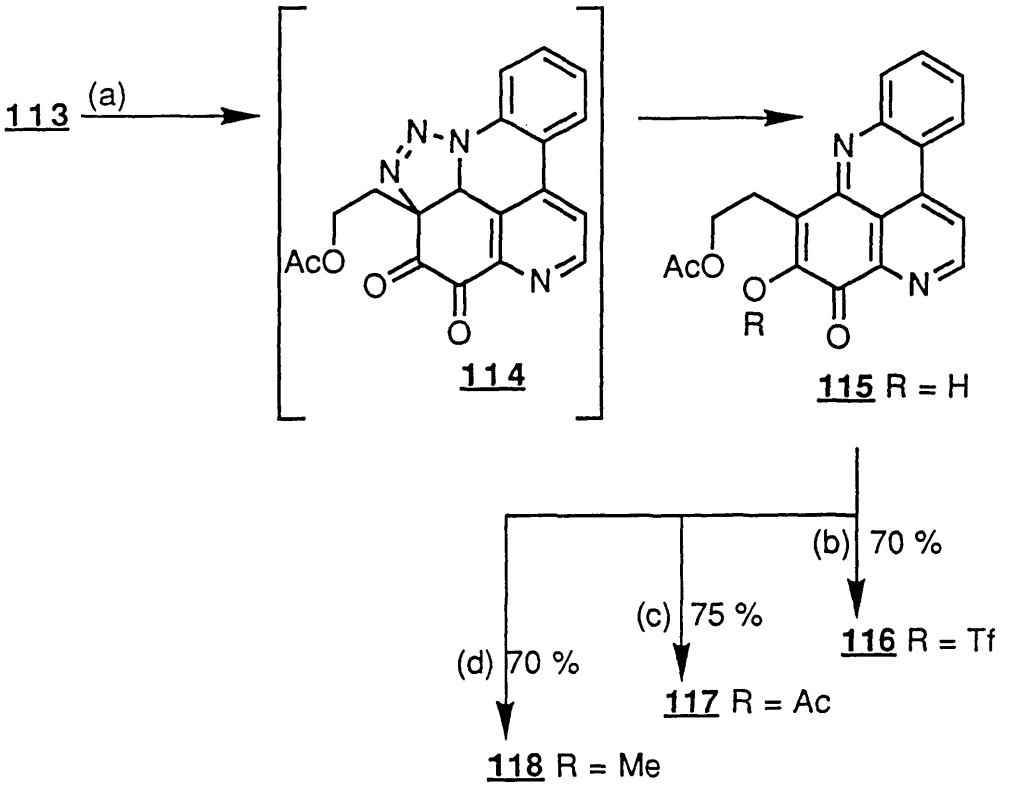
Scheme 12




(a) $O_3$, MeOH, -78 °C, then $Me_2S$. (b) isopropenyl acetate, cat. TfOH. (c) 1 eq. DDQ, PhMe, reflux, 15 min. (d) aq. $NaHCO_3$, MeOH, 25 °C, 12 h. (e) *o* - dichlorobenzene, >180 °C. (f) Fremy's salt, MeOH, phosphate buffer, 25 °C.

Ozonolytic cleavage of the remaining benzylidene group afforded the ketone (**108**), which was aromatised in three steps to give the phenol (**111**). It had been envisioned that thermolysis of the azide would then form the required pyridoacridine skeleton; unfortunately (but predictably) CH insertion by the incipient nitrene yielded the other regioisomer (**112**) as the only product. In an analogous fashion the ketone (**108**) gave the carboline (**109**) (Scheme 12).

Scheme 13




(a) PhMe, reflux. (b) $Tf_2O$, Hünig's base, $CH_2Cl_2$, 0 °C. (c) $Ac_2O$, Py. (d) $CH_2N_2$, ether, $CH_2Cl_2$.

Success was achieved by involving a different pathway for the azide decomposition (shown in Scheme 13). Thus the phenol (**111**) was oxidised with Fremy's salt to give the ortho-quinone (**113**), which on thermolysis underwent what appears to be a 1,3-dipolar cycloaddition of the azide group to the quinone followed by elimination of nitrogen to give the required tetracycle (**115**). This phenolic structure was derivatised to give (**116 - 118**).

## 1.5 SUMMARY.

This review has shown the range of marine alkaloids based on the pyrido[k,l]-acridine structure isolated to date. Their sources include a wide range of simple animals from three Phyla. A biosynthetic pathway has been described to assimilate the structural data, and by reference to this hypothesis the two "anomalous" structures have been discussed.

The varied and extremely interesting biological properties are outlined. The anticancer activity of the alkaloids, a common feature of all those tested, is examined with reference to recent results on the mode of action of intercalating drugs.

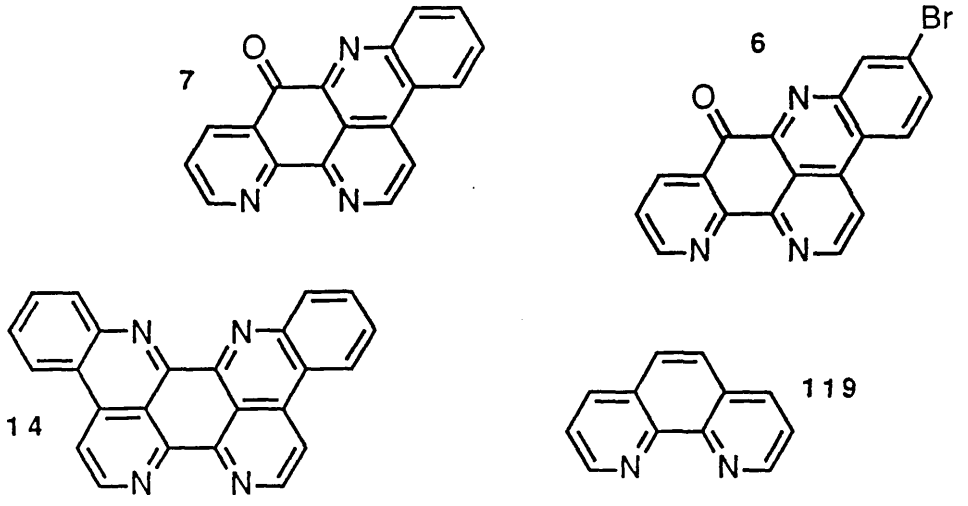
Finally the published syntheses of, and synthetic approaches to, the compounds are described.

# CHAPTER TWO.

# THE SYNTHESIS OF ASCIDIDEMIN.

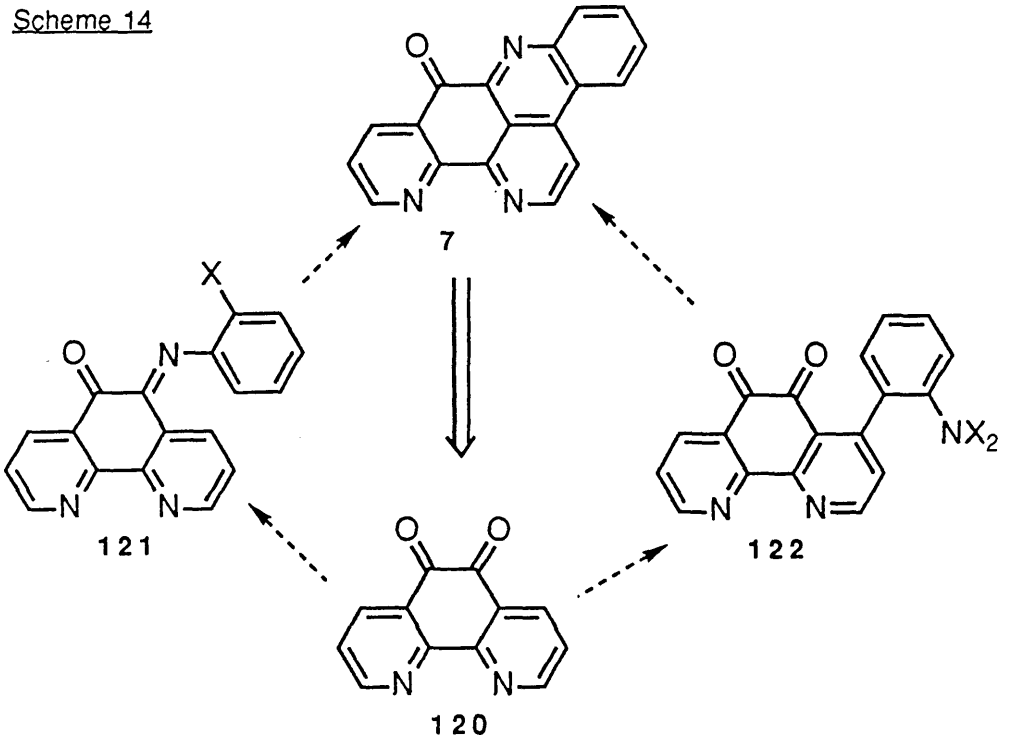
## 2.1 RETROSYNTHESIS.

In view of the 1,10-phenanthroline structure (**119**) common to ascididemin (**7**), eilatin (**14**) and 2-bromoleptoclinidinone (**6**) it was decided that this tricycle would serve as a suitable starting point for a synthesis of ascididemin which might also be extended to the other two.




Thus, concentrating on ascididemin it may be seen that two disconnections rapidly yield the known 1,10-phenanthroline-5,6-quinone (**120**) (Scheme 14).

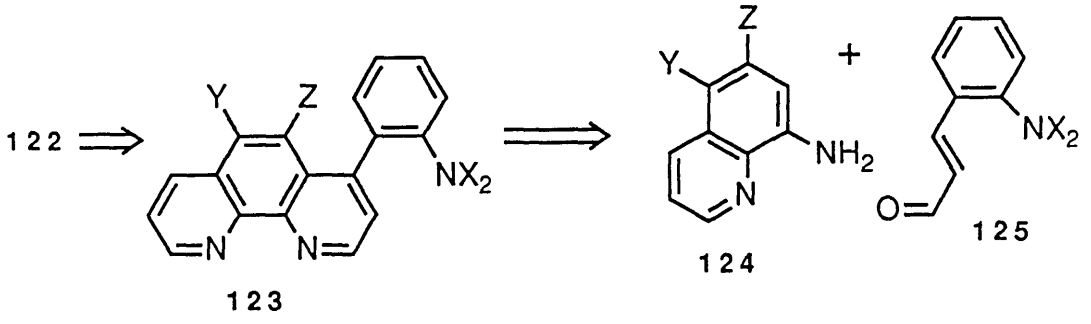
Scheme 14



As can be seen, two possible routes are made available by this retrosynthesis, one involving a 4-phenylphenanthroline (**122**), and one an N-arylquinoneimine (**121**). We chose the latter route for a number of reasons:

(a) Reaction of phenanthroline with nucleophiles (for example aryl lithiums) takes place predominantly at the C-2 centre rather than C-4, for both steric and electronic reasons. This means that synthetically viable incorporation of the phenyl group at C-4 in (**122**) would require the synthesis of the phenanthroline ring system with the required substituent already present, for example by a Skraup reaction (Scheme 15). This invalidates phenanthroline itself as a precursor and thereby lengthens the projected synthesis.

Scheme 15



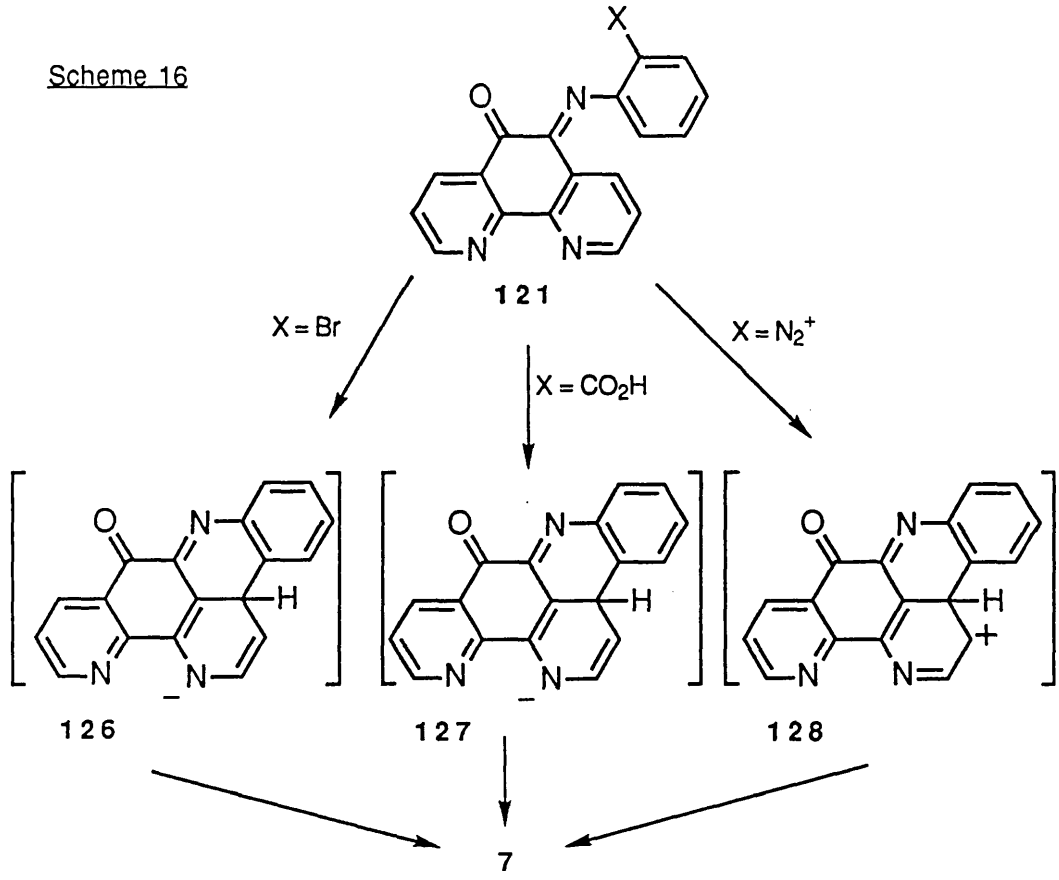

(b) The transformation of (**122**) into the alkaloid is a well trodden path in this area (for examples see Schemes 3a and 4 in Chapter 1), and so detracts from the originality of the proposed synthesis.

(c) It was thought that the quinoneimine could be synthesised in one step from the quinone (**120**) using an azaWittig reaction.

(d) The quinoneimine incorporates an azastilbene substructure well known to undergo photocyclisation.

(e) Suitable substitution on the quinoneimine (**121** X = Br) would lead to the possibility of an intramolecular nucleophilic reaction between an *in situ* generated aryl lithium (**121** X = Li) and the phenanthroline (Scheme 16). Alternatively other substituents (**121** X = $CO_2H$) would open the way for an intramolecular Minisci-type reaction,[38] or Pschorr ring closure (**121** X = $N_2^+$) (Scheme 16).

Scheme 16



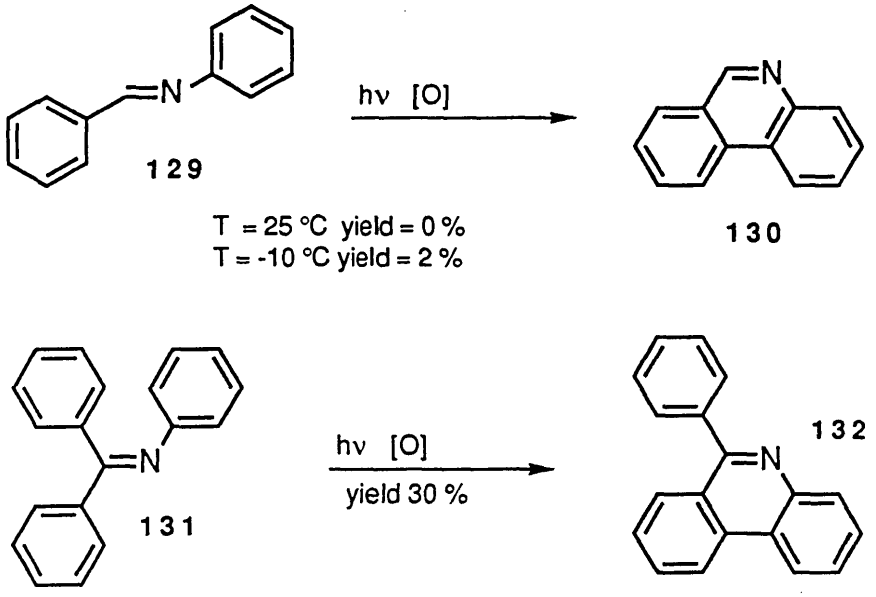

It is worth clarifying and expanding on statement (d) in order to highlight recent advances in transformations of this type.

Considerable effort has been expended in the area of imine and iminium photochemistry and there are three excellent reviews on the subject,[39] the last [39c] being concerned only with stilbene-type cyclisations. A summary of the relevant principles and examples will be given here to highlight the *status quo* of the azastilbene and closely related transformations. Unless otherwise stated the material below is from the reviews mentioned above.

The imine functionality, like the carbonyl group shows two major UV absorbances, at about 160 nm ($\pi,\pi^*$) and 255 nm ($n,\pi^*$). Photolysis at 254 nm causes isomerisation from the thermodynamic trans to cis isomer in direct comparison with alkenes. However, in the case of imines the higher energy cis isomer readily reverts to the trans ( $\tau_{1/2} \approx 2$ sec at 25 °C) so that the equilibrium concentration of the cis isomer is very low at ambient temperatures. This is elegantly demonstrated by the examples in Scheme 17. Whereas the benzaldehyde

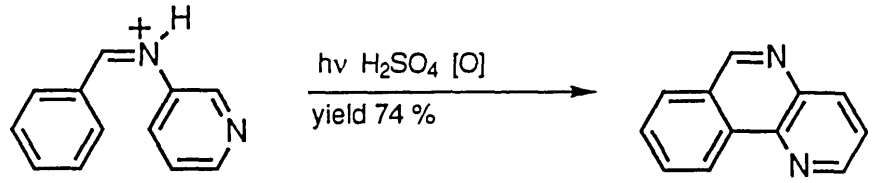
imine (129) is barely cyclised even at -10 °C, the benzophenone imine (131) - whose cis and trans isomers are identical - is converted to the phenanthridine (132) in 30 % yield. This latter result reveals a second point: unlike stilbenes, the cyclisation of these imines from the $^1(\pi,\pi^*)$ state must compete with rapid internal conversion to the lower energy $^1(n,\pi^*)$ state, thus lowering the quantum yield. (Stilbenes typically cyclise in very high yields).

Scheme 17




Protonation of Schiff's bases (as well as the other imines) radically alters their photochemical properties. The iminium species shows only one major transition in its UV spectrum, the $(\pi,\pi^*)$. Typically there is a high ground state rotational barrier (since there is no possibility of nitrogen inversion), and photolysis parallels that of alkenes exactly. The high concentration of the cis isomer coupled with the lack of internal conversion [since the $^1(\pi,\pi^*)$ is the lowest energy state available] means that photolysis of species such as (133) efficiently yields phenanthridines (Scheme 18). The reactions are normally carried out in concentrated sulphuric acid because of its acidic, non-hydrolysing and solubilizing properties. There has been a recent paper which successfully replaced this acid with boron trifluoride-etherate in dichloromethane.[40]

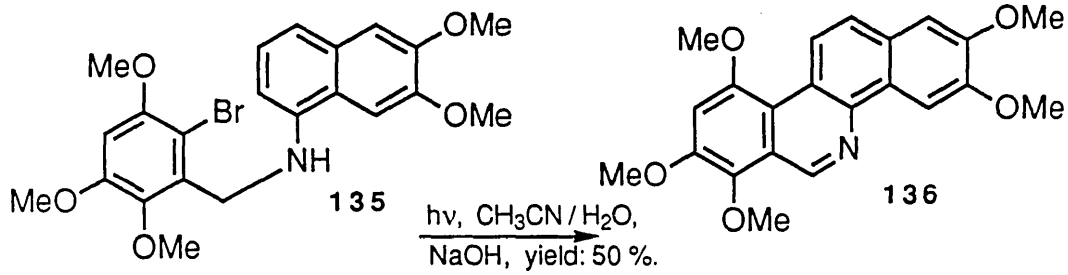
Scheme 18




133 134

Thus it can be seen that protonation of Schiff's bases alleviates the problems encountered in their photocyclisation, but creates one of its own (the use of sulphuric acid). There is a further modification that can be made to the imine in order to facilitate cyclisation, that is reduction to the amine.

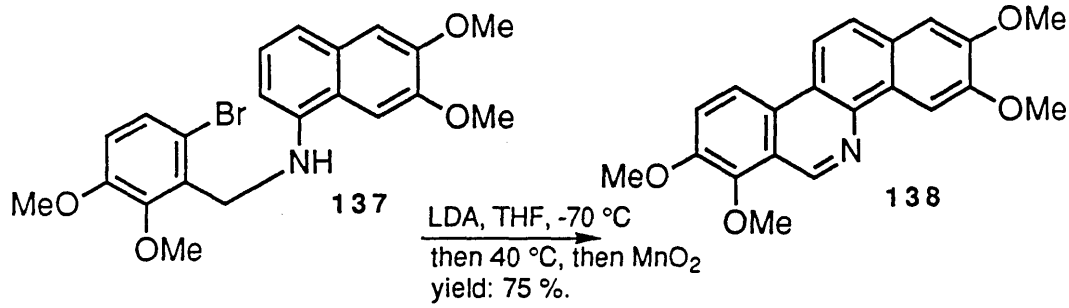
Scheme 19




135 136

Schemes 19, 20 and 21 show photochemical,[41] benzyne,[42] and free radical [43] mediated cyclisations respectively of benzylamines derived from Schiff's bases. In all cases the cyclisation step is assisted by the stabilization of the incipient Wheland intermediate by the amine nitrogen [for example (**143**)].

Scheme 20



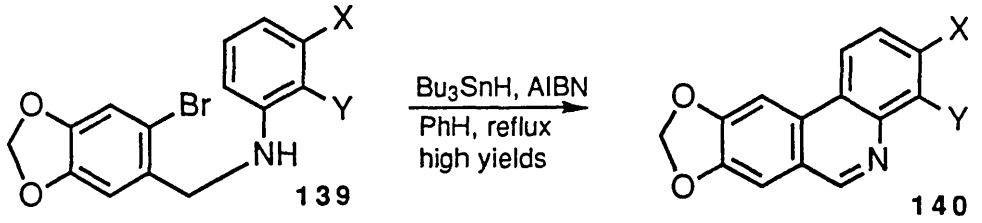

137 138

No reaction with **135**

The first (photochemical) example is claimed to occur via a single electron transfer (SET) mechanism (Scheme 22) involving the excited state charge transfer complex (**141**). This proposed mechanism is precedented by the arylation of dimethylaniline by phenyl

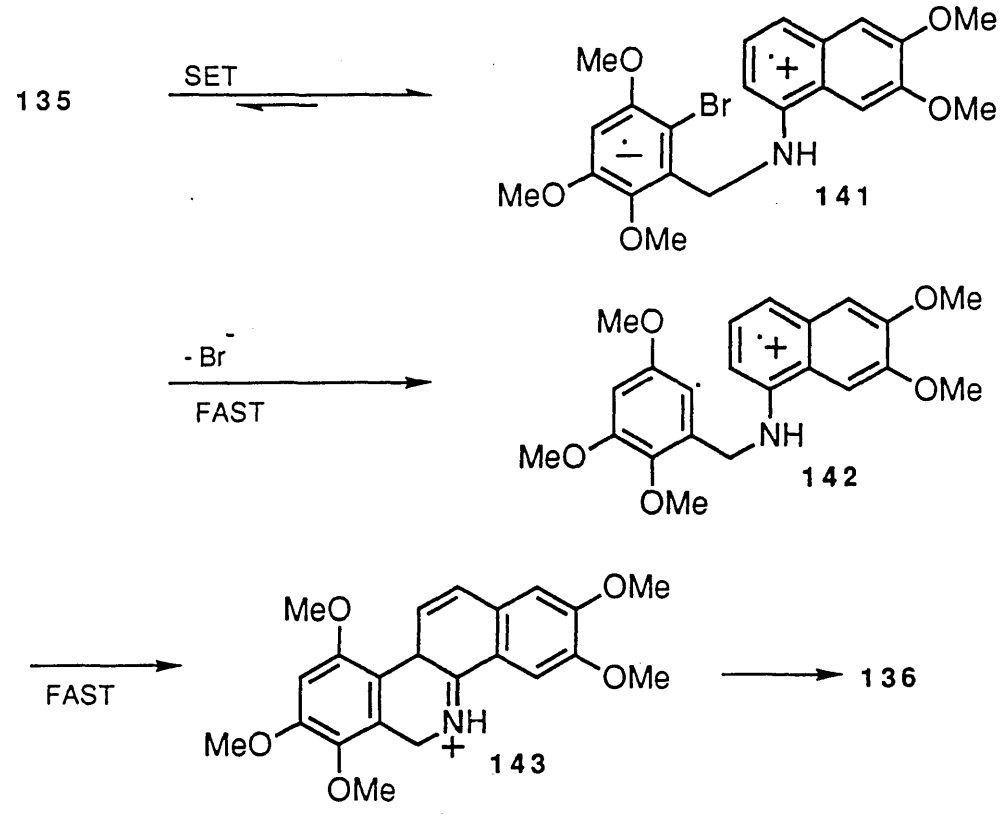
halides [44] which has been demonstrated to involve SET.[45] In the case of (135) the SET step is presumed to be rate determining at the very least because of the electron rich nature of the "acceptor" ring.

Scheme 21




To summarise, this section has shown the reasons for our retrosynthesis of ascididemin (7), and briefly reviewed the pivotal cyclisation around which the synthesis will be based. The applicability of the various reactions discussed in this section to our particular case will be discussed in Section 2.2.

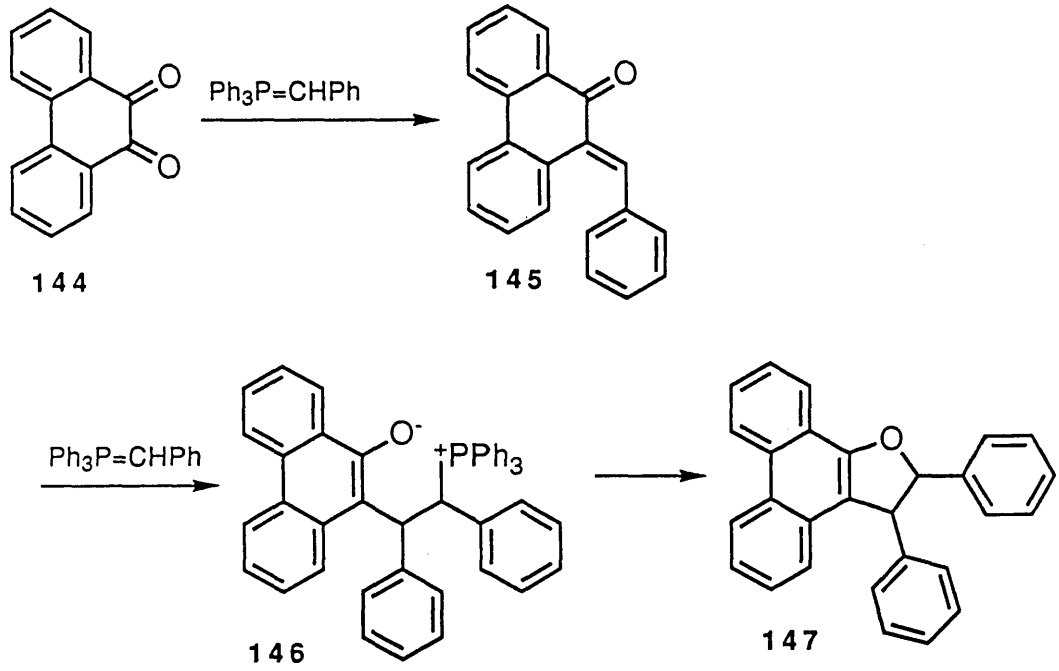
Scheme 22



## 2.2 RESULTS AND DISCUSSION.

The quinone (**120**) was synthesised from phenanthroline as reported by Gillard *et al* in 1970.[46] This preparation was less than perfect due to the use of fuming nitric and sulphuric acids in successive steps, coupled with the low overall yield (20 %). However with small quantities of the quinone available we turned our attention to the aza-Wittig reaction. Inspection of the literature showed that phenanthrene-5,6-quinone (**144**) underwent the Wittig reaction but that the quinonemethide product (**145**) reacted further in a Michael fashion producing the dihydrofuran (**147**) (Scheme 23).[47] Despite the complication this result boded well for aza-Wittig reactions on our quinone, since the quinoneimine product would not be susceptible to the same reaction as the methide.

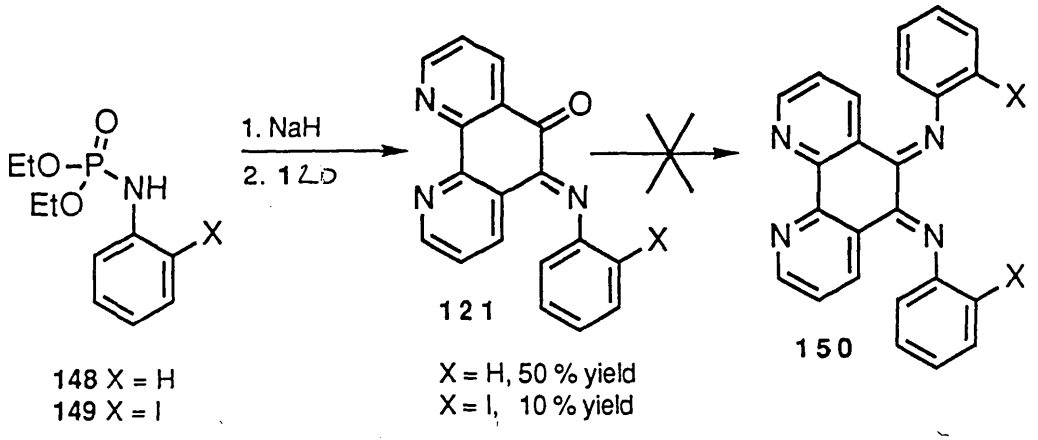
Scheme 23




Unfortunately the only synthetically viable intermolecular aza-Wittig reaction on quinones was effected with triphenylarsine phenylimine.[48] Presumably exchange of arsenic for phosphorus increased the polarisation of the Wittig reagent to counteract the negative-charge stabilization by nitrogen, and thus increased the nucleophilicity of the reagent. The difference in reactivity is quite marked, for example triphenylphosphine phenylimine reacts with benzophenone only when heated to 150 °C for 22 hours, whereas the analogous arsine reacts in excellent yield after a few minutes in boiling benzene.[48]

The hazard involved in applying this methodology to our case made us look a little further afield to the Wadsworth - Emmons reaction. As early as 1964 Wadsworth and Emmons [49] had examined the reaction of N-alkylphosphoramidate anions with a variety of carbonyl compounds, but this reaction has not been extended to the N-aryl analogues. The reason for this becomes obvious when it is noted that the products (for example Schiff's bases) can usually be prepared by more straightforward means.

Scheme 24



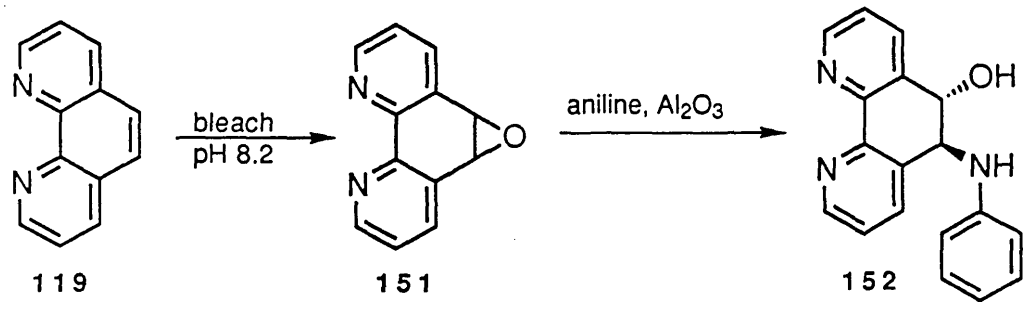

We synthesised the required phosphoramidate (**148**) and found that it did indeed react successfully (when deprotonated with sodium hydride) with (**120**) to give the purple N-phenyl-1,10-phenanthroline-5,6-quinonemonoimine (**121** X = H) in 50 % yield (Scheme 24). Extension of this reaction to form the bisimine (**150**) produced a green tar which was shown to be a complex mixture by NMR, and was not investigated further. A possible reason for the failure of this second reaction is the steric crowding about the remaining carbonyl of (**121**).

The synthesis of the iodo analogue, N-(2-iodophenyl)-1,10-phenanthroline-5,6-quinone monoimine (**121** X = I) was rather less satisfactory than that of (**121** X = H), and the purple compound could be isolated with only a 10 % yield. This can be explained by taking into consideration the stabilization of the negative charge of the reagent by electron withdrawal through the aromatic ring by the -I effect of the iodo group, combined with the shielding bulk of the iodine hindering reaction.

This route to the quinoneimines, though short, did not produce sufficient quantities for a full investigation of the photocyclisation, so an alternative, slightly longer route was devised.

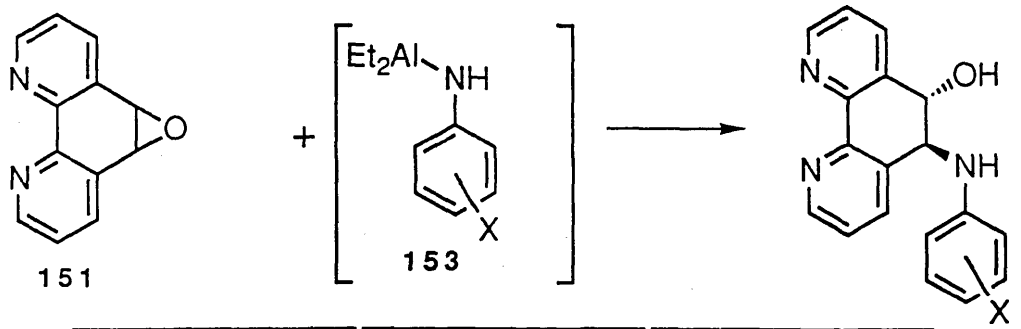
1,10-Phenanthroline was readily epoxidised in dilute bleach [50] to give (**151**) in excellent yield. This epoxide could be opened with aniline preadsorbed on basic alumina[51] to give 5,6-dihydro-5-anilino-6-hydroxy-1,10-phenanthroline (**152**) as a white solid (98 %) (Scheme 25).

Scheme 25




This protocol could not be extended to ortho-substituted anilines presumably due to steric congestion on the alumina reaction surface. However, the use of Overman's aluminium amide approach [52] yielded products from a number of substituted anilines (Table 1).

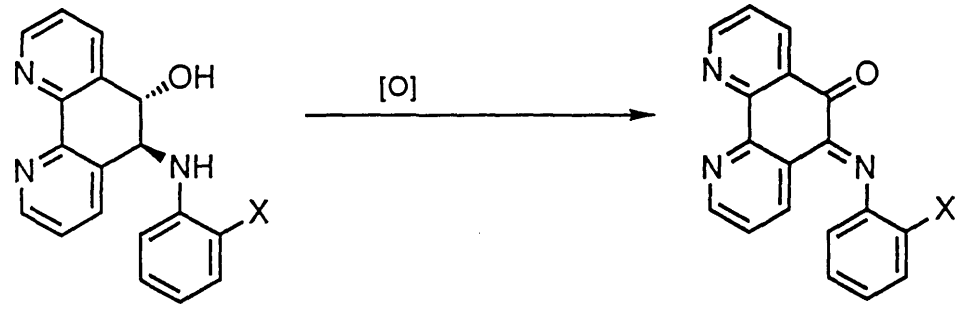
Table 1




| X in (153) | Product | yield |
|---|---|---|
| 2 - I | 154 | 79 % |
| 2 - Br | 155 | 76 % |
| 4 - MeO | 156 | 74 % |
| 2 - CN | 157 | 74 % |

The oxidation of these aminoalcohols to the quinoneimines was attempted using a number of oxidants (Table 2). Though most showed clean conversion of the starting materials to the purple imines, isolation of the products was difficult in a number of cases. Thus DDQ, though an excellent oxidant, was very difficult to remove from (**121** X = H) due to their similar chromatographic properties. The heterogeneous oxidants were examined to eliminate this problem. Apart from nickel peroxide (which caused extensive destruction) the oxidations were very successful. Barium manganate seems to be the reagent of choice because it causes less adsorption of the products than did Attenburrow activated manganese dioxide.

Table 2

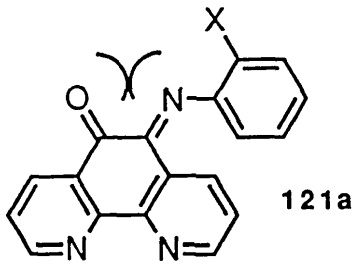



| aminoalcohol | X = | oxidant | Product | yield |
|---|---|---|---|---|
| 152 | H | $MnO_2$ | 121 X =H | 70 % |
| 152 | H | $NiO_x$ | 121 X =H | 23 % |
| 152 | H | DDQ | 121 X =H | 32 % |
| 154 | I | $MnO_2$ | 121 X =I | 65 % |
| 154 | I | $BaMnO_4$ | 121 X = I | 83 % |
| 155 | Br | $MnO_2$ | 121 X =Br | 67 % |

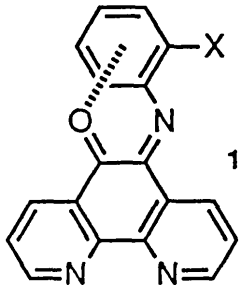
With gram quantities of a number of quinoneimines to hand we set about investigating their photolysis. Before beginning any experiments we attempted to find out which cis-trans isomer we had made. If the more thermodynamically stable isomer is (**121a**) then no photoisomerisation is required prior to cyclisation. This implies that photolysis may be carried out on the neutral imine without protonating it. However if the lower energy isomer is (**121b**) then photoisomerisation will be required before cyclisation can occur. This implies that in this case the irradiation must be carried out in sulphuric acid to prevent thermal retroisomerisation of the imine.

With this in mind an nOe experiment was carried out on (**121** X = H) in order to determine the stereochemistry about the imine bond (Diagram 4 & 5 in Appendix B). No real enhancements of the protons on the benzene ring were observed on irradiation of H-2, H-4, H-7, or H-9 on the phenanthroline ring. Although this suggests (**121b**), shown below, negative results produced by this type of experiment cannot be relied upon since the lack of an enhancement need not imply a large internuclear distance. It may be that there is an nOe as required but that it is not observed due to experimental idiosyncrasies of the molecule under study.

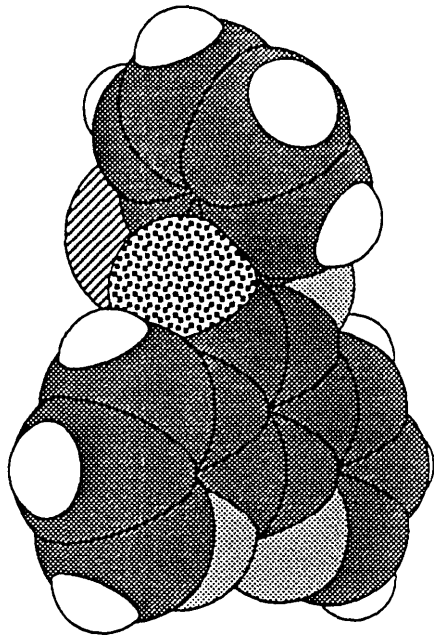
Examination of the two possible isomers (**121a**) and (**121b**) shows that both possess what appear to be energetically unfavourable interactions. (**121a**) is expected to show repulsive interactions between the electron pairs on the quinoneimine oxygen and nitrogen. This is replaced in the other isomer (**121b**) by interaction of the lone electron pairs on oxygen interacting with the π-system of the electron rich benzene ring. Interactions of this type are normally repulsive because of the electron rich nature of the two species involved. However, in this instance the carbonyl oxygen, being part of a quinoneimine, can act as a one or two electron acceptor, and conversely the benzene ring can act as a one electron donor. This suggests the possibility a charge transfer stabilisation of (**121b**). The intense purple colour of the compounds under discussion lends weight to this argument (as expected of a charge transfer complex the intensity of the purple is greatly diminished on going from chloroform or ether to nonpolar solvents such as hexane which are less able to solubilise the charged species generated).




**121a**




**121b**



[The van der Waals model shown above on the right represents (**121b** X =Br), and shows the proximity of the carbonyl oxygen (shown here with heavy dappling) to the face of the benzene ring.]

Computerised energy minimisation of the two isomers (**121a ,b** X = H) using the MM2 program gave the heat of formation of (**121b**) as 21 kJ less than (**121a**). This energy difference was due primarily to high values for the torsion (13.2 kJ) and electronic (7.7 kJ) terms, which translate to unfavourable twisting and electronic interactions in (**121a**). These effects were visible in the minimised structure of (**121a**), which possessed a noticeably curved phenanthroline ring system. This curving has the effect of skewing the oxygen and nitrogen lone pairs out of each others way (a similar effect is evident in the X-ray structure of eilatin (14) [37]). The benzene ring was certainly not perpendicular to the (approximate) plane of the phenanthroline - as found in the other isomer - and it appeared to be skewing the phenanthroline further, presumably in order to attain sufficient planarity with the imine bond to effect conjugation.

Although no strong conclusion could be drawn from the arguments given above we favoured (**121b**) as the thermodynamically more stable isomer. This implied that photochemical isomerisation would be necessary before cyclisation could take place. If the other isomer were preferred then no isomerisation would be necessary, and the cyclisation should occur in a non-acidic medium. This hypothesis was tested experimentally.

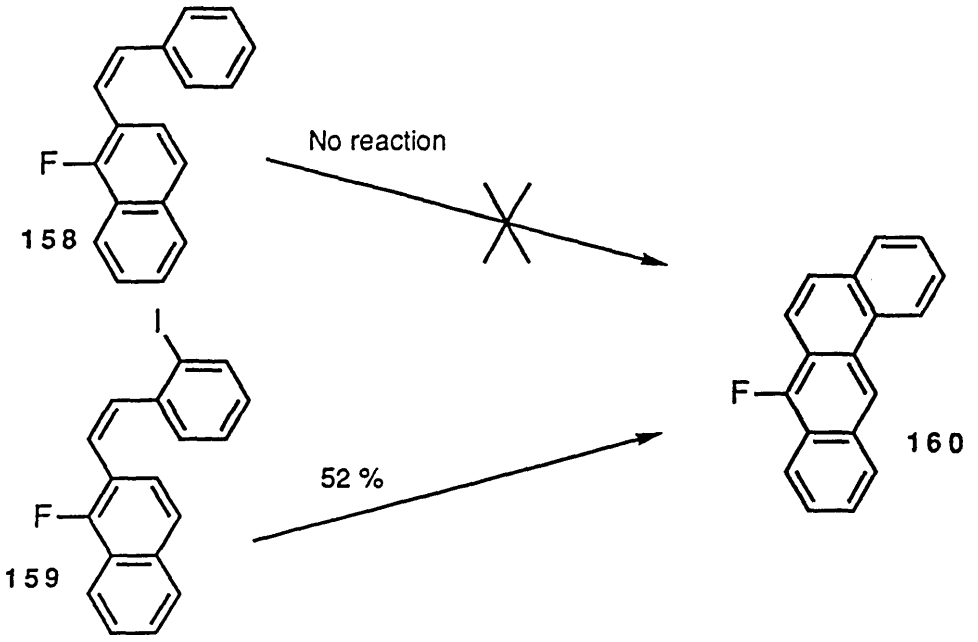
Thus photolysis was attempted in dichloromethane at ambient temperature, and in methylcyclohexane at -40 °C. Starting material was recovered nearly quantitatively in both cases, lending further support to our assignment.

Therefore the iminium type of cyclisation was examined. Treatment of (121 X = H) with boron trifluoride-etherate in dichloromethane lead to the precipitation of a totally insoluble yellow / brown solid. This material, either before or after irradiation, was shown (after treatment with water) to consist predominantly of phenanthrolinequinone (120).

Since this alternative to sulphuric acid was proving to be unprofitable we continued our investigation by irradiating solutions of the quinoneimines (121 X = H, I) in high dilution in Analar concentrated sulphuric acid. The parent compound (121 X = H) was found to give complex mixtures of products on photolysis with high or low pressure mercury lamps irradiating through quartz or pyrex filters. This was not a result of the high reactivity of (121 X = H), but, on the contrary, because of the long irradiation times required to achieve reasonable conversions. This suggests that the molecule had no major path for reaction. It is interesting to note in passing that the starting material could be recovered after short photolysis runs by basifying the sulphuric acid with ice and concentrated aqueous ammonia and extracting with chloroform. The isolation of products from these reactions was not feasible due to the complex nature of the reaction as well as the polar nature of the products on TLC (silica or alumina). NMR studies of the crude mixtures showed the presence of small amounts of (120) as well as a new material whose $^{1}$H-NMR was very similar to (120). Further identification of this material was not possible.

As stated above the failure of these reactions appears to be due to a lack of a major and preferred reaction pathway. In the related field of stilbene cyclisations this type of difficulty is often circumvented by the inclusion of an iodo group to serve as both a leaving group and as an activator to the reaction (cf. Scheme 26).[53] The mechanism by which this occurs is thought (in most cases) to be primary homolysis of the C-I bond followed by radical arylation and loss of a hydrogen atom.

Scheme26

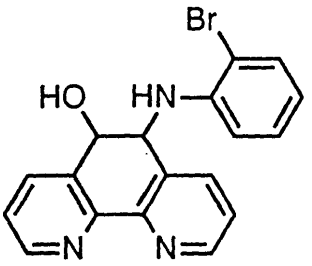



Therefore we irradiated our iodo analogue (**121** X = I) under a similar range of conditions as used previously, hoping for an assisted cyclisation. In this case the starting material was consumed in a much shorter time, reflecting the greater reactivity of the iodo compound. The TLC of the product mixture was also greatly simplified, showing that the incorporation of the iodo group had made available some favourable reaction path(s). Extensive chromatographic purification of the major yellow material (which possessed a characteristic fluorescence on TLC) gave ascididemin (**7**) in 32 % yield after optimisation. This reaction is the first example of an azastilbene photocyclisation applied to a quinoneimine.

Thus we had completed a total synthesis of ascididemin in a overall yield of 21 % from phenanthroline. However, the final cyclisation was not entirely satisfactory because of its low yield and because of the scale limitations imposed by the available photolysis apparatus. For these reasons we turned our attentions to ways of replacing this reaction with more amenable ones.

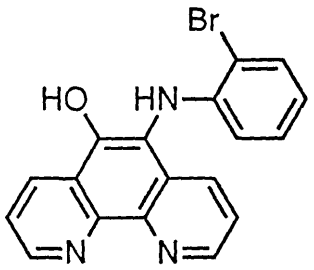
Initially we tried replacing the sulphuric acid with perchloric acid in 1,4-dioxane, but this led to the formation of a complex mixture of products. The irradiation of the aminoalcohol (**154**) in aqueous acetonitrile in the presence of sodium hydroxide [74] (cf. Scheme 19) also led to the formation of intractible mixtures.

For this reason we put aside our photolysis apparatus and investigated other transformations. The reactions of the aminoalcohol (**155**) were addressed first. Treatment with three equivalents of butyl lithium at low temperature followed by warming to room temperature gave a complex mixture of products which was discarded. Prior protection of the amine and alcohol functionalities with oxalyl chloride was unsuccessful - only intractable tars were formed.

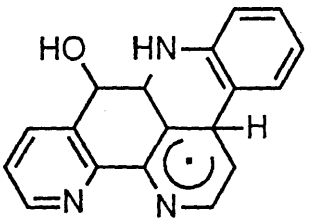



**155**

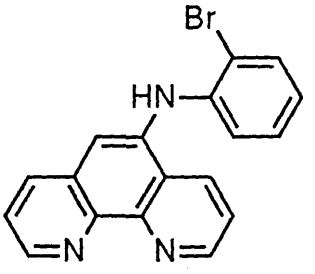
Attempted protection with phenylboric acid in refluxing acetone produced the anilinophenol (**169**). This is formally the product of an Oppenauer oxidation of the starting material (**155**). However, repeating the reaction with benzene in place of acetone to counteract this, also produced the anilinophenol.




**169**



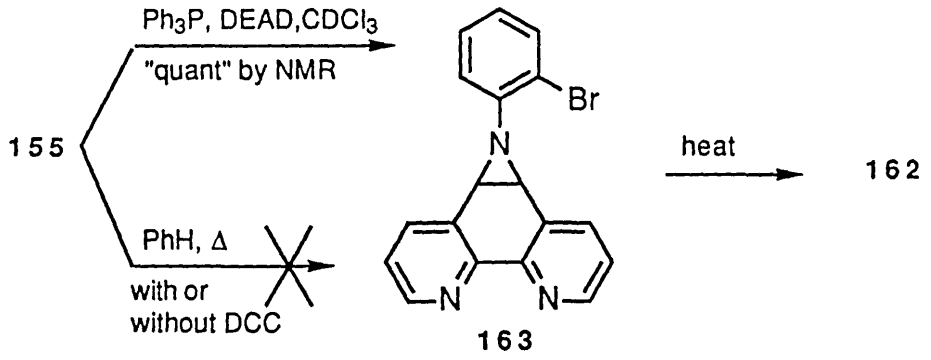

**161**




**162**

We then attempted a free radical cyclisation analogous to that in Scheme 21. In our case it must be noted that cyclisation, if it occurs, will not create a relatively stable nitrogen based radical cation, but rather a partially delocalised radical (**161**). Slow addition (48 h) of 1/2 equivalent of AIBN and one of tributyltin hydride to (**155**) in high dilution in refluxing benzene produced a single product on workup. Upon inspection this material was found to be the diarylamine (**162**). The presence of bromine in the product implies that the reaction proceeds via an entirely different mechanism to that of the example in Scheme 21.

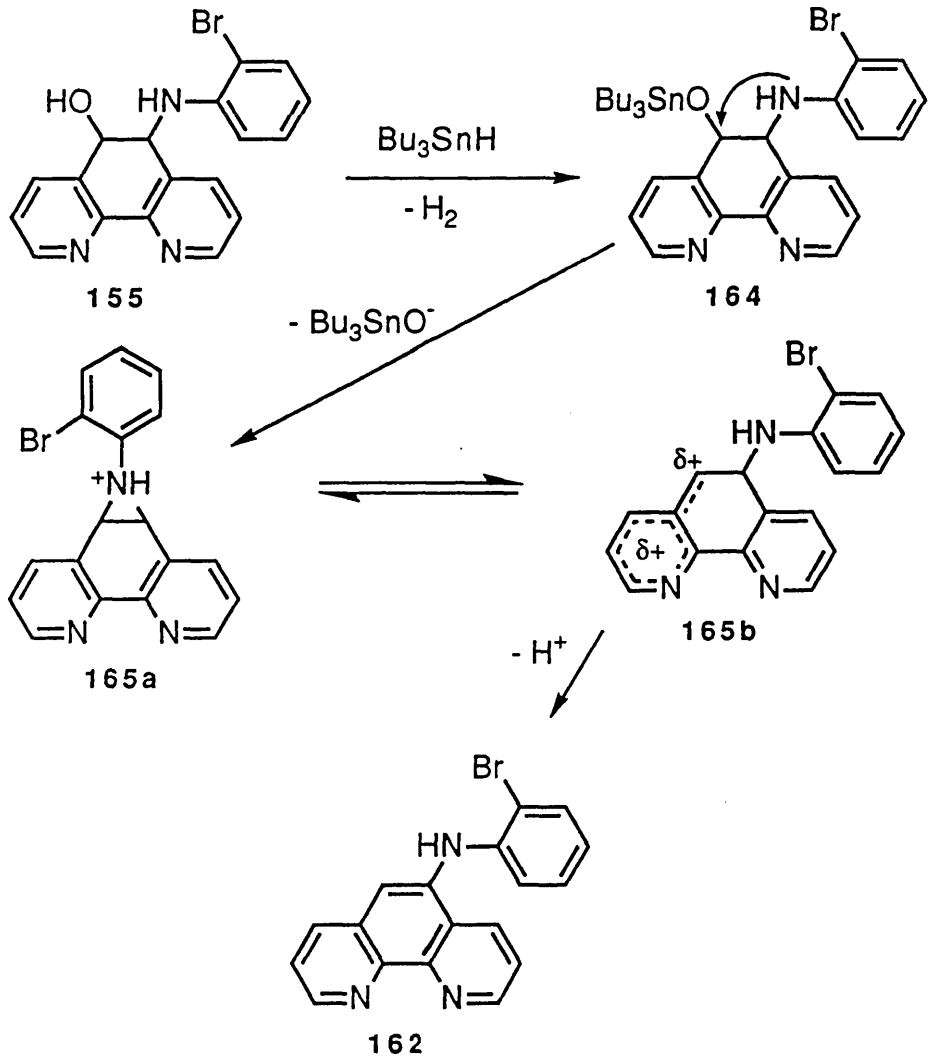
Scheme 27




The aniline (**162**) is formally the product of γ elimination of water followed by thermal rearrangement of the intermediate aziridine (**163**). For this reason we refluxed (**155**) in benzene with or without one equivalent of DCC to test this mechanism. The starting material was recovered after one week at reflux. On the other hand the Mitsunobu reaction using triphenyl phosphine and diethyl azodicarboxylate (DEAD) at room temperature produced a single new compound. This material could not be separated from the triphenylphosphine oxide due to its instability in the presence of silica or water. However the NMR showed a singlet at δ 4.2 ppm integrating to 2 H, and a symmetrical phenanthroline system, as predicted for the aziridine (**163**) (Scheme 27). Refluxing this crude product in benzene produced the aniline (**162**). These results show that the dehydration of (**155**) in the case of the tin hydride reaction is brought about by the action of the reagents, not merely the reaction temperature.

The presence of bromine in the product also suggests that the tributyltin radical (expected to be formed by hydrogen abstraction by the isobutyronitrile radical created on thermolysis of AIBN) is not formed. It is believed that the tributyltin hydride reacts with the benzylic alcohol in (**155**) giving (**164**) as shown in Scheme 28.

Scheme 28



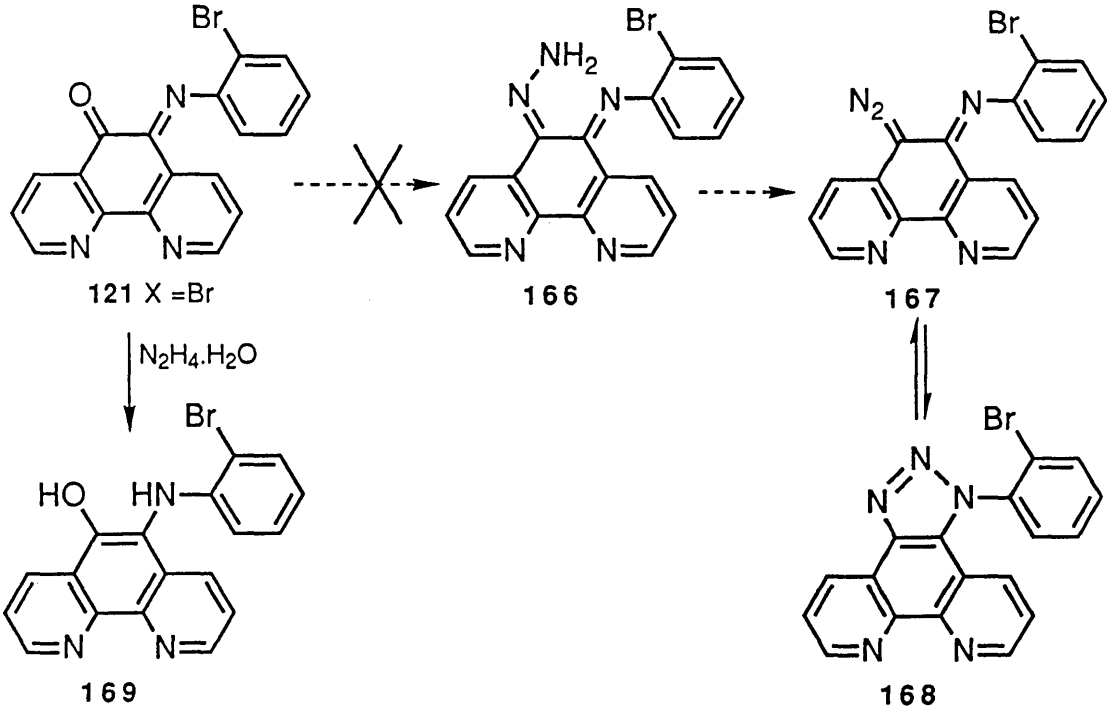

This is followed by a syn 1,2 - elimination of tributyltin hydroxide from (**164**) producing the diphenylamine (**162**). Anchimeric assistance by the amino group is possible. Such assistance will lead to the formation of the aziridine (**163**), which has already been shown to rearrange thermally to give the product. This neighbouring group effect means that elimination of $Bu_3SnO^-$ will be assisted, even though it is expected to be a poor leaving group (since it is not stabilised by charge delocalisation by $d\pi$ - $p\pi$ bonding, as is the case for the silicon analogue). As well as this, any carbocation character (**165b**) in the intermediate will be stabilised by delocalisation through the adjacent pyridine ring. Finally, although a small effect, the release of crowding strain caused by the bulky $Bu_3SnO$ must also be considered. These arguments support the idea that an elimination is occuring via an internal $S_N2$ substitution - rearrangement pathway.

The mechanism outlined above does not require the presence of AIBN, so the reaction was repeated exactly as before but without this reagent. Again the diphenylamine was isolated in high yield, lending credence to the proposed mechanism.

Since attempts at the cyclisation of the aminoalcohol (**155**) were unfruitful, at least partially because of deleterious involvement by the hydroxyl and amino groups, and that protection of these with oxalyl chloride had failed, we tried a completely different approach to the protection.

We treated the quinoneimine (**121** X = Br) with hydrazine hydrate and catalytic acid in the (naïve) hope of forming the hydrazone (**166**), which could then be oxidised to the triazole (**168**) as shown in Scheme 29. This would have the effect of fixing the benzene ring spatially in such a way as to assist cyclisation. However, the only material isolated after treatment with the hydrazine hydrate was the reduced product (**169**), reflecting the quinonoid structure of the material.

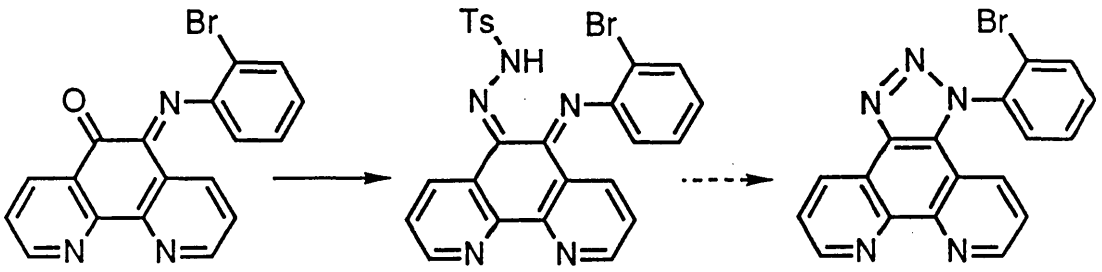
Scheme 29




To minimise this redox process and facilitate the formation of the intermediate diazo compound we repeated the reaction with tosylhydrazide. This time none of the reduction

product (**169**) was detected. The predominant product was a colourless solid which became rapidly purple and insoluble in the presence of strong sunlight or ultraviolet light. Its NMR spectrum corresponded exactly to that expected of the tosylhydrazone (**170**) (Scheme 30).

Scheme 30



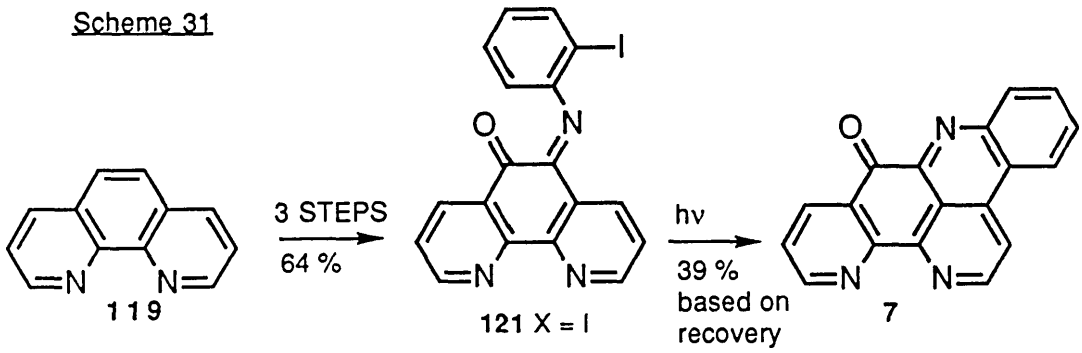

**121** X =Br **170** **168**

Our attempts to hydrolyse the tosylhydrazone (**170**) to produce the triazole using methods described in the literature [73] only led to the isolation of 2-bromoaniline from the organic phase after workup. The aqueous phase remained a pale yellow colour indicating the possible presence of further reaction products, but these were not isolable.

## 2.3 CONCLUSION.

A rapid and short synthesis of the marine alkaloid ascididemin (**7**) in four steps from phenanthroline has been described. The synthesis is summarised below (Scheme 31). This synthesis is designed around the azastilbene photocyclisation of a quinoneimine, and represents the first example of this reaction, which has rich potential for the rapid synthesis of polycyclic natural products from simple precursors. For example the reaction could be directly applied to the synthesis of eilatin (**14**) from ascididemin (**7**) in two steps.

Scheme 31




The functionalisation of the phenanthroline via its epoxide, rather than by the traditional nucleophilic or more recent free radical substitution methods, appears to be the first of its kind. The formation of the diarylamine (**162**) from phenanthroline may be viewed as an efficient, selective and mild alternative to the few aromatic amination procedures available at the present. This methodology has great potential in other aromatic systems showing partial bond fixation (this being a proviso for the synthesis of their epoxides).

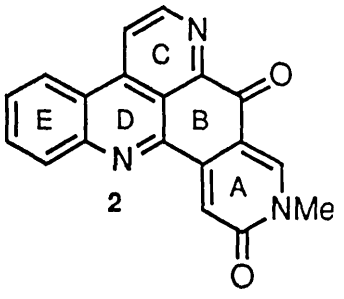
Also in this chapter has been reviewed a variety of reactions which have successfully replaced the electrocyclisation under certain circumstances. These alternatives have been explored, and, though unsuccessful in their aim, have produced a number of interesting results.

# CHAPTER THREE

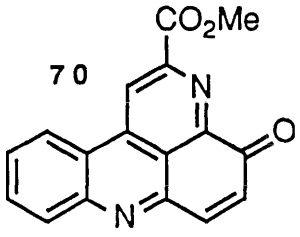
# AN APPROACH TO AMPHIMEDINE.

## 3.1 RETROSYNTHESIS.

There has been ongoing interest in amphimedine (2) within our group for a number of years. This began with an earlier attempted synthesis which exploited the vinyl azide decomposition route to pyridine ring synthesis.[28] This synthetic route is shown in Scheme 6, Chapter 1. As shown, the synthesis of the tetracycle (70) was both short and capable of being used to synthesise a wide range of analogues for screening. It is evident that the failure of this synthesis was due to the lack of reactivity of the $2\pi$ component of the Diels - Alder reaction (70). The most obvious solution to this problem is to include the elements of the A ring [IUPAC lettering, see (2) above] at an early stage in the synthesis to obviate the need for the Diels - Alder reaction.



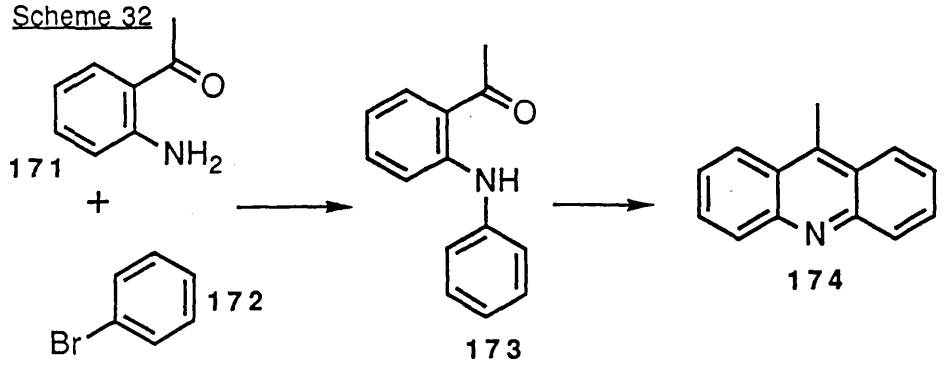
2



70

It is worth noting, however, that the synthesis described in Scheme 6 starts from a known acridine - 9 - aldehyde (66). This hides the fact that this class of compound can, for two reasons, be very difficult to prepare. Firstly the acridine is almost always prepared by an Ullmann reaction between an aryl bromide and a 2 - aminoacetophenone, followed by cyclodehydration to form the central ring of the acridine (Scheme 32). The yield of this Ullmann reaction is extremely sensitive to changes in substitution of the reagents.

Scheme 32

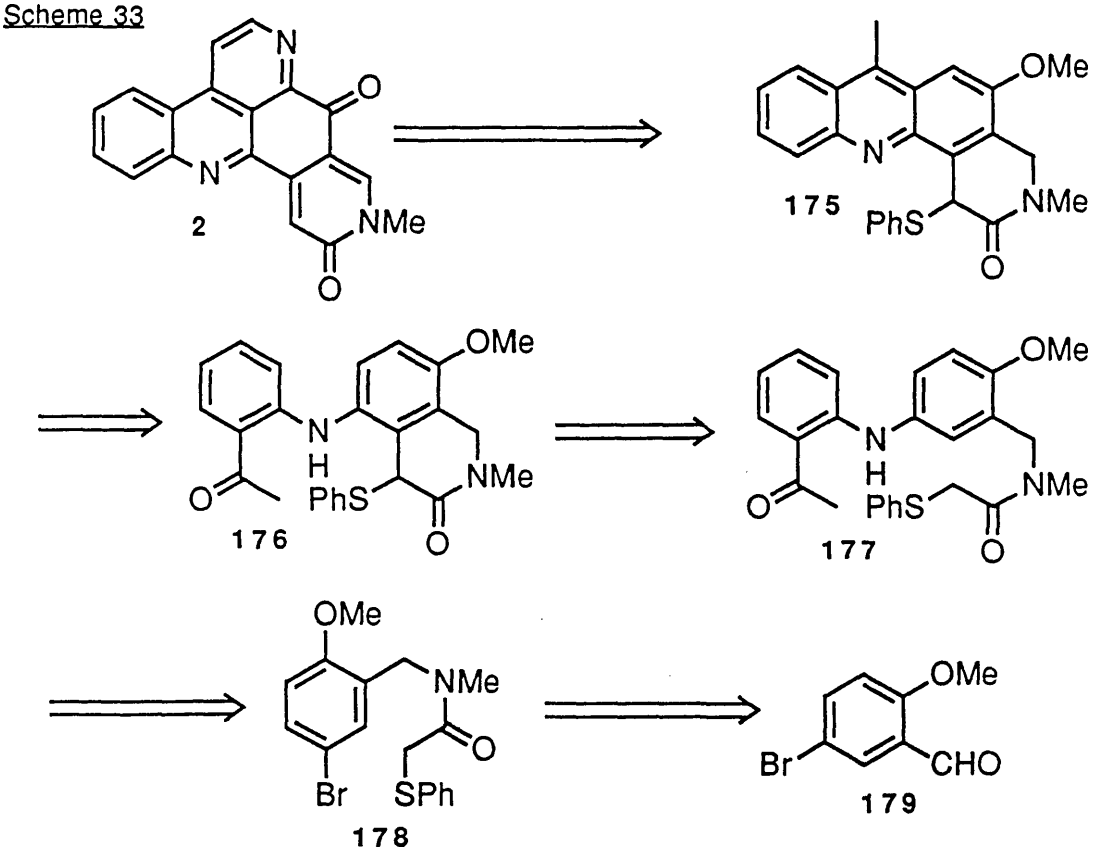



The second complication often arising during the synthesis of acridine-9-aldehydes is that obtaining the aldehyde functionality is difficult in a number of common cases. This functionality is most often derived from the 9 - methyl group by condensation with a nitrosoarene and hydrolysis of the resultant imine. This works well for the simple acridines but obviously fails in cases with other (competing) acidic centres, and although 9

- esters have been reduced in two steps to the aldehydes, yields are often low due to reduction of the acridine to acridan, and though this process is reversible, substantial losses often occur by way of polymerisation.[55] A recently introduced alternative is the oxidation of the protonated 9-methylacridine with potassium persulphate.[56] Although this oxidation is selective for the 9-methyl, any other functionality in the molecule must be able to withstand the excess of aqueous trifluoroacetic acid in which the reaction is carried out.

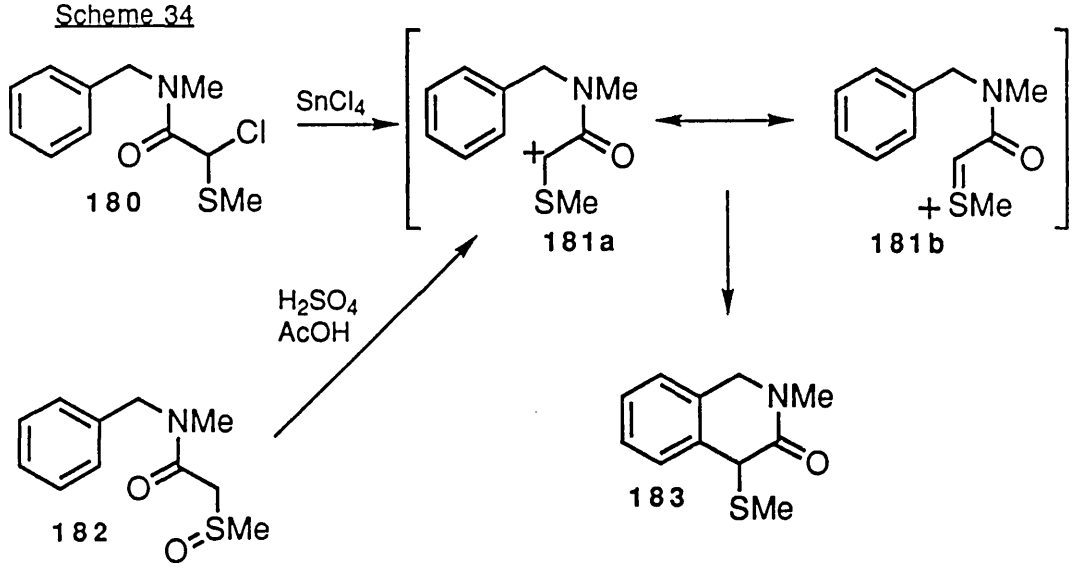
Despite these potential problems, the retrosynthesis outlined in Scheme 33 was decided upon because of its analogy with the earlier synthesis, and because the A - ring annulation problem seemed to be efficiently dealt with.

Scheme 33




The retrosynthesis was designed around the elegant dihydroisoquinolone synthesis developed by Tamura *et al.* [57] This involves an intramolecular Friedel - Crafts alkylation by a 2-chloro amide [for example (**180**)], and is facilitated by the stabilisation of the intermediate 2 - acyl carbocation (**181**) by an α sulphur atom (Scheme 34).

Scheme 34




The first disconnection produces a 9 - methylacridine (**175**) in preparation for the azido - cinnamate pyridine annulation. The disconnection shown also masks the reactive isoquinolone "diene" as an allyl sulphide. Thus oxidation to the sulphoxide followed by elimination of phenyl suphenic acid regenerates the target.

As stated above, the other steps envisaged for the synthesis paralleled those of the earlier attempt. However, potential complications with these reactions present themselves - particularly in retrospect!

Firstly, the additional functionality present in the Ullmann reaction might be cause for concern since it may not be stable under the forcing conditions of the reaction, as well as possibly hampering the efficiency of the coupling.

Second, the proton α to the amide carbonyl in (**176**) is expected to be relatively acidic, and this must be taken into consideration when choosing reactions on this type of compound, in particular the elaboration of the aryl methyl group.

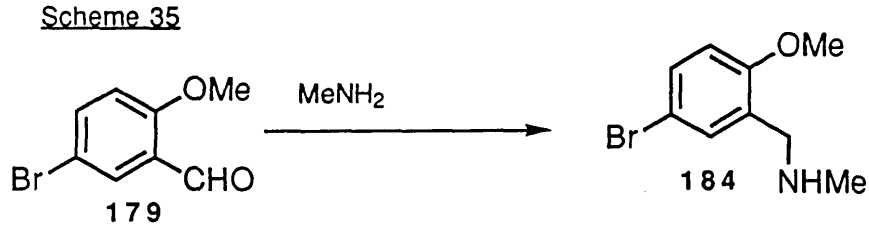
Finally, dihydroisoquinolones tend to undergo rapid oxidation to the isoquinolones.

Despite these presages the synthesis was embarked upon, with the earlier attempt acting as a model study.

## 3.2 RESULTS AND DISCUSSION.

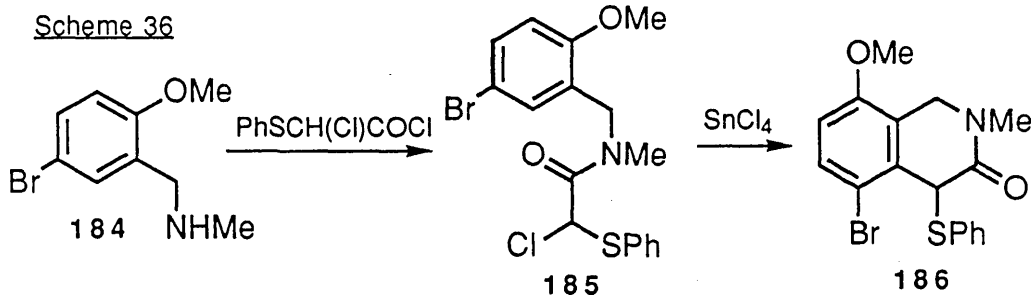
The benzylamine (**184**) was readily synthesised by reductive amination of the commercially available benzaldehyde (**179**) with sodium cyanoborohydride (Scheme 35).

Scheme 35



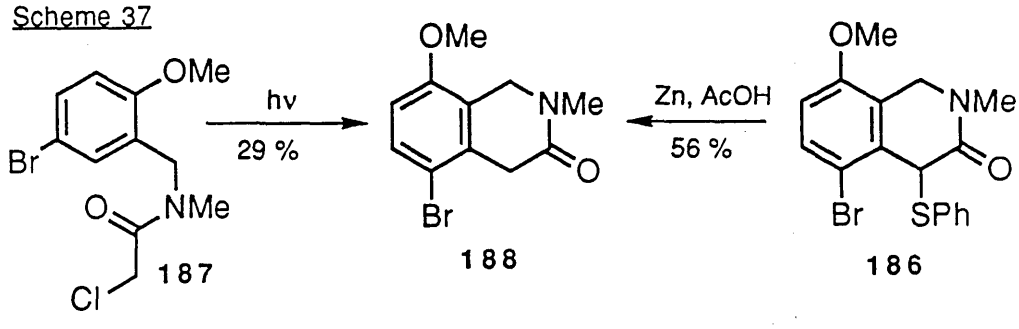

Before embarking on the actual synthesis a number of reactions was carried out to test the scope and efficiency of the A ring annulation. Thus acylation with α - chloro - α - phenylthioacetyl chloride followed by treatment with tin tetrachloride yielded the dihydroisoquinolone (**186**) in 69 % in a rapid one - pot synthesis (Scheme 36).

Scheme 36

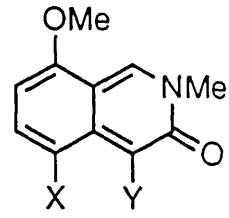



Encouraged by earlier work carried out in our laboratory on photochemical alkylation of arenes with chloroacetamides as part of the synthesis of lyngbyatoxin A,[58] we irradiated the 2-chloroamide (**187**) and achieved the required cyclisation, albeit in an unsatisfactory 29 % yield (Scheme 37). The product (**188**) could also be obtained by reduction of (**186**) with zinc in acetic acid (56 %).

Scheme 37

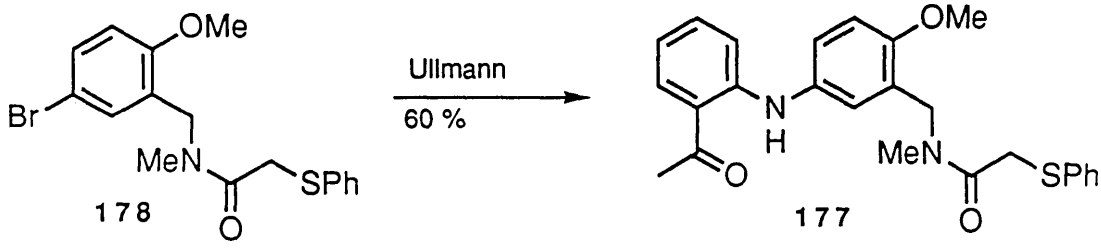


Having demonstrated the efficiency of the Friedel - Crafts cyclisation we were ready to begin the synthesis proper. It had already been demonstrated in our group [59] that neither the dihydroisoquinoline (**186**), the aldehyde (**179**) or the amine (**184**) underwent the required Ullmann reaction due to extensive side reactions, notably in the case of (**186**) to the isoquinolones (**189**) and (**190**). For this reason we synthesised the relatively inert phenylthioacetamide (**178**), and carried out the Ullmann reaction with 2 - aminoacetophenone on this material (Scheme 38). This reaction was optimised to a very respectable 60 % yield on 5 g of bromide.



**189** X = Br, Y = H
**190** X = H, Y = PhS

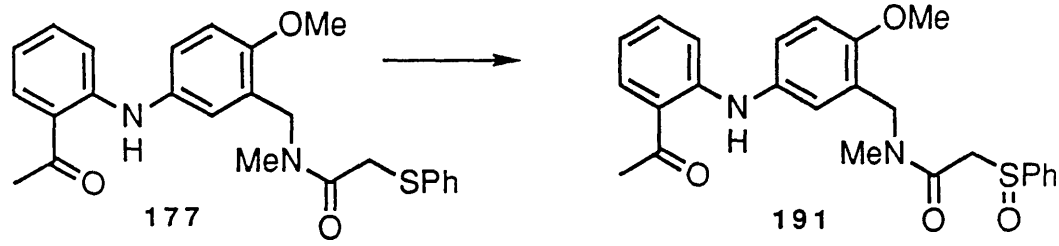
Scheme 38




While the two rings may, in principal be closed in either order, the cyclodehydration can produce two regioisomers unless the isoquinolone is formed first, blocking one position. For this reason we set about this latter closure first.

The diarylamine (**177**) was readily oxidised to the sulphoxide (**191**) in 87 % yield with MCPBA.

Scheme 39



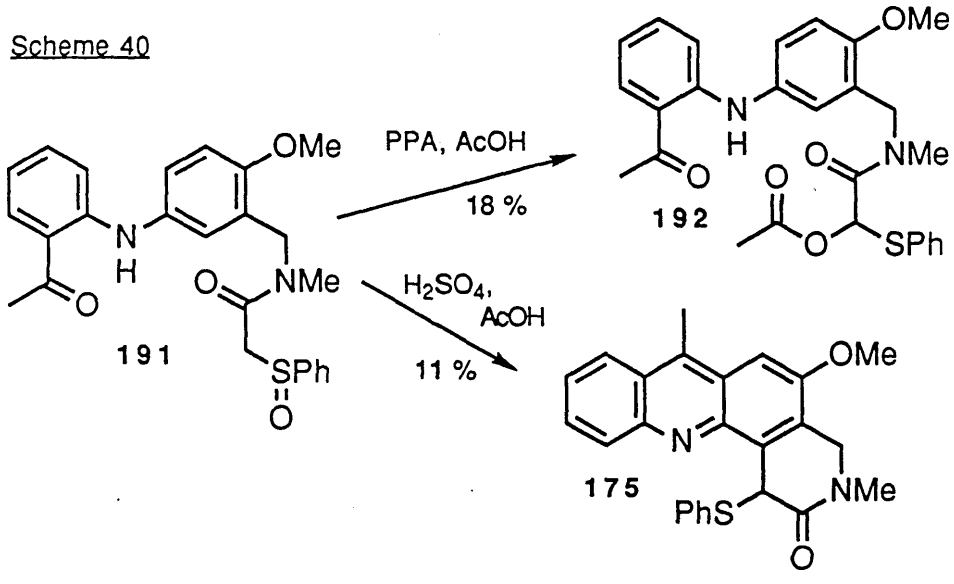

However, this material resisted all our attempts at synthetically viable single or double cyclisations. Table 3 shows a selection of reagents and conditions tried.

Table 3

| REAGENT | SOLVENT | CONDITIONS |
|---|---|---|
| $H_2SO_4$ | AcOH | reflux, air / $N_2$ |
| $H_2SO_4$, $Ac_2O$ | AcOH | reflux, air / $N_2$ |
| PPA | none | 100 °C |
| PPA | AcOH | 35 °C |
| PPA | xylene | reflux |
| PPA / $SiO_2$, 1:1 | DCM | ambient |
| HBr, 48 % | AcOH | reflux |
| $POCl_3$ | DCM | ambient |
| $TiCl_4$ | DCM | - 78 °C |
| $AlCl_3$ | none | 130 °C |
| $AlCl_3$ | $PhNO_2$ | reflux |
| $AlCl_3$ | $CS_2$ | reflux |
| $AlCl_3$ | $CH_3CN$ | reflux |

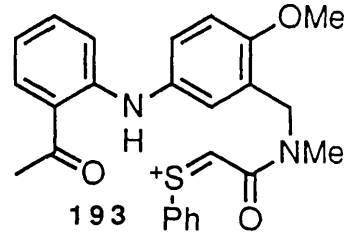
Some of the conditions used did produce interesting results (Scheme 40).

Scheme 40




The sulphuric acid / acetic acid mixture yielded the tetracycle (**175**) by consecutive Pummerer type cyclisation and cyclodehydration. However, this reaction was both

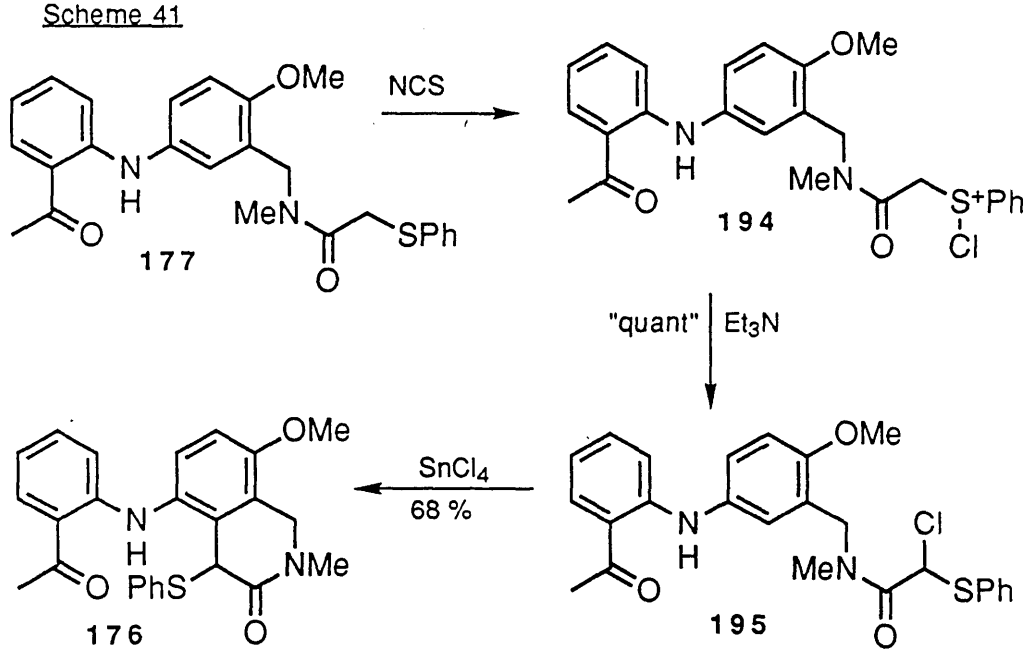
-capricious and low yielding. The intermediate sulphur stabilised cation formed in this Pummerer reaction (**193**) appeared to be formed in the reaction with PPA in acetic acid, since the acyloxylated product (**192**) was isolated in 18 % yield. The absence of acridines in the product shows that this reagent system is obviously a more powerful acylating than dehydrating agent. The other reactions outlined in Table 3 produced prolific varieties and mixtures of products, and were not further investigated.



**193**

Since this cyclisation strategy was proving to be unviable, we attempted the Friedel - Crafts type ring closure. Thus we chlorinated the thioacetamide (**177**) with NBS and treated the resultant chloroacetamide (**195**) with tin tetrachloride. A reassuring 68 % yield of the dihydroisoquinolone (**176**) was obtained.

Scheme 41

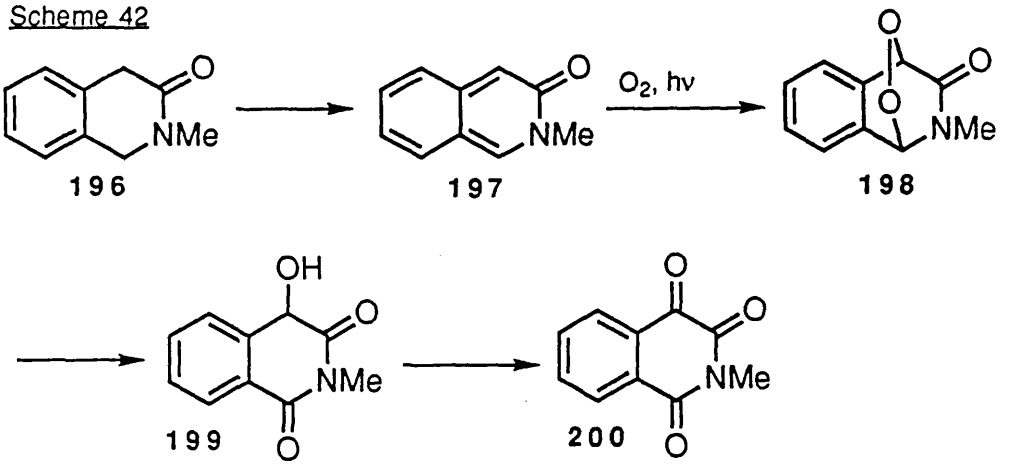



Interestingly, in small runs the chlorination could be carried out without triethylamine, but in the larger runs (ca. 4 g of starting material) the base was found to be critical to the success of the chlorination. Since treatment with water of the chlorinated product produced in large runs without base lead to the formation the sulphoxide, it may be assumed that the chlorination stopped at the intermediate salt (**194**), and that the succinimide was not basic enough to deprotonate this material (Scheme 41).

dihydro-

It soon became apparent that this isoquinolone (**176**) decomposed rapidly in the presence of air and light, and even when these were excluded considerable decomposition took place at room temperature. Samples stored under argon wrapped in foil at 5 °C for six months were almost entirely decomposed. This feature of dihydroisoquinolone chemistry has been reported before. [60]

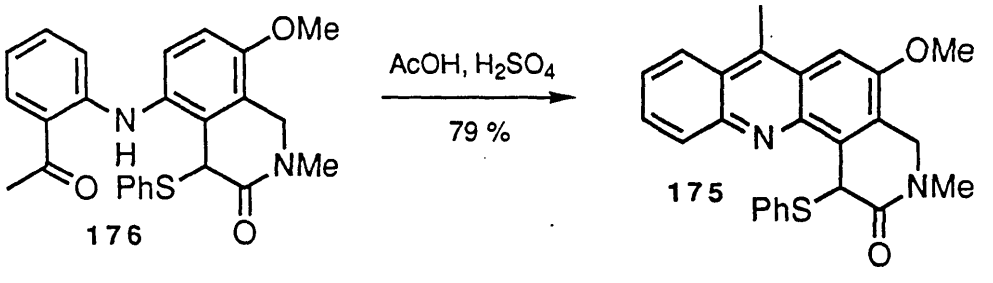
Scheme 42




It appears that these compounds oxidise to the isoquinolones on standing, and a photochemical $4\pi + 2\pi$ reaction with oxygen then gives endoperoxides of the type (**198**). These then rearrange and oxidise as shown in Scheme 42.

Despite this difficulty (**176**) could be cyclised to produce the acridine (**175**) in excellent yield (Scheme 43).

Scheme 43

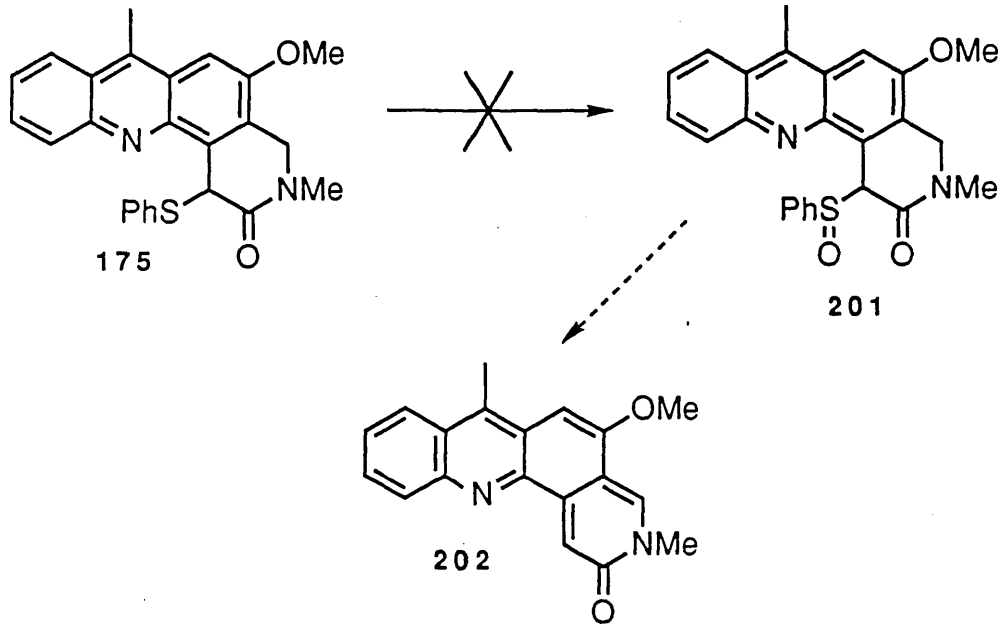



Although this material was also extremely susceptible to photooxidation, it was rather less intrinsically unstable. However, since this compound decomposed in the presence of oxidants, the standard procedure for the azide annulation (c.f. Scheme 6, Chapter One),

involving as a first step the oxidation of the aryl methyl group to an aldehyde was not practicable at this stage.

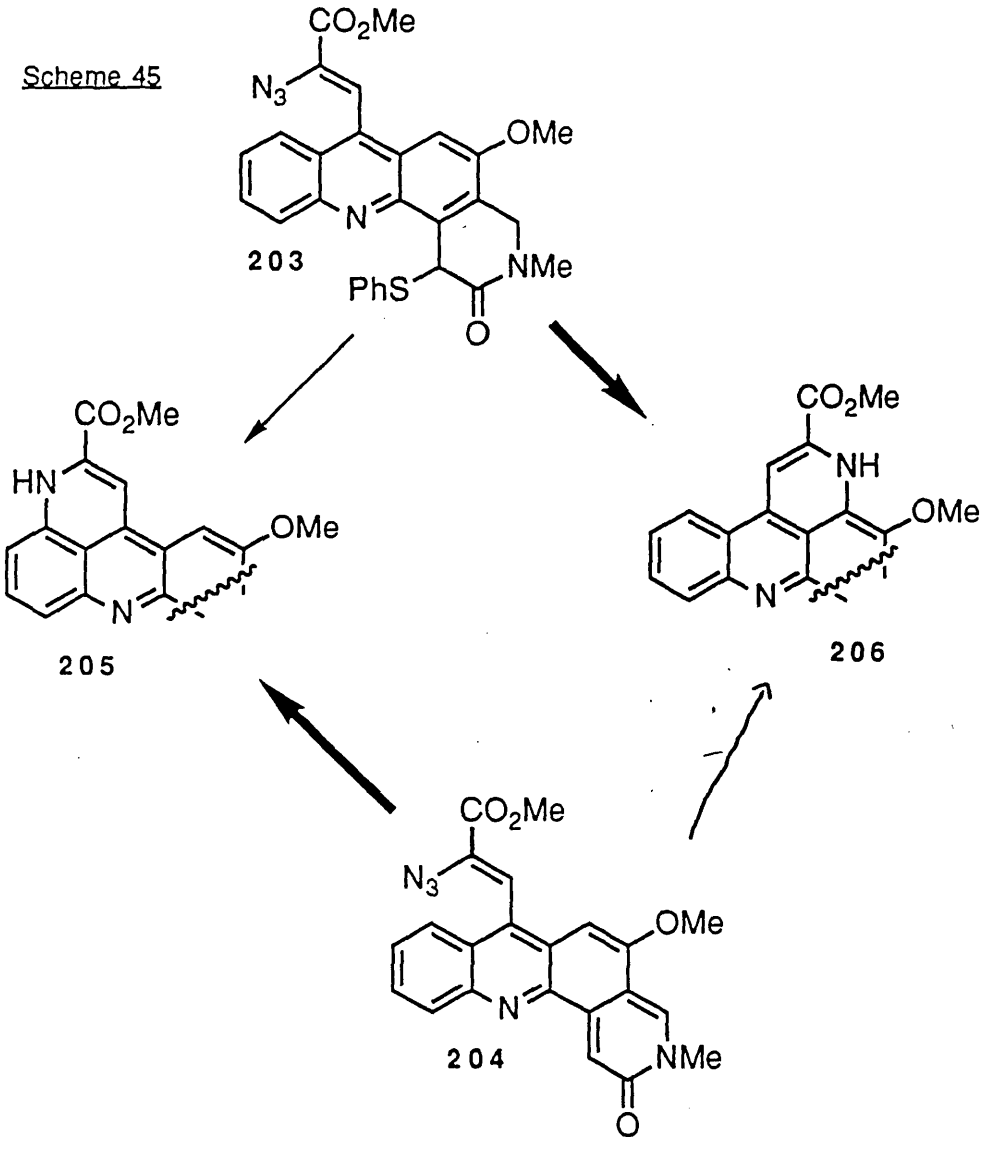
Attempts at selective oxidation of the sulphide to sulphoxide in order to unmask the isoquinolone functionality (Scheme 44) led to destruction of the ring system in the case of MCPBA and ozone at - 78 °C; sodium periodate was inactive due to the insolubility of the sulphide in the usual solvent systems associated with this oxidant.

Scheme 44



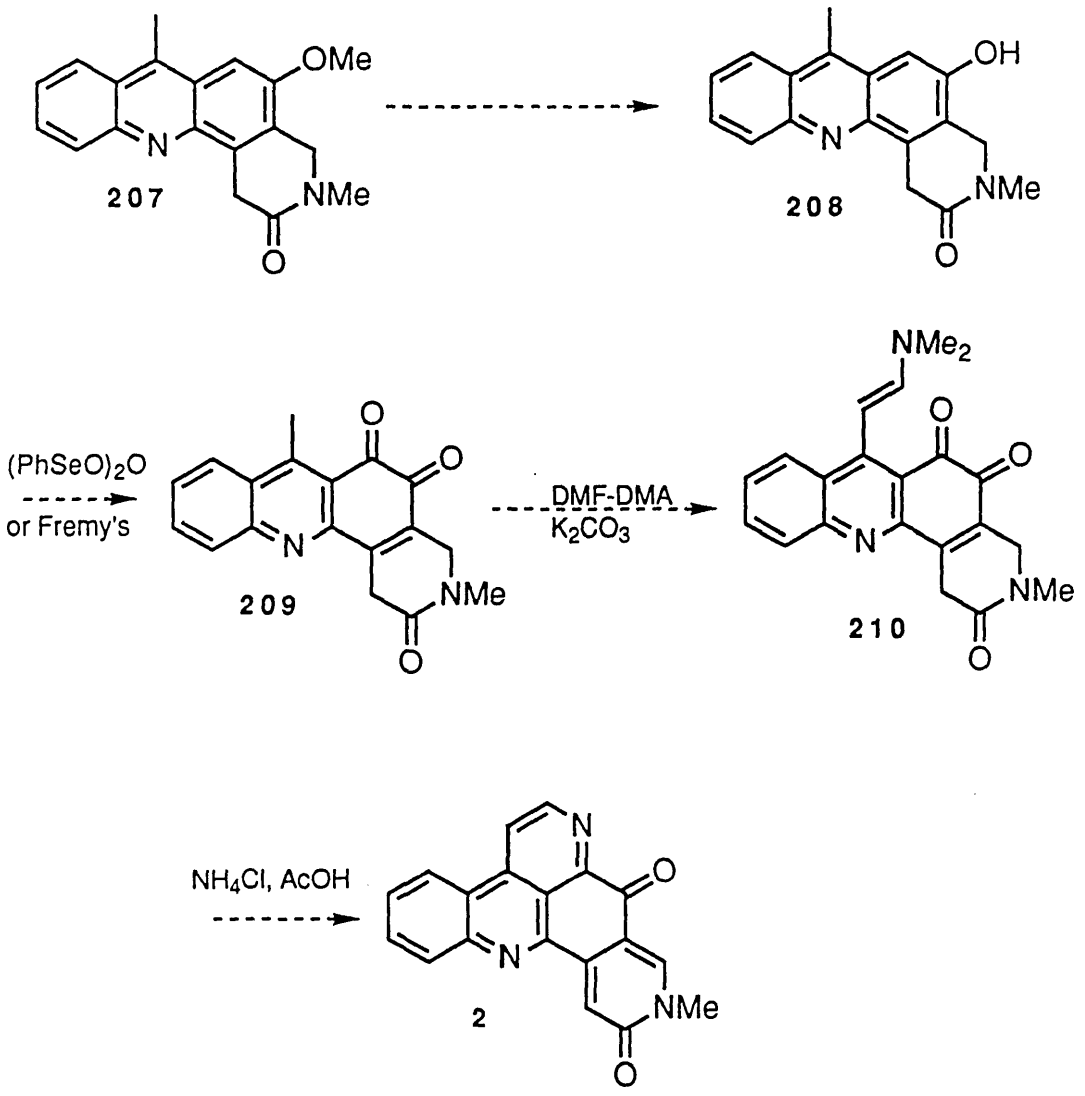

Our failure to unmask the isoquinolone at this stage was not a great cause for concern. Our synthetic plan was to complete the annulation first and unmask at the latest possible stage. The reason for this is that the azide decomposition involves insertion of an electrophilic nitrene into a C-H bond of an electron rich aromatic ring. Two regioisomers are possible so any selectivity must be based on electronic differences in the two benzo rings of the acridine. In the case of the dihydroisoquinoline (**203**) one of the benzene rings is unsubstituted and one has two "alkyl" and one methoxy substituents, which are expected to throw the isomer ratio well over to the required side. However, in the case of the isoquinolone (**204**), this electron rich ring is replaced by an electron deficient system with decreased aromaticity. This system is expected to produce a less favourable isomer ratio (Scheme 45).

Scheme 45



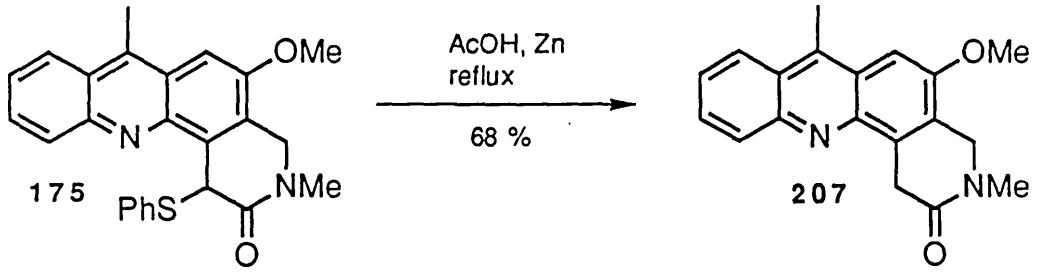

Since oxidation of the aryl methyl was not possible in the reactive molecule (**175**) we decided upon a different approach to the annulation (shown in Scheme 46). This envolved the creation of the orthoquinone (**209**) followed by Bracher's annulation procedure (cf. Scheme 10, Chapter One).[30]

Scheme 46




We decided to reduce off the phenylthio group, since it was not behaving as the mask it was designed to be, and because we hoped that this would improve the stability of the remaining system (the captodative nature of the PhSCH(Ar)CO grouping would be expected to facilitate one electron oxidation of the methylene, possibly the cause of the ready oxidation of the compound). The reduction was carried out with zinc in acetic acid, and the product (**207**) was obtained in 68 % yield (Scheme 47).

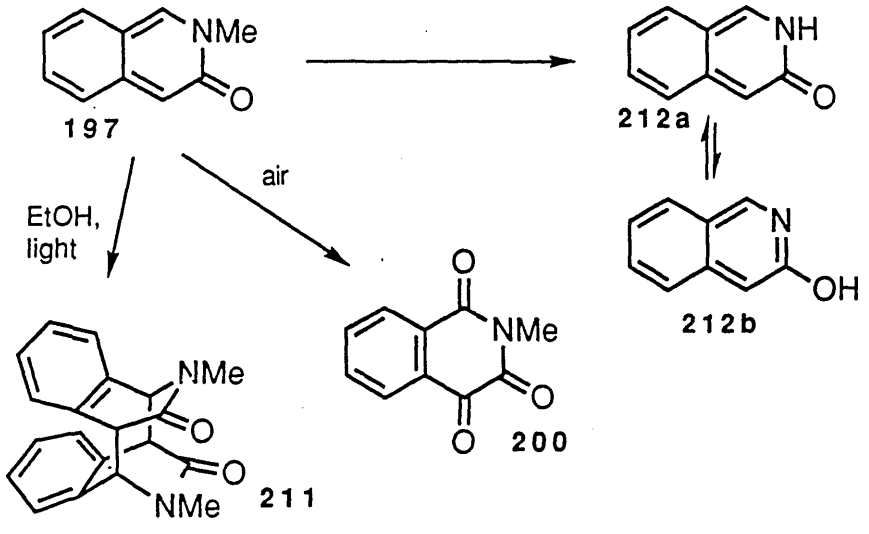
Scheme 47




This product was just as unstable as its predecessor. Since we needed to carry out the orthoquinone synthesis on reasonable quantities in order to be able to purify the intermediates by crystallisation (their polar nature would presumably invalidate the use of chromatographic techniques), we were forced to conclude that we could not continue with the synthesis due to the unavailability of sufficient quantities of intermediates, as well as the handling difficulties associated with them.

Solutions to this problem did occur to us. Firstly, demethylating the isoquinolone nitrogen in (**197**) imparts considerable aromatic stability to the system (Scheme 48); in particular, the N-methylisoquinolones are sensitive to light, giving the 1,4-photodimers, and in the presence of oxygen producing the phthalonimide as mentioned earlier. The desmethyl analogues on the other hand do not present these problems.[60]

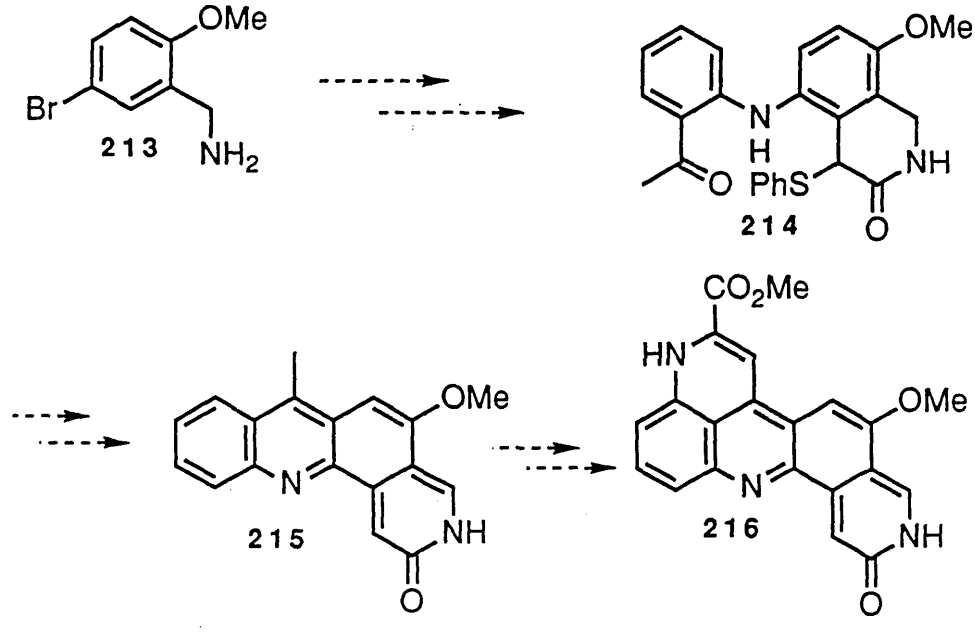
Scheme 48




Implementing this idea in our system is not simple. Since there is an aryl methoxy group also present in our molecule, which would complicate the demethylation of the

amide, the only efficient way of producing the desmethyl analogue is to leave out the methyl group from the start. Dehydrogenation of the dihydroisoquinolone soon after its synthesis would then give us the required isoquinolone. However, further elaboration then produces (215). This material, like its methyl analogue, would probably go on to yield the wrong isomer from the azide decomposition (Scheme 49).

Scheme 49




This suggests that the Bracher route to annulation would be more profitable. However this requires the orthoquinone functionality mentioned above. The inclusion of an oxygen functionality ortho to the methoxy group from the start would greatly simplify the production of this orthoquinone.

Unfortunately these suggestions not only lengthen a synthesis which is already becoming unwieldy, but also require its repetition from the beginning. Because of time limitations we were forced to call a halt to our studies.

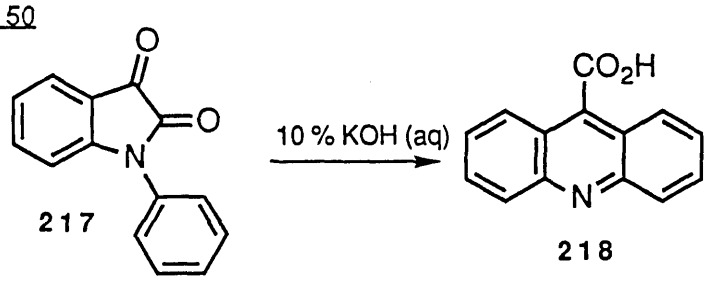
## 3.3 OTHER REACTIONS.

### 3.3.1 Introduction.

Our continuing interest with acridine - 9 - aldehydes has led us to investigate alternative methods of producing this system. In particular we required a synthesis which replaced the Ullmann reaction and yielded a 9 - substituent in a higher oxidation state, allowing us to produce the aldehyde functionality by reduction rather than oxidation.

This section shows our initial studies on the chemistry of N - arylisatins (**217**). These compounds are known to undergo saponification followed by cyclodehydration in aqueous base (Scheme 50).[61]

Scheme 50

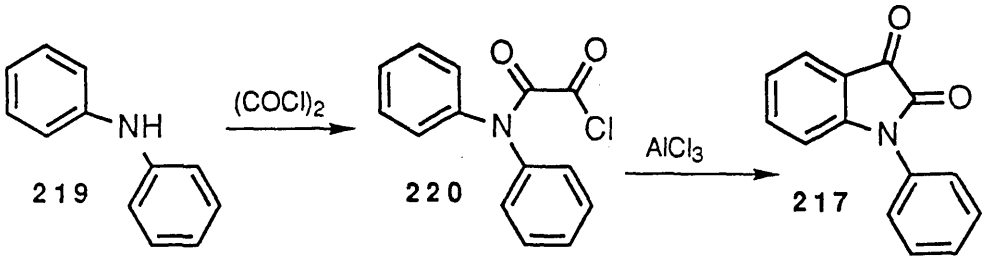



**217** **218**

It can be seen that this reaction produces an acid, potentially amenable to reduction to the required aldehyde. Since the reaction is carried out in aqueous base it actually complements the usual acridine synthesis (shown in Scheme 32), in which the cyclodehydration takes place under strongly acidic conditions. Thus correct choice of one of these two options allows the inclusion of base or acid sensitive functional groups.

The problem remains as to how to synthesise the isatins themselves. The simplest method is the acylation of a diarylamine with oxalyl chloride followed by Friedel - Crafts acylation with the remaining acyl group (Scheme 51).[62]

Scheme 51

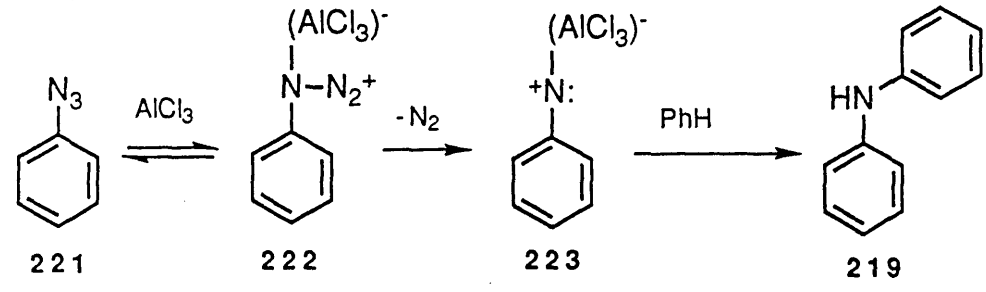



**219** **220** **217**

Despite the rapidity of this one - pot synthesis there is a major drawback; we are again required to synthesise a diarylamine.

It is for this reason that we investigated the viability of aryl azide decomposition reactions for the purpose. Two papers have been published in recent years on this subject. The first by Nakamura *et al* [63] shows a combination of high yields and regioselectivities for a number of systems. The azide decomposition is carried out at low temperatures (typically -60 °C) in the presence of aluminium chloride and a proton source such as phenol (other proton sources such as alcohols require higher temperatures for reaction and are typified by lower yields and regioselectivities). The second paper, by Takeuchi's group, [64] omits the proton source completely and is carried out at room temperature. Yields and selectivities both suffer in this modification, and the real value of the paper is the rigorous nature of the mechanistic studies. These show that in this case the reactive intermediate is a nitrenium species, presumably (**223**). The mechanism is shown in Scheme 52.

Scheme 52




221 222 223 219

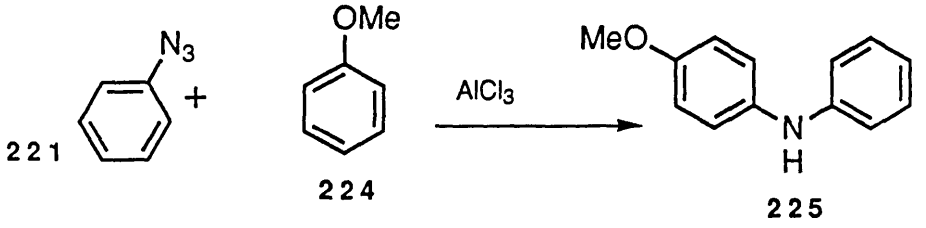
This mechanism when combined with the knowledge that the azide complex (**222**) is stable at low temperatures (in the absence of proton sources) sheds light on the reason for the beneficial effects of the phenol used in the earlier paper. This proton source effects reaction at -60 °C rather than 20 °C, and the nitrenium intermediate (**223**) is thus more discriminating in its reactivity. This has the effect of increasing the yield as well as regioselectivity.

It is interesting to note that this type of diarylamine synthesis works for electron rich systems, in contrast to the Ullmann synthesis, and so complements that reaction.[63]

### 3.3.2 Reactions.

We began our investigation with a simple case, the formation of a diarylamine from phenyl azide and anisole. Thus decomposition of the red phenyl azide - aluminium trichloride complex in anisole / DCM at - 60 °C with phenol in DCM produced 4 - methoxy - diphenylamine (**225**) in 80 % yield (Scheme 53). Interestingly this contradicted Nakamura's result (o:p ratio of 140 : 1!). This was disappointing since we were trying to make the 2 - isomer.

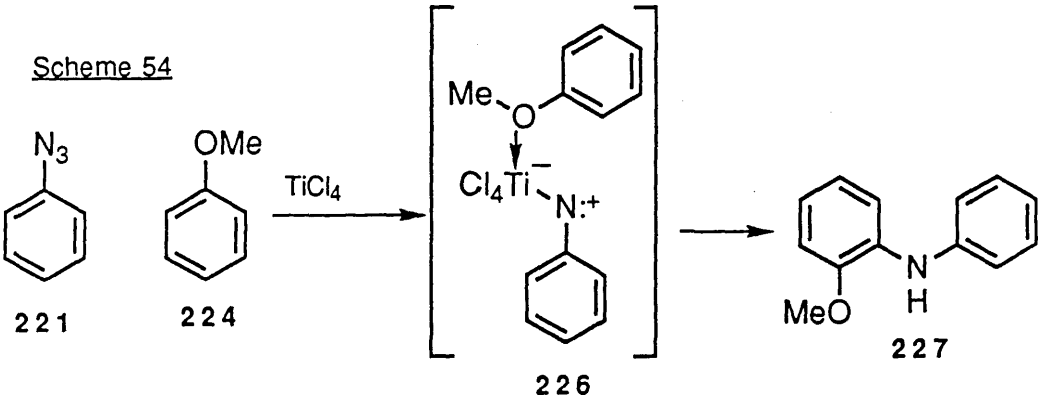
Scheme 53




221 224 225

Since the alternative technique of Takeuchi produced an almost 1:1 mixture of the two isomers, we did not try this, but instead we repeated our reaction with titanium tetrachloride in place of aluminium chloride. The idea behind this move was that by changing from aluminium to titanium we would make d orbitals available for at least partial coordination to the oxygen of the anisole, thus bringing the nitrenium centre into close proximity of the required position of attack. We were delighted to find that the sole isomer formed in this reaction was the 2 - methoxydiphenylamine (**227**) in 87 % yield (Scheme 54).

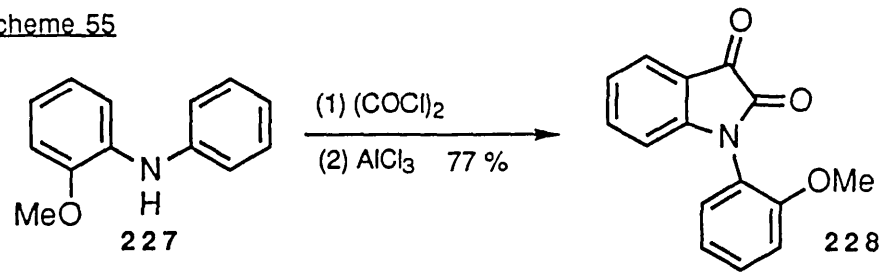
Scheme 54




221 224 226 227

The diarylamine (**227**) was readily converted to the isatin (**228**) by treatment with oxalyl chloride followed by aluminium chloride (Scheme 55).

Scheme 55

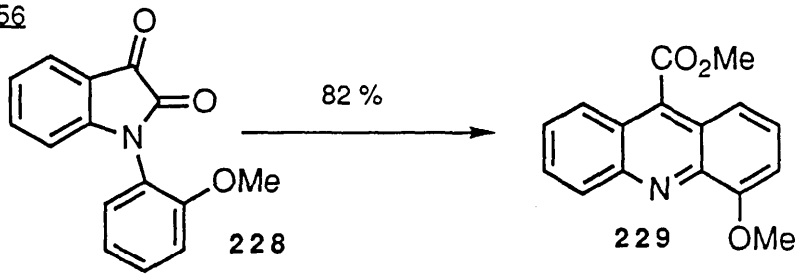



227 228

The Friedel - Crafts acylation took place exclusively as shown (see COSY 16, Diagram 6, Appendix B) presumably because of a combination of statistical effects and chelation effects of the aluminium chloride on the structure of the intermediate.

This isatin (**228**) was readily converted into the acridine - 9 - ester (**229**) by refluxing in aqueous 10 % potassium hydroxide and treatment of the crude product with diazomethane.

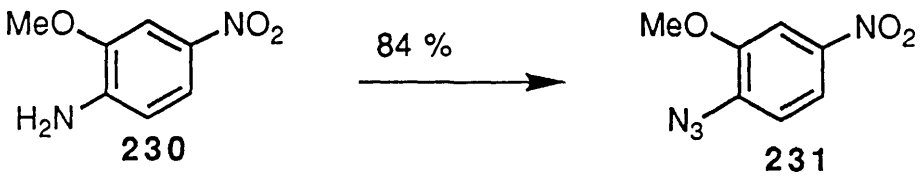
Scheme 56




228 229

With the success of this series of transformations quite evident, we decided to add a nitro group to our azide to gauge the effect of an electron withdrawing group on the reaction. Thus the azide (**231**) was prepared by diazotisation of the amine (**230**) followed by treatment with sodium azide (Scheme 57).

Scheme 57

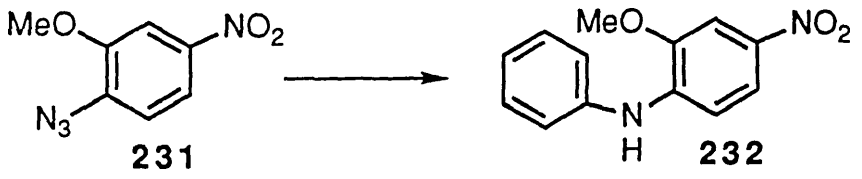



230 231

This azide gave an 88 % yield of diarylamine (**232**) when subjected to Takeuchi's procedure (no phenol) (Scheme 58). When the reaction was carried out in the presence of phenol the yield dropped to 75 %. This may be due to poor mixing at the low temperature used in this reaction. The azide decomposition was also attempted using catalytic dirhodium

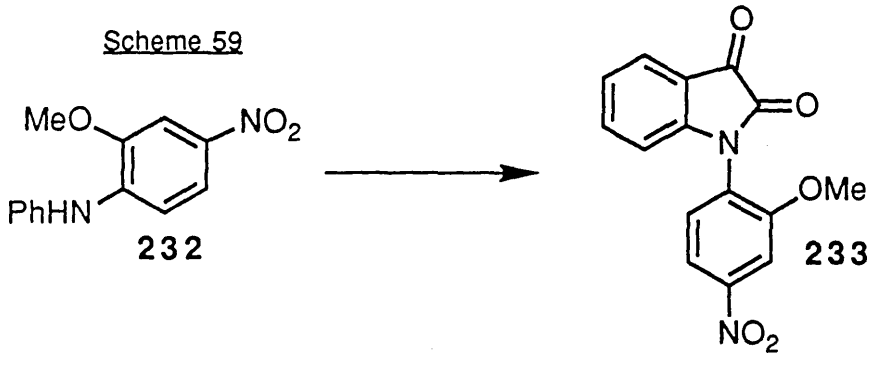
tetraacetate or copper (I) iodide in refluxing benzene, but under these conditions none of the diarylamine was formed. On the other hand, heating the azide in refluxing benzene in the presence of excess boron trifluoride produced the required product in 69 % yield.

Scheme 58



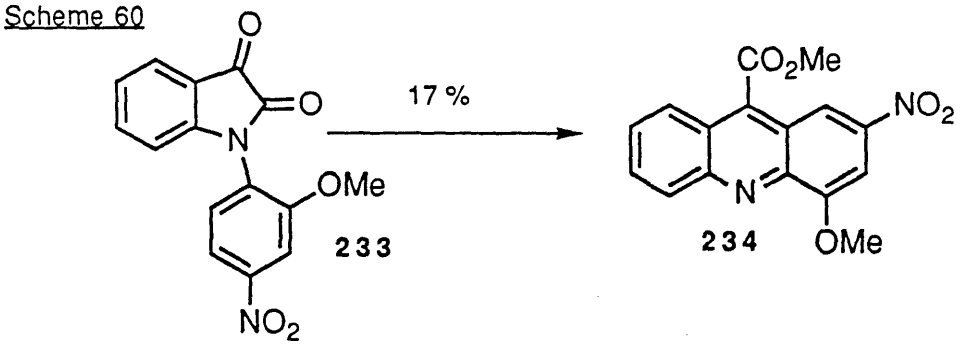

The diphenylamine (**232**) was readily converted into the isatin (**233**) in 88 % yield. Again the regioselectivity was for cyclisation onto the unsubstituted ring (Scheme 59).

Scheme 59



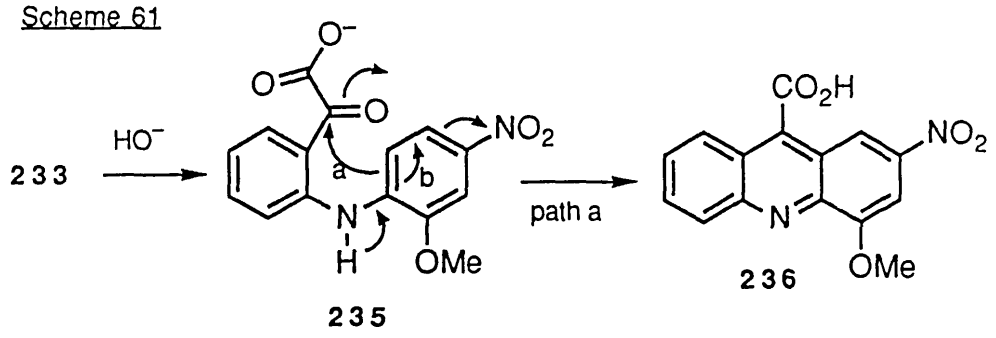

However the acridine formation was not as efficient as its simpler predecessor, and only a 17 % yield of the acridine (**234**) was obtained (Scheme 60).

Scheme 60




This unsatisfactory yield can be explained by noting the mechanism (Scheme 61).

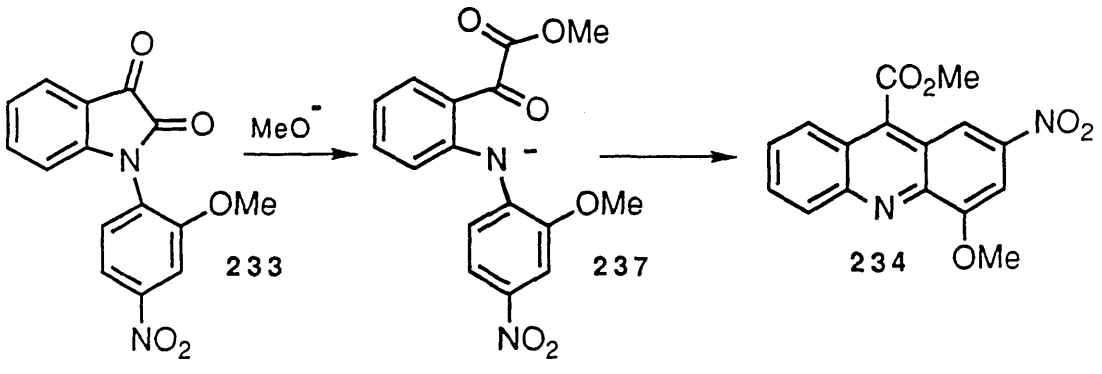
Scheme 61




It can be seen that the electron pair on the amine nitrogen in (**235**) may delocalise in two distinct directions (labelled a and b in Scheme 61). One leads to reaction as required (path a), however the other feeds straight into the nitro group electron sink. It is this effect which presumably lowers the yield of this reaction to such an extent.

In order to shorten the acridine ester preparation, we attempted the reaction with nucleophiles other than hydroxide. The idea behind this was that if we could open the isatin with (for instance) methoxide we would form the benzoyl methylformate (**237**) as an intermediate, which on cyclisation would give the ester directly (Scheme62). However, refluxing the isatin (**233**) in a solution of sodium methoxide in methanol, although producing a single new and very polar material, did not produce any of the required ester (234). The product was tentatively assumed to be the intermediate (**237**) on the basis of its colour (deep red) and tlc properties (polarity and characteristic UV fluorescence), which compared well with the properties of the single intermediate of the reaction with potassium hydroxide. If this is the case, the reaction may have failed to go to completion because of the low temperature of the refluxing methanol in which it was carried out. For this reason we repeated the reaction using sodium methoxide in refluxing dry dioxane. This time the acridine ester was isolated, albeit in low yield (9 %).

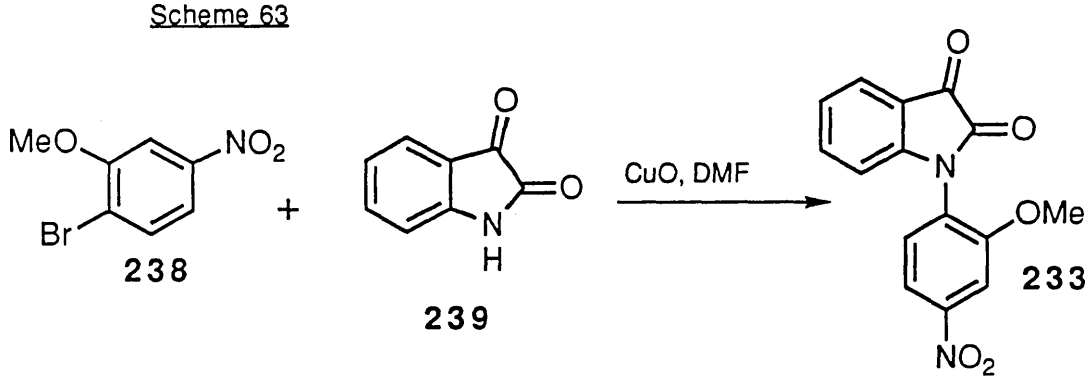
Scheme 62



The low yield of this reaction appears to have been due to the hydrolysis of the ester by sodium hydroxide being formed from the one equivalent of water produced during the cyclisation. Esterification of the extremely polar coproduct yielded a further 17 % of the acridine ester.

Time considerations meant that we were unable to continue this work, but before leaving this area we attempted a one step synthesis of the isatin (**233**) using a modified Ullmann procedure published in 1987. [65] Despite the extremely variable results published we obtained a 40 % yield of (**233**) on refluxing the aryl bromide (**238**) with isatin (**239**) in DMF in the presence of copper (II) oxide (Scheme 63).

Scheme 63



## 3.4 CONCLUSION.

The first half of this chapter has described our approach to the synthesis of amphimedine (**2**). This culminated in the synthesis of some highly reactive tetracyclic compounds. This partial synthesis yielded considerable information about the hidden pitfalls of the retrosynthesis around which it was structured, as well as the reactivities and stabilities of intermediates called upon. In effect this work has laid strong foundations on which to build a slightly modified synthesis.

The second half of the chapter has decribed a number of model studies designed to complement the more standard acridine - 9 - aldehyde syntheses. The results gained have been very encouraging, and further promising work is ongoing within our group. [55]

# CHAPTER FOUR.

# EXPERIMENTAL SECTION.

## 4.1 GENERAL EXPERIMENTAL PROCEDURES.

### 4.1.1 Solvents and Reagents.

Ether refers to diethyl ether which was dried by standing over sodium wire. THF was dried by distillation from potassium - benzophenone ketyl. Benzene, toluene, hexane and xylene were dried by standing over sodium wire. DMF was dried by stirring over barium oxide at room temperature for 12 h, decanting, and distillation from oven dried alumina at reduced pressure. Chloroform, dichloromethane, ethanol and methanol (unless required dry) were used as supplied. Dry methanol was distilled from magnesium methoxide. Dry dichloromethane, chloroform and tetrachloromethane were distilled from phosphorus pentoxide. Methylcyclohexane was distilled from sodium, and acetonitrile from calcium hydride twice followed by distillation from small quantities of phosphorus pentoxide. Light petroleum refers to the fraction boiling in the range 60 - 80 °C, and was distilled before use. Triethylamine was distilled from sodium hydroxide. Aniline was distilled from lithium aluminium hydride. All other commercial anilines were purified by filtration of a chloroform solution though a pad of oven dried alumina. Analar concentrated sulphuric acid was 99±0.5 %, as supplied by BDH. Alumina was Brockmann I grade. All other reagents (with the exception of the two below) and solvents were obtained from commercial suppliers and were used without purification.

Manganese dioxide was prepared as in the literature,[66] and stored at 75 °C. Barium manganate was prepared as in the literature [67] and powdered immediately before use.

### 4.1.2 Chromatographic Procedures.

Analytical thin layer chromatography (TLC) was performed on Merck Kieselgel 60 $GF_{254}$ aluminium - backed plates, or Merck aluminium oxide 60 $GF_{254}$ neutral (Type E) aluminium backed plates . Visualisation was either by viewing under UV light (at 254 and/or 360 nm), or by staining with molybdate or permanganate dips, or with iodine vapour.

Preparative chromatography was carried out using the Flash technique [72] when the stationary phase was silica [Merck Kieselgel 60H (70 - 230 mesh)], and standard gravity type when using alumina [acidic, neutral, or basic Brockmann I grade as necessary]. Samples were applied preadsorbed on silica or as a saturated solution in the appropriate

solvent. Crystallisation of solids after isolation by chromatography was attempted in all cases. If this was satisfactory, or if the purity of the sample was improved by partial crystallisation or precipitation, then the method is mentioned in the relevant experimental.

### 4.1.3 Spectroscopic Techniques.

Infrared spectra were recorded using a Perkin Elmer 1710 FT spectrometer, with internal calibration. All spectra were recorded as solutions.

Ultraviolet - visible spectra were recorded using a Pye Unicam SP8 - 100 spectrophotometer.

Proton NMR spectra were recorded using Bruker WM 250 (250 MHz), Jeol GSX270 (270 MHz), or Bruker AM500 (500 MHz) instruments.All spectra employed a homonuclear lock (deuterium of the solvent). $^{13}C$ NMR spectra were recorded on a Bruker AM500 (125 MHz) or Jeol GSX270 (67.9 MHz). Signals are measured in ppm, and referenced to the residual peak of the solvent. In the case of proton spectra this is 7.260 ppm for deutero chloroform, 2.040 ppm for deutero acetone, or 2.490 ppm for deutero dimethyl sulphoxide. They are described as singlets (s), doublets (d), triplets (t), quartets (q), multiplets (m), double doublets (dd) etc.

Mass spectra were recorded at low resolutions using a VG Micromass 7070B instrument, in the electron impact mode at 70 eV, using a direct insertion probe. High resolution EI spectra were recorded on this instrument or a VG Analytical ZAB-E instrument (courtesy of the SERC mass spectrometry centre at Swansea). The SERC service was used for all CI spectra.

### 4.1.4 Other Data and Instrumentation.

Melting points were determined on a Reichert Kofler hot stage apparatus, with thermometers as supplied, and are uncorrected.

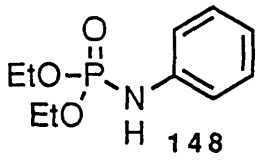
Microanalyses were carried out by Mr. K. Jones and his staff in the Imperial College Chemistry Department microanalytical laboratory.

## 4.2 EXPERIMENTAL FOR CHAPTER 2.

### 1,10-Phenanthroline-5,6-quinone (120).

To a stirred suspension of 5-nitrophenanthroline [68] (2.5 g, 11.1 mmol) in 5 % aqueous potassium hydroxide (22 ml) was added cautiously sodium borohydride (1.1 g, 29 mmol) in portions such as to keep the temperature below 80 °C. After the addition was complete the temperature was maintained at 80 °C for a further 2.5 h, before the slurry was cooled and filtered. The solids were washed with ice cold water (30 ml) and acetone (15 ml) and air dried at 60 °C. This solid was then powdered and added to cold concentrated sulphuric acid (11 ml) in small portions, and then fuming nitric acid (11 ml) was added. The resultant solution was heated to 120 - 130 °C for 2 h. After this time the reaction mixture was cooled as much as possible (while maintaining a reasonable rate of stirring) and ice cold water (20 ml) was added. The stirred cold suspension was neutralised with concentrated aqueous ammonia (**caution**), before being extracted with chloroform (3 x 150 ml) and ethyl acetate (3 x 150 ml). The combined organic extracts were dried over magnesium sulphate and the solvents removed *in vacuo*. Recrystallisation from methanol gave the title compound (0.9 g, 40 %) as a yellow solid, m.p. 246 - 248 °C (Lit. 245 - 248 °C) [46]; $\delta_H$ (270 MHz, $CDCl_3$ ) 9.09 (2H, dd 4.6, 1.7 Hz, phen<u>H</u>-2 & 9), 8.48 (2H, dd 7.8, 1.7 Hz, phen<u>H</u>-4 & 7), 7.57 (2H, dd 7.8, 4.6 Hz, phen<u>H</u>-3 &8).

### Diethyl N-phenyl phosphoramidate (148).

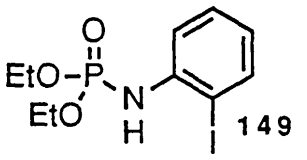


148

To a stirred solution of freshly distilled aniline (2.19 g, 10 mmol) and triethylamine (1.54 ml, 1.1 eq.) in dry benzene (25 ml) under argon at room temperature was added dropwise diethyl phosphorochloridate (1.45 ml, 10 mmol). After 4 days the suspension was filtered and the filtrate washed with water (2 x 40 ml) and brine (40 ml) and dried over sodium sulphate. Removal of the solvents *in vacuo* yielded the title compound (3.30 g, 92 %) as a white gum; $\delta_H$ (270 MHz, $CDCl_3$ ) 7.22 (2H, "t" 7.2 Hz, Ph<u>H</u>), 7.15 (2H, d 7.2 Hz, Ph<u>H</u>), 6.94

(1H, "t" 7.2 Hz, PhH), 6.45 (1H, brd, 10.1 Hz, NH), 4.00 - 4.24 (4H, m, $CH_2$), 1.26 (6H, dt 7.2, 1.1 Hz, $CH_3$).

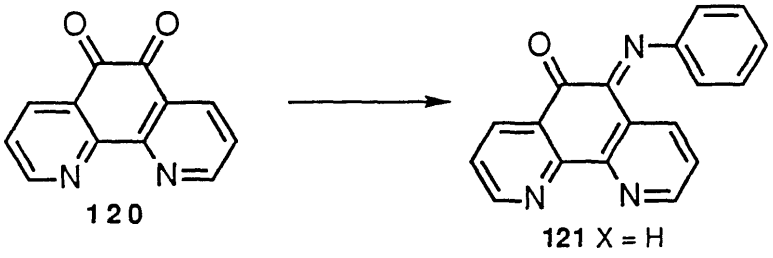
**Diethyl N-(2-iodophenyl)- phosphoramidate (149).**



149

This was prepared as above, and the title compound was isolated as an off white gum in a yield of 98 %; $\delta_H$ (270 MHz, $CDCl_3$ ) 7.67 (1H, dt 7.8, 1.5 Hz, PhH-6), 7.27 (1H, dd 8.0, 1.7 Hz, PhH-3), 7.20 (1H, ddd 8.0, 7.1, 1.5 Hz, PhH-4), 6.65 (1H, ddd, 7.8, 7.1, 1.7 Hz, PhH-5), 5.42 (1H brd 8.05 Hz, NH), 4.01 - 4.22 (4H, m, $CH_2$), 1.28 (6H, dt 7.1, 1.0 Hz, $CH_3$).

**N-Phenyl-1,10-phenanthroline-5,6-quinone monoimine (121 X = H).**

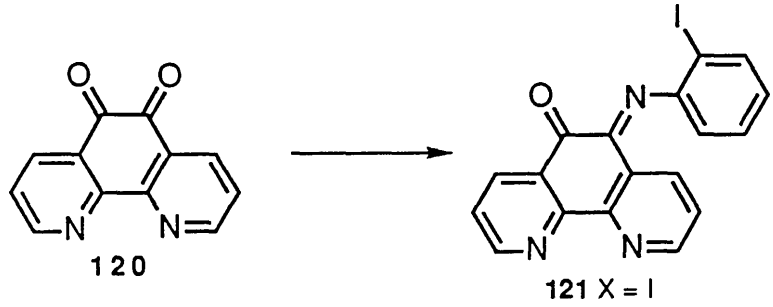


120 121 X = H

To a solution of the phosphoramidate (**148**) (248 mg, 0.7 mmol) in dry benzene (20 ml) under argon was added sodium hydride (37.3 mg, 1.1 eq., 45 % in hexanes) with stirring. After 30 min this solution was added to the quinone (**120**) (147 mg, 0.7 mmol) in dry benzene (120 ml) under argon, and stirred over night. The solvents were removed in vacuo and the remaining oil triturated well with ether and then DCM. The solvents were removed *in vacuo* and the oil purified by chromatography on alumina (eluting with chloroform) to give the *title compound* (157 mg, 55 %) as a purple solid, m.p. 135 - 136 °C (Found: $M^+$ 285.0902. $C_{18}H_{11}N_3O$ requires M 285.0902); $\lambda_{max}$ ($CH_3OH$) 203.2 (log ε 4.42), 206.0 (4.43), 232.3 (4.42), 553.6 (2.83); $\nu_{max}$ ($CHCl_3$) 1693, 1578, 1463, 1298; $\delta_H$ (250 MHz, $CDCl_3$) 9.08 (1H, dd 4.7, 1.8 Hz, phenH-2 or 9), 9.02 (1H, dd 4.7, 1.8 Hz, phenH-9 or 2), 8.64 (1H, dd 8.2, 1.8 Hz, phenH-7 or 4), 8.32 (1H, dd 8.2, 1.8 Hz, phenH-4 or 7), 7.53 (1H, dd 8.2, 4.7 Hz, phenH-8 or 3),

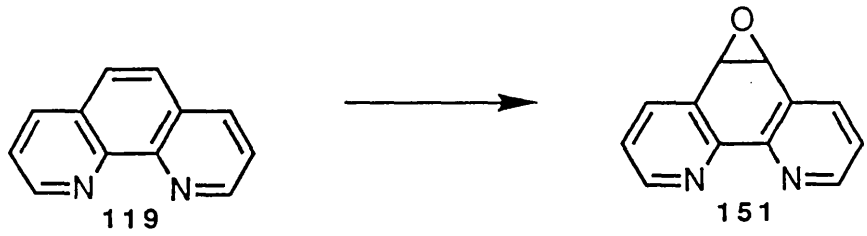
7.48 (1H, dd 8.2, 4.7 Hz, phen<u>H</u>-3 or 8), 7.39 (2H, brt 8.2 Hz, Ph<u>H</u>), 7.17, (1H, brt 8.2 Hz, Ph<u>H</u>), 6.82 (2H, brd 8.2 Hz, Ph<u>H</u>) (see also Diagram 4 & 5 in Appendix B); *m/z* (200 °C) 287 ($M^+$ + 2, 36 %), 285 ($M^+$, 52 %), 257 (100 %), 182 (19 %).

**N-(2-Iodophenyl)-1,10-phenanthroline-5,6-quinone monoimine (121 X = I).**



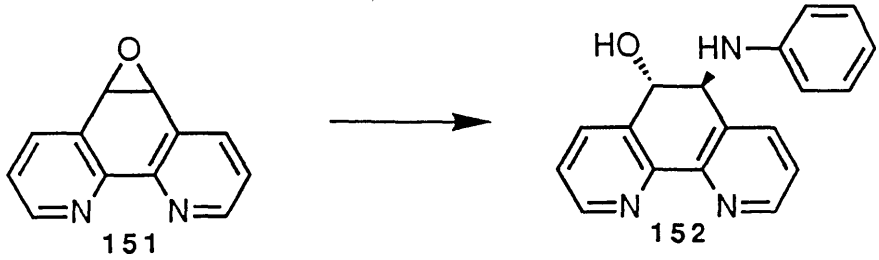

This was prepared in the same way as N-phenyl-1,10-phenanthroline-5,6-quinone monoimine, and the *title compound* was isolated as a purple solid in 11 % yield, m.p. 124 °C dec. (Found: $M^+$ 410.9869. $C_{18}H_{10}N_3OI$ requires M 410.9869); $\lambda_{max}$ ($CH_3OH$) 211.8 (log ε 4.56), 248.0 (4.46), ca. 560 (2.88); $\nu_{max}$ ($CHCl_3$) 3060 (br), 2973, 1692, 1615, 1578, 1461; $\delta_H$ (250 MHz, $CDCl_3$) 9.00 (1H, dd 4.7, ca. 1.2 Hz, phen<u>H</u>-9 or 2), 8.97 (1H, dd 4.6, 1.6 Hz, phen<u>H</u>-9 or 2), 8.69 (1H, dd 8.0, 1.6 Hz, phen<u>H</u>-7 or 4), 8.26 (1H, dd 7.6, ca. 1.2 Hz, phen<u>H</u>-7 or 4), 7.83 (1H, brd ca. 8 Hz, Ph<u>H</u>), 7.50 (1H, dd 8.0, 4.6 Hz, phen<u>H</u>-8 or 3), 7.43 (1H, dd 7.6, 4.7 Hz, phen<u>H</u>-8 or 3), 7.30, (1H, brt ca. 8 Hz, Ph<u>H</u>), 6.82 (2H, brd ca. 8 Hz, Ph<u>H</u>), 6.67 (1H, brd ca. 8 Hz, Ph<u>H</u>); *m/z* (200 °C) 411 ($M^+$, 35 %), 285 (100 %), 256 (39 %). Despite numerous modifications to the experimental procedure, the yield of this reaction could not be significantly improved.

**1,10-Phenanthroline-5,6-epoxide (151).**




To a mechanically stirred mixture of industrial bleach (900 ml) and water (600 ml) adjusted to pH 8.2 - 8.3 with concentrated hydrochloric acid was added a mixture of tetrabutylammonium hydrogen sulphate (5 g) and phenanthroline monohydrate (6 g) dissolved in chloroform (500 ml). The reaction was followed by NMR. After completion the organic layer was separated and washed with water (3 x 500 ml) and brine (500 ml). Drying over sodium sulphate and removal of the solvents *in vacuo* yielded the title compound as a white powder (6.4 g, 98 %), m.p. 164 - 165 °C (Lit. 163 - 165 °C) [50]; $\delta_H$ (270 MHz, $CDCl_3$ ) 8.92 (2H, dd 4.6, 1.7 Hz, phen<u>H</u>-9 & 2), 8.02 (2H, dd 7.6, 1.7 Hz, phen<u>H</u>-4 & 7), 7.42 (2H, dd 7.6, 4.6 Hz, phen<u>H</u>-8 & 3), 4.64 (2H, s, phen<u>H</u>-5 & 6).

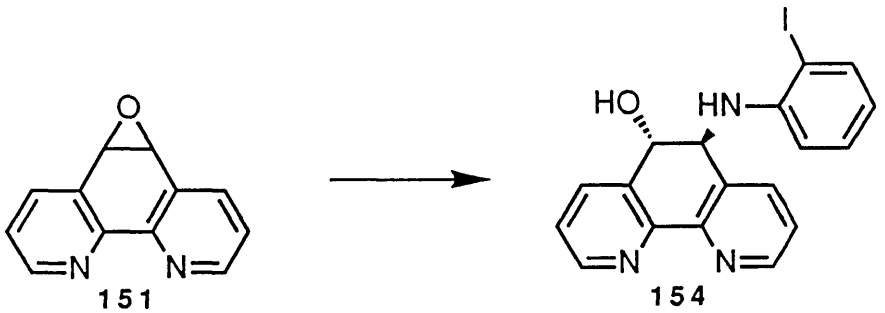
***trans*-5-Anilino-6-hydroxy-5,6-dihydro-1,10-phenanthroline (152).**




To a slurry of basic alumina (22.5 g) with DCM was added aniline (0.9 g, 4 wt% alumina). After 10 min stirring phenanthroline epoxide (**151**) (588 mg, 3 mmol) in the minimum of DCM was added dropwise. After a further 5.5 h methanol (200 ml) was added and after 5 min the suspension allowed to stand for 4 h. Filtration and removal of most of the solvent was followed by addition of hexane. The *title compound* was obtained (850 mg, 98 %) as a fine white powder, m.p. 206 °C dec (Found: C, 74.8; H, 5.2; N, 14.3. $C_{18}H_{15}N_3O$ requires C, 74.7; H, 5.2; N, 14.5 %); $\nu_{max}$ ($CHCl_3$) 3071, 2961, 2931, 2874, 1728, 1603, 1582, 1270 (br); $\delta_H$ (270 MHz, $d_6$-DMSO) 8.67 (1H, dd 4.9, 1.5 Hz, phen<u>H</u>-2 or 9), 8.64 (1H, dd 4.6, 1.7 Hz, phen<u>H</u>-

2 or 9), 7.90 (1H, dd 7.8, 1.7 Hz, phen<u>H</u>-4 or 7), 7.76 (1H, dd 7.6, 1.5 Hz, phen<u>H</u>-4 or 7), 7.44 (1H, dd 7.8, 4.6 Hz, phen<u>H</u>-3 or 8), 7.39 (1H, dd 7.6, 4.9 Hz, phen<u>H</u>-3 or 8), 7.19 (2H, brt 7.6 Hz, Ph<u>H</u>), 6.71 (2H, brd 7.6 Hz, Ph<u>H</u>), 6.56 (1H, dd 5.9, 5.9 Hz, Ph<u>H</u>), 5.95 (1H, d 7.1 Hz, N<u>H</u> or O<u>H</u>), 5.83 (1H, d 5.3 Hz, N<u>H</u> or O<u>H</u>), 4.83 (1H, dd 5.4, 10.4 Hz, PhC<u>H</u>), 4.68 (1H, dd 7.1, 10.4 Hz, PhC<u>H</u>); $\delta_C$ (67.5 MHz, $d_6$-DMSO) 150.5, 150.1, 149.1, 149.0, 148.3, 136.4, 135.7, 135.2, 135.15, 133.6, 129.0, 124.1, 124.0, 116.1, 112.4, 68.4, 68.3, 56.9; *m/z* (190 °C) 289 ($M^+$,8 %), 271 (16 %), 197 (100 %).

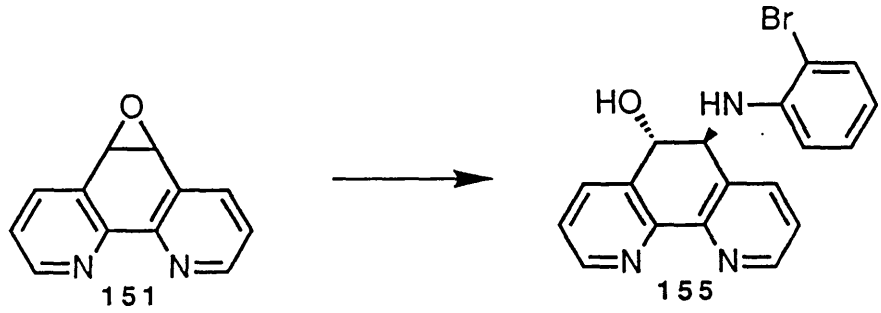
***trans*-5-(2-Iodoanilino)-6-hydroxy-5,6-dihydro-1,10-phenanthroline (154).**




To a stirred solution of 2-iodoaniline (1.25 g, 5.71 mmol) in dry DCM (28 ml) at 5 °C under argon in the dark was added triethylaluminium (3 ml, 5.70 mmol, 1.9 M in toluene) in one portion. This solution was then allowed to warm to room temperature. After 30 min phenanthroline epoxide (**151**) (1.09 g, 5.58 mmol) in dry DCM (8 ml) was added dropwise. The resulting solution was stirred for a further 22 h, when an excess of sodium sulphate decahydrate - Celite mixture (1:3) was added in portions. After 4 h the slurry was filtered, the solids washed with DCM and the solution concentrated *in vacuo*. Crystallisation by addition of hexane gave the *title compound* (1.83 g, 79 %) as a white powder , m.p. 128 - 130 °C (Found: $M^+$ 415.0176. $C_{18}H_{14}N_3OI$ requires M 415.0182); $\lambda_{max}$ ($CH_3CN$) 246.4 (log ε 3.24), 296.6 (3.05); $\nu_{max}$ ($CHCl_3$) 3575 (br), 3372 (br), 3062, 2970; $\delta_H$ (270 MHz, $CDCl_3$) 8.76 (1H, ddd 4.9, 1.7, 0.8 Hz, phen<u>H</u>-2 or 9), 8.74 (1H, ddd 4.9, 1.7, 0.8 Hz, phen<u>H</u>-2 or 9), 8.08 (1H, ddd 7.8, 1.7, 1.0 Hz, phen<u>H</u>-4 or 7), 7.72 (1H, dd 7.8, 1.7 Hz, phen<u>H</u>-4 or 7), 7.72 (1H, brdd 7.8, ca. 1.5 Hz, Ph<u>H</u>), 7.38 (1H, dd 7.8, 4.9 Hz, phen<u>H</u>-3 or 8), 7.28 (1H, dd 7.8, 4.9 Hz, phen<u>H</u>-3 or 8), 7.18 (1H, ddd 7.8, 7.8, ca. 1.5 Hz, Ph<u>H</u>), 6.96 (1H, dd 7.8, ca. 1.5 Hz, Ph<u>H</u>-3'), 6.55 (1H, ddd 7.8, 7.8, ca. 1.5 Hz, Ph<u>H</u>), 5.14 (1H, dd 10.7, 3.9 Hz, PhC<u>H</u>OH), 4.90 (1H, dd 10.7, 8.5 Hz, PhC<u>H</u>NH), 4.59 (1H, d 8.5 Hz, N<u>H</u>), 3.41 (1H, d 3.9 Hz, O<u>H</u>); $\delta_C$ (125 MHz, $CDCl_3$) 150.1, 149.1 ($C_2$ and $C_9$), 146.6 ($C_{1'}$), 139.0, 135.6, 134.7 ($C_4$ or $C_7$), 134.1 ($C_4$ or $C_7$), 133.1, 129.2,

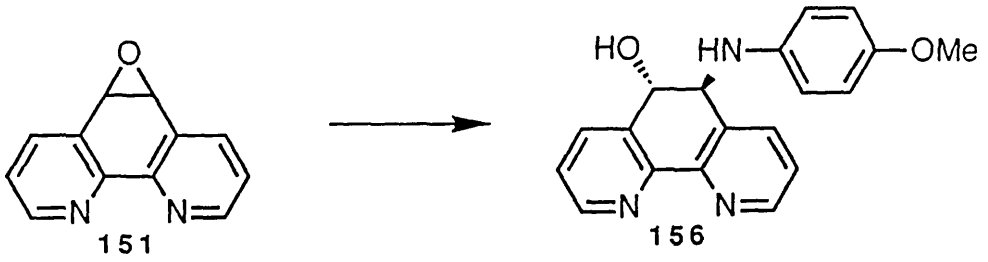
124.2 ($C_3$ or $C_8$), 124.1 ($C_3$ or $C_8$), 119.5, 111.5 ($C_{3'}$), 85.8 ($C_{2'}$), 69.9 ($C_5$), 58.9 ($C_6$) (see also Diagram 8 in Appendix B); *m/z* (220 °C) 415 ($M^+$, 0.3 %), 397 (100 %), 270 (73 %), 197 (13 %).

**_trans_-5-(2-Bromoanilino)-6-hydroxy-5,6-dihydro-1,10-phenanthroline (155).**



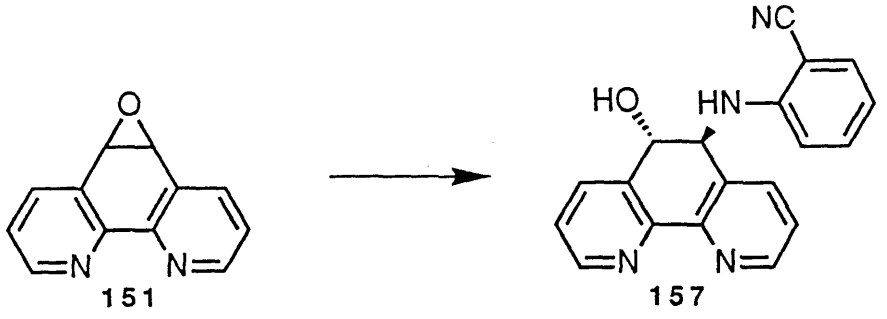

This was prepared by the same procedure as for the iodo analogue, and was isolated as *white crystals* (76 % yield), m.p. 128 °C (from benzene) (Found: C, 64.6; H, 4.4; N, 9.35. $C_{18}H_{14}N_3OBr.C_6H_6$ requires C, 64.6; H, 4.5; N, 9.4 %) (Found: $M^+$ 367.0320. $C_{18}H_{14}N_3OBr$ requires M 367.0320); $\nu_{max}$ ($CHCl_3$) 3581 (br), 3398 (br), 3071, 3039, 2960; $\delta_H$ (270 MHz, $CDCl_3$) 8.80 (1H, ddd 4.9, 1.2, 0.5 Hz, phen<u>H</u>-2 or 9), 8.79 (1H, ddd 4.9, 1.2, 0.5 Hz, phen<u>H</u>-2 or 9), 8.08 (1H, ddd 7.8, 1.2, 1.5 Hz, phen<u>H</u>-4 or 7), 7.73 (1H, ddd 7.8, 1.5, 1.2 Hz, phen<u>H</u>-4 or 7), 7.53 (1H, dd 8.1, 1.5 Hz, Ph<u>H</u>), 7.42 (1H, dd 7.8, 4.9 Hz, phen<u>H</u>-3 or 8), 7.33 (1H, dd 7.8, 4.9 Hz, phen<u>H</u>-3 or 8), 7.16, (1H, ddd 8.3, 8.1, 0.5 Hz, Ph<u>H</u>), 6.80 (1H, dd 8.3, 1.2 Hz, Ph<u>H</u>), 6.71 (1H, ddd 8.1,8.1, 1.5 Hz, Ph<u>H</u>), 5.10 (1H, dd 10.3, 3.7 Hz, PhC<u>H</u>), 4.93 (1H, dd 10.3, 9.3 Hz, PhC<u>H</u>), 4.71 (1H, d 9.3 Hz, N<u>H</u> or O<u>H</u>), 2.96 (1H, d 3.7 Hz, N<u>H</u> or O<u>H</u>); *m/z* (170 °C) 369, 367 ($M^+$, 2 %), 349, 350 (13 %), 270 (16 %), 197 (68 %), 78 (100 %).

*trans*-5-(4-Methoxyanilino)-6-hydroxy-5,6-dihydro-1,10-phenanthroline (156).




This was prepared by the same procedure as for the iodo analogue, and was isolated as a *white amorphous solid* (74 % yield), m.p. 233 - 235 °C (Found: $M^+$ 319.1321. $C_{18}H_{17}N_3O_2$ requires M 319.132); $\nu_{max}$ ($CHCl_3$) 3547 (br), 3384 (br), 3000, 2957; $\delta_H$ (270 MHz, $CDCl_3$) 8.775 (1H, ddd 4.6, 1.7, 0.7 Hz, phen<u>H</u>-2 or 9), 8.74 (1H, ddd 4.6, 1.5, 0.7 Hz, phen<u>H</u>-2 or 9), 8.05 (1H, ddd 7.8, 1.7, 0.7 Hz, phen<u>H</u>-4 or 7), 7.78 (1H, ddd 7.6, 1.5, 0.7 Hz, phen<u>H</u>-4 or 7), 7.38 (1H, dd 7.8, 4.6 Hz, phen<u>H</u>-3 or 8), 7.26 (1H, dd 7.6, 4.6 Hz, phen<u>H</u>-3 or 8), 6.83 (2H, d 9.0 Hz, Ph<u>H</u>), 6.71, (2H, d 9.0 Hz, Ph<u>H</u>), 5.00 (1H, brd 10.5 Hz, PhC<u>H</u>), 4.75 (1H, brd 10.5 Hz, PhC<u>H</u>), 3.92 (1H, brs, N<u>H</u> or O<u>H</u>), 3.77 (3H, s, C<u>H</u>$_3$), 3.29 (1H, brs, N<u>H</u> or O<u>H</u>); *m/z* (170 °C) 319 ($M^+$, 3 %), 301 (100 %), 286 (67 %), 197 (40 %), 83 (48 %).

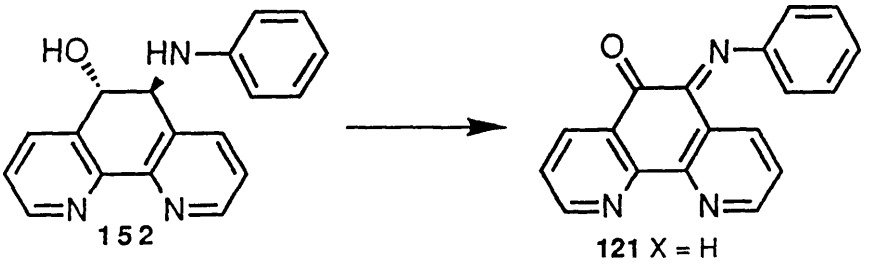
*trans*-5-(2-Cyanoanilino)-6-hydroxy-5,6-dihydro-1,10-phenanthroline (157).




This was prepared by the same procedure as for the iodo analogue, and was isolated as a *white amorphous solid* (74 % yield), m.p. 130 - 131 °C (Found: $M^+$ 296.1062. $C_{19}H_{14}N_4O$ requires M 296.1062); $\nu_{max}$ ($CHCl_3$) 3693 (br), 3608 (br), 3407 (br), 3065, 3026, 2972 (br), 2216; $\delta_H$ (500 MHz, $CDCl_3$) 8.61 (1H, ddd 4.7, 1.5, 0.6 Hz, phen<u>H</u>-2 or 9), 8.60 (1H, ddd 4.8, 1.6, 0.6 Hz, phen<u>H</u>-2 or 9), 8.01 (1H, ddd 7.8, 1.6, 0.6 Hz, phen<u>H</u>-4 or 7), 7.61 (1H, ddd 7.8, 1.5, 0.6 Hz, phen<u>H</u>-4 or 7), 7.31 (1H, dd 8.1, 1.3 Hz, Ph<u>H</u>), 7.27 (1H, dd 7.8, 4.8 Hz, phen<u>H</u>-3 or 8), 7.23 (1H, ddd 8.1, 7.4, 1.7 Hz, Ph<u>H</u>), 7.17 (1H, dd 7.8, 4.7 Hz, phen<u>H</u>-3 or 8), 6.63 (2H, brt 7.8 Hz,

PhH), 5.28 (1H, brs, NH or OH), 5.22 (1H, brd 7.6 Hz, NH or OH), 5.11 (1H, brd 10.7 Hz, PhCH), 4.85 (1H, brdd 10.7, 7.6 Hz, PhCH); *m/z* (160 °C) 314 ($M^+$, 0.2 %), 396 (100 %), 270 (9 %), 197 (3 %).

**N-Phenyl-1,10-phenanthroline-5,6-quinone monoimine (121 X = H).**




**(a) By oxidation with Attenburrow activated manganese dioxide.**

To a solution of the aminoalcohol (**152**) (289 mg, 1 mmol) in chloroform (50 ml) was added Attenburrow activated manganese dioxide (3 g), and the suspension stirred over night before being filtered though a pad of neutral alumina, and the solids washed well with chloroform. The solvent was removed *in vacuo* to give the title compound (200 mg, 70 %) identical to that prepared from the quinone (**120**).

**(b) By oxidation with DDQ.**

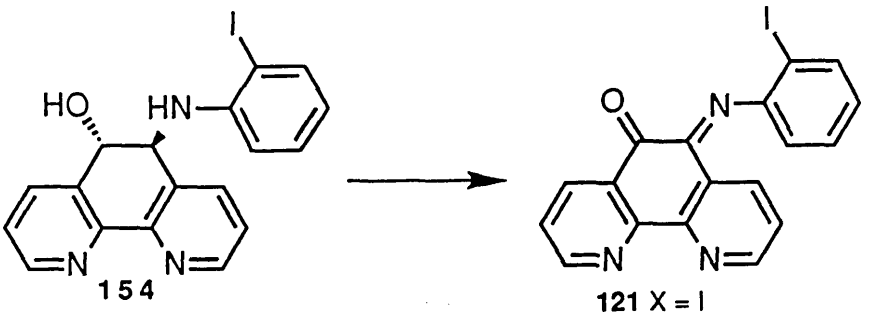
To a stirred solution of the aminoalcohol (**151**) (144.5 mg, 0.5 mmol) in chloroform (20 ml) under argon was added dichlorodicyanobenzoquinone (DDQ) (250 mg, 2.2 eq.) in one portion. After 3 h the solution was washed repeatedly with saturated aqueous sodium bicarbonate until the aqueous washings were colourless. The organic solution was dried over potassium carbonate, and the solvent removed *in vacuo*. Repeated chromatography on silica (eluting with chloroform / methanol) gave the title compound (47.6 mg, 32 %) as a purple solid, with data as previously.

**(c) By oxidation with nickel peroxide.**

To a solution of the aminoalcohol (**151**) (144.5 mg, 0.5 mmol) in benzene (100 ml) was added nickel peroxide (170 mg, ca. 1.2 eq. [O]) in one portion, and the suspension stirred for 3 h, before being filtered though a pad of neutral alumina, and the solids washed well with benzene. The solvent volume was reduced to a minimum *in vacuo*, and the residue passed

through a short pad of silica (eluting with chloroform) to give the title compound (33.2 mg, 23 %) with data as previously.

**N-(2-Iodophenyl)-1,10-phenanthroline-5,6-quinone monoimine (121 X = I).**



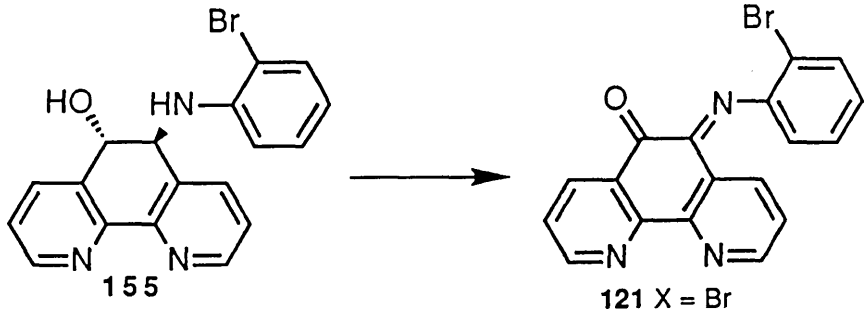

**(a) By oxidation with barium manganate.**

To a stirred solution of the aminoalcohol (**154**) (809 mg, 1.95 mmol) in DCM (80 ml) in the dark was added freshly powdered barium manganate (8 g) in portions over 20 min. The green suspension was stirred until all the starting material had been consumed (TLC), before being filtered though a pad of neutral alumina, and the solids washed well with chloroform. The solvent was removed *in vacuo* to give the title compound (665 mg, 83 %) with data as before.

**(b) By oxidation with Attenburrow activated manganese dioxide.**

This was prepared by the same procedure as for N-phenyl-1,10-phenanthroline-5,6-quinone monoimine in a yield of 65 %. Data were as given above.

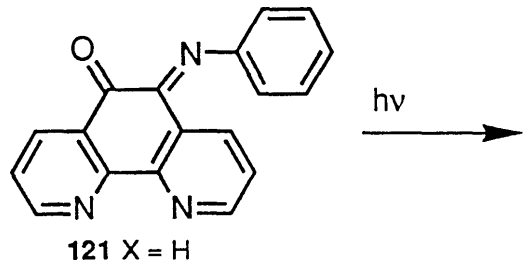
**N-(2-Bromophenyl)-1,10-phenanthroline-5,6-quinone monoimine (121 X = Br).**




**By oxidation with Attenburrow activated manganese dioxide.**

This was prepared by the same procedure as for N-phenyl-1,10-phenanthroline-5,6-quinone monoimine, and was isolated as a *purple solid* (67 %), m.p. 178 - 179 °C (Found: $M^+$ 363.0007. $C_{18}H_{10}N_3OBr$ requires M 363.0007); $\nu_{max}$ ($CDCl_3$) 3060, 1693, 1618, 1579,643; $\delta_H$ (270 MHz, $CDCl_3$) 9.07 (1H, dd 4.6, 1.9 Hz, phen<u>H</u>-2 or 9), 9.03 (1H, dd 4.6, 1.9 Hz, phen<u>H</u>-2 or 9), 8.72 (1H, dd 8.1, 1.7 Hz, phen<u>H</u>-4 or 7), 8.31 (1H, dd 7.8, 1.4 Hz, phen<u>H</u>-4 or 7), 7.62 (1H, dd 8.1, 1.2 Hz, Ph<u>H</u>), 7.55 (1H, dd 8.1, 4.6 Hz, phen<u>H</u>-3 or 8), 7.48 (1H, dd 7.8, 4.6 Hz, phen<u>H</u>-3 or 8), 7.33, (1H, ddd 7.3, 7.8, 1.2 Hz, Ph<u>H</u>), 7.02 (1H, ddd 7.3, 8.1, 1.5 Hz, Ph<u>H</u>), 6.77 (1H, dd 7.8, 1.5 Hz, Ph<u>H</u>); *m/z* (220 °C) 365, 363 ($M^+$, 4 %), 337, 335 (7 %), 284 (100 %), 256 (35 %).

**Photolysis of N-phenyl-1,10-phenanthroline-5,6-quinone monoimine (121 X = H).**




**(a) In methyl cyclohexane.**

The quinoneimine (**121** X = H) (192 mg, 0.7 mmol) was dissolved in freshly distilled methyl cyclohexane (500 ml) in a Hanovia type photoreactor with an internal high pressure mercury lamp, quartz filter, cooling jacket and nitrogen sparge. The whole system was immersed in a dry ice - acetone cooling bath, from which the acetone was pumped through the internal cooling jacket. The solution was sparged for 30 min and then irradiated. The

internal temperature stabilised at - 34 °C after a few minutes. Irradiation was continued for 4 h, whereupon it became clear by TLC that no reaction had taken place. The experiment was discontinued.

**(b) In dichloromethane.**

A solution of the quinoneimine (**121** X = H) (14.8 mg, 0.05 mmol) and iodine (14.5 mg, 1.1 eq.) in DCM (50 ml) was degassed using the freeze - pump - thaw technique, then sparged for 30 min and finally irradiated at ambient temperature in a pyrex tube immersed in a 1000 W Rayonet photoreactor emitting predominantly at 254 nm. The irradiation was discontinued after 3 h with no reaction having occurred.

**(c) In dichloromethane with boron trifluoride etherate.**

To a solution of quinoneimine (**121** X = H) (23.3 mg, 0.08 mmol) in dry DCM (30 ml) was added boron trifluoride etherate (4.1 ml, 400 eq.), producing a yellow - brown suspension. This was divided into two portions. One was irradiated as in (b) above, the other washed with saturated sodium bicarbonate (3 x 10 ml). After irradiating for 3 h the photolysed suspension was also washed with bicarbonate. TLC of the two separate aliquots showed that they were identical. The two were combined and the products partitioned between methanol (100 ml) and hexane (100 ml). The methanolic extracts were reduced to a volume of 10 ml *in vacuo*, and ether was added to precipitate a yellow solid (13.8 mg), m.p. 143 - 146 °C, whose NMR was identical to that of authentic 1,10-phenanthroline-5,6-quinone (**120**).

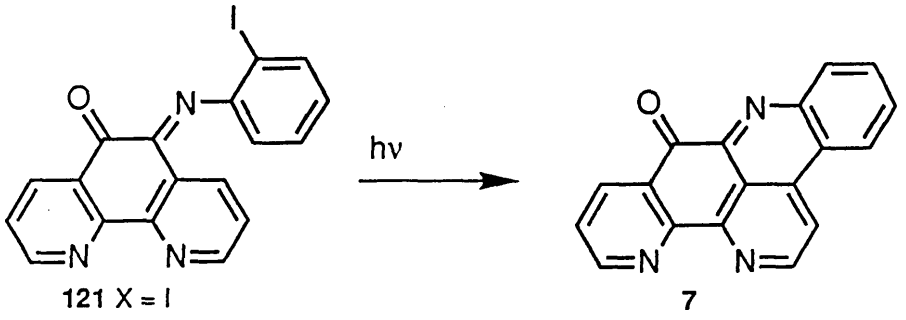
**(d) In sulphuric acid.**

The quinoneimine (**121** X = H) (127 mg) was dissolved in cold concentrated sulphuric acid (300 ml) and the dark green solution transferred to a Hanovia type photoreactor with quartz filter, internal water cooling, and high pressure mercury lamp. After sparging with nitrogen for 30 min, the solution was irradiated. After 4 h a large number of products had begun to appear (monitoring by TLC of a neutralised aliquot extracted into ethyl acetate). As the photolysis proceeded, more products began appearing. Purification of any products from the reaction mixture was impossible due to its complex nature (TLC): the reaction was abandoned.

The reaction was repeated a number of times, exchanging pyrex for the quartz filter, air instead of nitrogen to sparge, and a low pressure mercury source instead of the high

pressure one. In each case the photolysis began slowly but after 3 to 4 h large numbers of products started appearing on TLC. In all runs using the pyrex filter the starting material could be isolated at early stages in the photolysis by pouring the sulphuric acid solution onto ice, neutralising with concentrated aqueous ammonia, extracting with chloroform, and passing this solution through a neutral alumina pad.

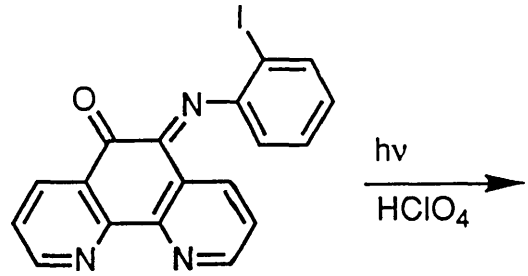
**Ascididemin (7).**




121 X = I 7

The *iodoquinoneimine* (**121** X = I) (131 mg, 0.319 mmol) was dissolved in cold 99 % Analar sulphuric acid (300 ml) and the solution transferred to a Hanovia type photoreactor with nitrogen sparge and water jacketed internal pyrex filter. After sparging for 30 min the solution was irradiated with a Phillips HPK125 high pressure mercury lamp for 2 h. The solution was then poured onto ice (500 g) and concentrated aqueous ammonia added to neutralise the acid. The product was extracted with chloroform (3 x 150 ml) and ethyl acetate (3 x 150 ml), and the combined extracts dried over magnesium sulphate. The solvents were removed *in vacuo* and the residual oil purified by chromatography first on neutral alumina (eluting with chloroform) and then silica (eluting with chloroform) to give some starting material (22.0 mg, 17 % recovery) and the title compound as a yellow solid (28.9 mg, 32 %) m.p. > 320 °C (Found: $M^+$ 283.0746. $C_{18}H_9N_3O$ requires M 283.0746); $\nu_{max}$ ($CHCl_3$) 1683, 1604, 1582, 1415,1267, 740; $\delta_H$ (270 MHz, $CDCl_3$) 9.27 (1H, d 5.7 Hz, H-6), 9.17 (1H, dd 4.6, 1.7 Hz, H-9), 8.80 (1H, dd 7.8, 1.7 Hz, H-11), 8.68 (1H, dt 8.1, 1.5Hz, H-4), 8.65 (1H, dt 8.05, 1.5 Hz, H-1), 8.55 (1H, d 5.7 Hz, H-5), 8.02 (1H, ddd 8.05, 7.1, 1.5 Hz, H-2), 7.94, (1H, ddd 8.1, 7.1, 1.5 Hz, H-3), 7.68 (1H, dd 7.8, 4.6 Hz, H-10) (see also Diagram 2 in Appendix B); *m/z* (C.I.) 284 ($M^+$ + 1), (E.I.) 283 ($M^+$), 270, 255. All data were in complete agreement with the literature values.[7, 30]

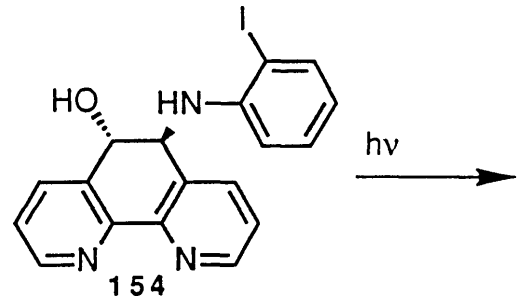
**Photolysis of N-(2 -iodophenyl)-1,10-phenanthroline-5,6-quinone monoimine (121 X = I) in dioxane with perchloric acid.**




**121 X = I**

The quinoneimine (**121** X = H) (192 mg, 0.7 mmol) was dissolved in anhydrous dioxane (100 ml) in a pyrex tube, and perchloric acid (45 µl, 3 eq.) added slowly. The resultant grey - green solution was sparged with nitrogen for 20 min, and then irradiated in a 1000 W Rayonet photoreactor emmiting predominantly at 254 nm. After 1 h the solution was neutralised with concentrated aqueous ammonia and partitioned between brine (300 ml) and chloroform (3 x 50 ml). The organic extracts were combined and dried over sodium sulphate, and the solvents removed *in vacuo*. TLC examination of the residual tar showed that complete decomposition had taken place.

**Photolysis of *trans*-6-hydroxy-5-(2-iodoanilino)-5,6-dihydro-1,10-phenanthroline (154).**[74]

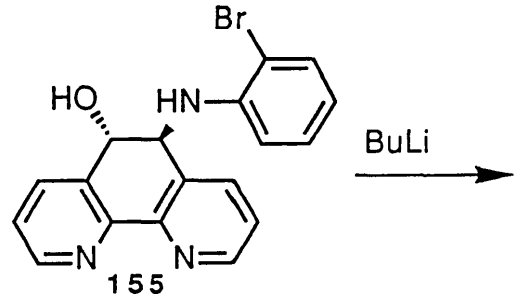



**154**

To a well agitated solution of the aminoalcohol (**154**) (119 mg, 0.29 mmol) in acetonitrile (180 ml) in a Hanovia type photoreactor with a pyrex filter, nitrogen sparge and water jacket was added sodium hydroxide (30 mg, 2.6 eq.) in water (20 ml). The solution was sparged for 20 min and then irradiated with a high pressure mercury source. A slow and indiscriminate reaction took place (monitored by TLC of a neutralised aliquot extracted

into chloroform), and the reaction was terminated after 4 h. The mixture was neutralised with saturated ammonium chloride and partitioned between brine (300 ml) and chloroform (3 x 100 ml).TLC examination of the organic extracts showed the product mixture to be too complex to purify by chromatography, and they were discarded.

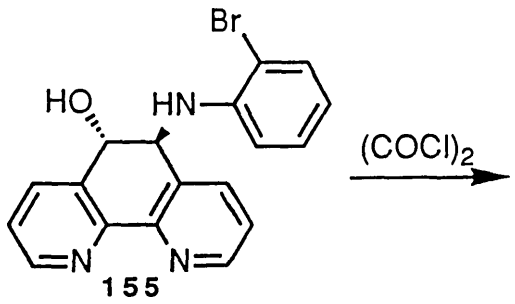
**Reaction of butyl lithium with *trans*-5-(2-bromoanilino)-6-hydroxy-5,6-dihydro-1,10-phenanthroline (155).**




155

To a solution of the aminoalcohol (**155**) (154 mg, 0.419 mmol) in dry THF (10 ml) and HMPA (2 ml) at -60 °C under argon was added n-butyl lithium (1.05 ml, 3 eq., 1.2 M in hexane). After 30 min the red solution was allowed to warm to room temperature over 2 h. After a further 30 min at room temperature acetic acid (100 µl) was added. TLC of this solution showed the presence of starting material which streaked in such a way on the plate as to obscure any products. The solution was diluted to 100 ml with ethyl acetate and washed with saturated sodium bicarbonate (3 x 100 ml), water (3 x 100 ml) and brine (2 x 50 ml). The organic extracts were dried over sodium sulphate and the solvents removed *in vacuo*. The residual tan oil was redissolved in chloroform (50 ml) and Attenburrow activated manganese dioxide (1.5 g) added. The suspension was stirred over night, before being filtered through a pad of neutral alumina and the solids washed well with chloroform / methanol (95:5). Removal of the solvents *in vacuo* left a dark tar which was subjected to chromatography on silica (eluting with chloroform / methanol). The only material isolated from this column was identified by NMR as N-phenyl-1,10-phenanthroline-5,6-quinone monoimine (**121** X = H) (3.2 mg, 3 %).

Reaction of oxalyl chloride with *trans*-5-(2-bromoanilino)-6-hydroxy-5,6-dihydro-1,10-phenanthroline (155).




155

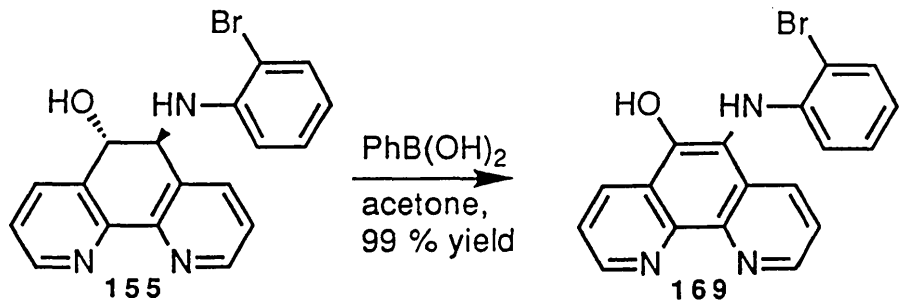
(a) With triethylamine as base.

To a stirred refluxing mixture of the aminoalcohol (**155**) (230 mg, 0.552 mmol) and triethylamine (0.5 ml, excess) in chloroform (25 ml) under argon was added dropwise oxalyl chloride (72 µl, 1.5 eq.). The pale tan solution turned black during the addition. After 30 min the solution was cooled and washed with saturated sodium bicarbonate (3 x 50 ml) and water (3 x 50 ml) and dried over sodium sulphate. Removal of the solvents *in vacuo* produced a black intractable tar which was not investigated further.

(b) With sodium hydride as base.

To a stirred suspension of sodium hydride (56.4 mg, 2.35 mmol) in dry THF (50 ml) at room temperature under argon was added the aminoalcohol (**155**) (305 mg, 0.735 mmol). When the effervescence had subsided, oxalyl chloride (200 µl, ca. 2.3 mmol) was added dropwise. The pale tan solution turned black during the addition. After 45 min the oily solution was washed with saturated ammonium chloride (3 x 50 ml) and water (3 x 50 ml) and dried over sodium sulphate. Removal of the solvents *in vacuo* produced a black tar which was subjected to chromatography on silica (eluting with chloroform). The aminoalcohol (128 mg, 42 % recovery) was the only material isolable.

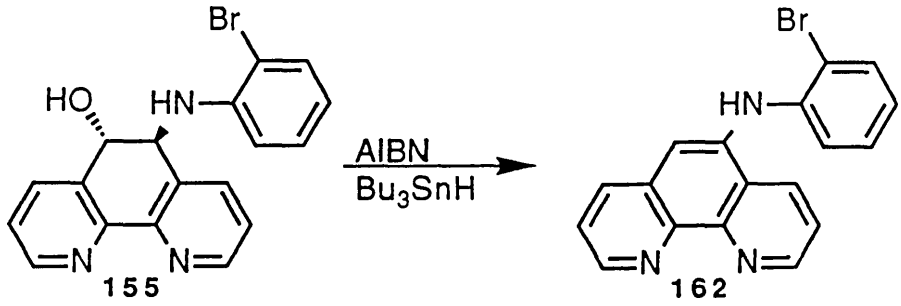
**Reaction of phenylboric acid in acetone with *trans*-5-(2-bromoanilino)-6-hydroxy-5,6-dihydro-1,10-phenanthroline (155).**




A mixture of the aminoalcohol (**155**) (290 mg, 0.70 mmol) and phenylboric acid (102 mg, 1.2 eq.) in acetone (25 ml) under argon was refluxed for 24 h. After this time, the solution was allowed to cool and concentrated *in vacuo*. Addition of ether to this concentrated solution produced a pale yellow powder, which was filtered off and washed with more ether to give the phenol (**169**) (252 mg, 99 %) as a colourless solid, m.p. ca. 143 °C dec.; $\delta_H$ (270 MHz, $CDCl_3$) 9.17 (1H, dd 4.4, 1.7 Hz, phen<u>H</u>-2 or 9), 9.05 (1H, dd 4.4, 1.7 Hz, phen<u>H</u>-2 or 9), 8.39 (1H, dd 8.3, 1.7 Hz, phen<u>H</u>-4 or 7), 8.05 (1H, dd 8.1, 1.7 Hz, phen<u>H</u>-4 or 7), 7.60 (1H, dd 8.3, 4.4 Hz, phen<u>H</u>-3 or 8), 7.56 (1H, dd 8.1, 4.6 Hz, Ph<u>H</u>), 7.53 (1H, dd 8.1, 4.4 Hz, phen<u>H</u>-3 or 8), 7.32 (1H, s, O<u>H</u>), 7.11 (1H, ddd 7.8, 7.3, 1.2 Hz, Ph<u>H</u>), 6.89 (1H, dd 7.8, 1.5 Hz, Ph<u>H</u>), 6.78 (1H, ddd 8.1, 7.3, 1.5 Hz, Ph<u>H</u>), 6.39 (1H, brs, N<u>H</u>); this compound was readily oxidised to the quinone (**121** X = Br) by exposing a well stirred chloroform solution to air.

The reaction was repeated as above, except that benzene was used in place of acetone, and a Dean - Stark tube was employed. The same product was isolated (95 %).

**Reaction of *trans*-5-(2-bromoanilino)-6-hydroxy-5,6-dihydro-1,10-phenanthroline (155) with tributyltin hydride and AIBN.**

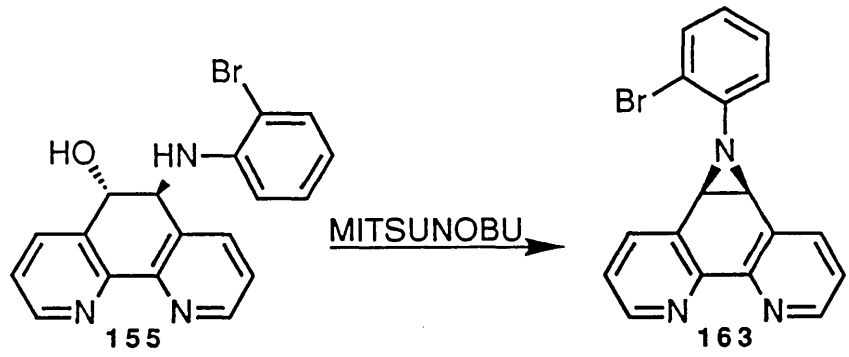



To a stirred refluxing solution of the aminoalcohol (**155**) (129 mg, 0.35 mmol) in dry benzene (170 ml) under argon were added solutions of tributyltin hydride (113 µl, 1.2 eq.) in benzene (20 ml) and AIBN (29 mg, 0.5 eq.) in benzene (20 ml) dropwise over 48 h. The resultant solution was cooled and the benzene removed *in vacuo*. The solids remaining were redissolved in chloroform (100 ml), washed with 5 % aqueous potassium fluoride (3 x 50 ml), water (3 x 100 ml) and brine (50 ml) and then dried over sodium sulphate. Removal of the solvent *in vacuo* and chromatography on silica (eluting with chloroform) gave *N-(2-bromophenyl)-5-amino-1,10-phenanthroline* (**162**) (105 mg, 85.5 %) as a pale yellow solid, m.p. ca. 250 °C dec. (Found: $M^+$ 349.0215. $C_{18}H_{12}N_3Br$ requires M 349.0215); $\nu_{max}$ ($CDCl_3$) 3393 (br), 2960, 2928, 2216, 1622, 1591, 1506, 740; $\delta_H$ (270 MHz, $CDCl_3$) 9.22 (1H, dd 4.4, 1.7 Hz, phen<u>H</u>-2 or 9), 9.10 (1H, dd 4.4, 1.7 Hz, phen<u>H</u>-2 or 9), 8.43 (1H, dd 8.5, 1.7 Hz, phen<u>H</u>-4 or 7), 8.09 (1H, dd 8.1, 1.7 Hz, phen<u>H</u>-4 or 7), 7.64 (1H, dd 8.5, 4.4 Hz, phen<u>H</u>-3 or 8), 7.60 (1H, s, phen<u>H</u>-6), 7.60 (1H, dd 8.1, 1.2 Hz, Ph<u>H</u>), 7.57 (1H, dd 8.1, 4.4 Hz, phen<u>H</u>-3 or 8), 7.13, (1H, dt 8.3, 1.2 Hz, Ph<u>H</u>), 6.92 (1H, dd 8.3, 1.5 Hz, Ph<u>H</u>), 6.80 (1H, ddd 8.1, 7.3, 1.5, Ph<u>H</u>), 6.40 (1H, brs, N<u>H</u>); *m/z* 351, 349 ($M^+$), 270.

Repetition of the reaction exactly as above but without the addition of AIBN gave the same product in 81 % yield.

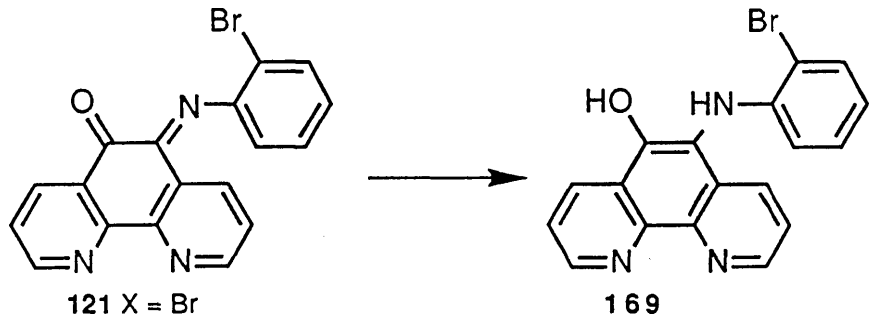
Repeating the reaction without the addition of either reagent produced no reaction after 1 week at reflux. 1.2 Equivalents of DCC were then added, but after a further 48 h at reflux no reaction had occurred.

**The Mitsunobu reaction of *trans*-5-(2-bromoanilino)-6-hydroxy-5,6-dihydro-1,10-phenanthroline (155) with triphenyl phosphine and DEAD.**




To a stirred solution of triphenyl phosphine (159 mg, 0.61 mmol) in deuterochloroform (1.2 ml) under argon at 0 °C was added DEAD (96 µl, 1 eq.). After 30 min the aminoalcohol (**155**) (175.6 mg, 1 eq.) was added portionwise. After 24 h an NMR of the reaction mixture was taken, showing complete conversion of the staring material into a single product. The spectrum corresponded to that of a symmetrically substituted cis-5,6-dihydro-1,10-phenanthroline, (Diagram 3 in Appendix B) assigned as the aziridine (**163**). This crude product was refluxed in benzene (150 ml) over night and the solvents removed *in vacuo*. Repeated chromatography on alumina (eluting with chloroform) gave the isomeric phenanthroline (**162**) (108.5 mg, 65 %) with data as previously.

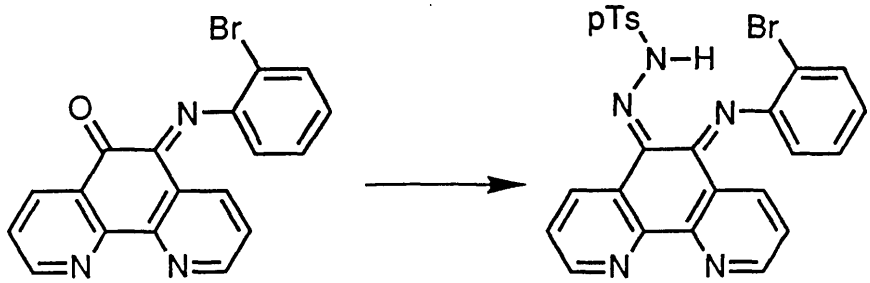
**5-(2-Bromophenylamino)-6-hydroxy-1,10-phenanthroline (169).**




To a stirred solution of the quinone (**121** X = Br) (72.1 mg, 0.198 mmol) in absolute ethanol (6 ml) and chloroform (2 ml) was added hydrazine hydrate (10 µl, 1 eq.) followed by concentrated hydrochloric acid (1 drop from a Pasteur pipette). After 2 h a yellow suspension had formed from the original purple solution. The suspension was redissolved

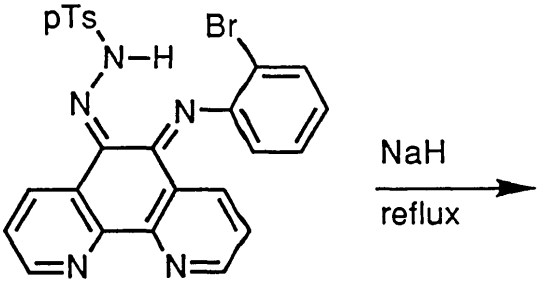
by addition of chloroform (5 ml) and the solution washed with saturated aqueous sodium bicarbonate (3 x 50 ml) and brine (50 ml) before being dried over sodium sulphate. Removal of the solvents *in vacuo* gave the title compound (69.9 mg, 96 %) as a colourless foam with data as previously.

**1,10-Phenanthroline-5,6-quinone-6-(N-2-bromophenyl-imine)-5-(4-toluenesuphonyl hydrazone) (170).**




To a stirred solution of the quinone (**121** X = Br) (71.1 mg, 0.195 mmol) in absolute ethanol (15 ml) was added 4-tosylhydrazide (40.2 mg, 1.2 eq.) followed by concentrated hydrochloric acid (1 drop from a Pasteur pipette). The purple solution began to decolourise, and after 6 days the pale yellow solution was diluted with chloroform (20 ml) and the solution washed with saturated aqueous sodium bicarbonate (3 x 100 ml) and brine (100 ml) before being dried over sodium sulphate. Removal of the solvents *in vacuo* gave the title compound (67.7 mg, 67 %) as a colourless crystalline solid, m.p. 80 - 100 °C dec. then 158 - 160 °C; $\delta_H$ (270 MHz, $CDCl_3$) 9.17 (1H, dd 4.9, 1.6 Hz, phenH-2 or 9), 8.84 (1H, dd 4.9, 1.6 Hz, phenH-2 or 9), 8.71 (1H, dd 8.2, 1.8 Hz, phenH-4 or 7), 7.70 - 7.53 (4H, m, ArH), 7.52 (1H, dd 8.2, 4.9 Hz, phenH-3 or 8), 7.32 (2H, brd 8.2 Hz, PhH on the pTs group), 7.12 (2H, brt 7.4 Hz, PhH), 6.74 (1H, brd, 8.2 Hz, PhH), 6.45 (1H, brt 7.4 Hz, PhH), 2.07 (3H, s, $CH_3$) (no NH visible).

**Reaction of sodium hydride with 1,10-Phenanthroline-5,6-quinone-6-(N-2-bromophenyl-imine)-5-(4-toluenesuphonylhydrazone) (170).**

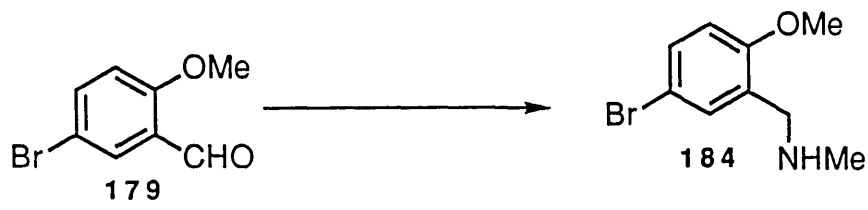



**170**

To a stirred solution of the tosylhydrazone (**170**) (41.2 mg, 0.076 mmol) in dry THF (20 ml) under argon, was added sodium hydride (23.2 mg, 40 % in hexanes, 5 eq.). The resultant solution was refluxed for 4 h. After this time, the dark suspension was allowed to cool, and was then diluted with chloroform (50 ml). The suspension was then washed with saturated aqueous sodium bicarbonate (3 x 100 ml) and brine (100 ml) before being dried over sodium sulphate. The aqueous washings remained a purple colour, but attempted extraction with ethyl acetate was unsuccessful. Removal of the water *in vacuo*, followed by trituration with methanol was also unsuccessful in dissolving the purple material. Filtration of the chloroform solution through a pad of silica, followed by removal of the solvents *in vacuo* gave 2-bromoaniline (3.0 mg, 25 %), with identical TLC and NMR properties as an authentic sample.

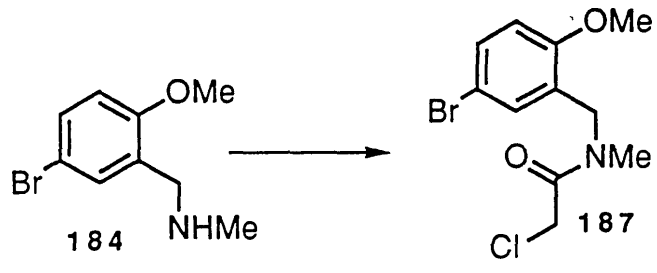
## 4.3 EXPERIMENTAL FOR CHAPTER 3.

### N-Methyl-5-bromo-2-methoxybenzylamine (184).




To methylamine (36.3 ml, 33% in IMS) diluted to 125 ml with methanol and cooled to 0°C was added concentrated hydrochloric acid (4.3 ml) diluted to 10 ml with methanol. To this solution was added 4-bromo-3-anisaldehyde (**179**) (10.75 g, 53 mmol) with stirring followed by sodium cyanoborohydride (1.9 g, 30 mmol) in one portion. The suspension was stirred at room temperature for 48 h, after which the pH was adjusted to pH1 with concentrated hydrochloric acid (**CAUTION**). After washing with ether (2 x 100 ml) the aqueous phase was basified with 2N sodium hydroxide, the product extracted with ether (3 x 100 ml), and the organic solution dried over sodium sulphate. Filtration and removal of the ether under reduced pressure gave the *title compound* (9.82 g, 85 %) as a colourless mobile oil, b.p. 120 °C / 0.03 mmHg (Found: C, 46.9; H, 5.5; N, 6.0; Br, 34.65. $C_9H_{12}BrNO$ requires C, 47.0; H, 5.2; N, 6.1; Br, 34.75 %); $\nu_{max}$ ($CHCl_3$) 3330 (NH), 2920, 2840, 2800, 1592, 1406; $\delta_H$ (250 MHz, $CDCl_3$) 7.26 - 7.37 (2H, m), 6.72 (1H, d 8 Hz, Ar<u>H</u>-3), 3.80 (3H, s, O<u>CH</u>$_3$), 3.67 (2H, s, <u>CH</u>$_2$), 2.38 (3H, s, N<u>CH</u>$_3$); *m/z* (170 °C) 230 / 228 ($M^+$, 38 %), 216 / 214 (20 %), 200 / 198 (30 %), 171 / 169 (20 %), 150 (66 %), 44 (100 %).

### N-Chloroacetyl-N-methyl-5-bromo-2-methoxybenzylamine (187).

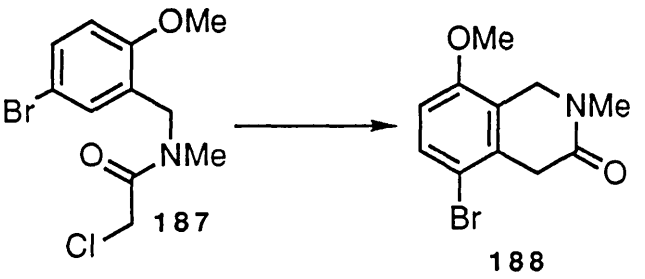



To a well stirred mixture of the benzylamine (**184**) (92.7 mg, 0.405 mmol) in DCM (2 ml) and sodium hydroxide (162 mg, 10 eq.) in water (3.2 ml) at 0 °C was added chloroacetyl

chloride (64.5 µl, 2 eq.) in one portion. After 3 h the organic layer was separated and dried over sodium sulphate. The solution was then filtered through a pad of silica and the solvents removed *in vacuo* to give the title compound (113.5 mg, 92 %) as a colourless oil; $\nu_{max}$ ($CHCl_3$) 2840 (br), 1666; $\delta_H$ (270 MHz, $CDCl_3$) 7.40, 7.34 (1H, 2 dd 9.4, 2.7 Hz, Ar<u>H</u>-4), 7.26, 7.17 (1H, 2 d 2.7 Hz, Ar<u>H</u>-6), 6.79, 6.75 (1H, 2 d 9.4 Hz, Ar<u>H</u>-3), 4.57, 4.50 (2H, 2 s, Cl<u>CH</u>$_2$), 4.17, 4.14 (2H, 2 s, Ar<u>CH</u>$_2$), 3.83, 3.81 (3H, 2 s, O<u>CH</u>$_3$), 3.04, 2.92 (3H, 2 s, N<u>CH</u>$_3$) corresponding to 2 rotamers; *m/z* (100 °C) 307 / 305 ($M^+$, 94 %), 271 / 270 (100 %), 229 / 228 (35 %), 215 / 213 (32 %).

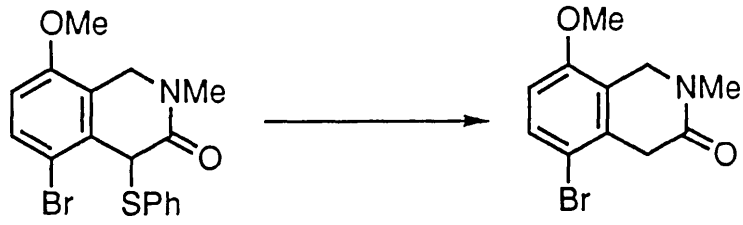
**5-Bromo-1,4-dihydro-8-methoxy-2-methylisoquinol-3-one (188).**

**(a) By cyclisation.**




A solution of the chloroacetate (**187**) (113.5 mg, 0.37 mmol) in anhydrous acetonitrile (100 ml) in a quartz vessel was sparged with nitrogen for 30 min before being irradiated at 254 nm in a 1000 W Rayonet photolysis chamber. After 45 min the irradiation was ceased and the acetonitrile removed *in vacuo*. The remaining brown oil was subjected to chromatography on silica (eluting with DCM / ether) to give the *title compound* (29.5 mg, 29 %) as a yellow solid, m.p. 196.5 - 198 °C (Found: C, 48.6; H, 4.4; N, 5.1. $C_{11}H_{12}NO_2Br$ requires C, 48.9; H, 4.45; N, 5.2 %); $\nu_{max}$ ($CHCl_3$) 1638, 1590, 1460, 1290; $\delta_H$ (250 MHz, $CDCl_3$) 7.45 (1H, d 8.7 Hz, Ar<u>H</u>), 6.65 (1H, d 8.7 Hz, Ar<u>H</u>), 4.46 (2H, br"t" ca. 2 Hz, <u>CH</u>$_2$CO), 3.84 (3H, s, O<u>CH</u>$_3$), 3.62 (2H, br"t" ca. 2 Hz, <u>CH</u>$_2$NMe), 3.12 (3H, s, N<u>CH</u>$_3$); *m/z* (170 °C) 271 / 269 ($M^+$, 58 %), 214 / 212 (42 %), 190 (100 %).

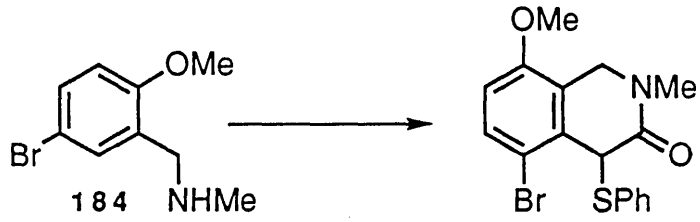
(b) By reduction of the phenylthio compound (186).




186 188

A mixture of the phenylthio compound (**186**) (0.250 g, 0.66 mmol) in acetic acid (8 ml) and powdered zinc (0.630 g, 9.60 mmol) was refluxed for 6 h, then filtered hot through silica,and the solvent removed *in vacuo*, to leave an orange oil which crystallised on standing. This crystalline mass was subjected to chromatography on silica (eluting with DCM / ether) to give the title compound as a yellow solid (0.099 g, 56 %) with data as above.

**5-Bromo-1,4-dihydro-8-methoxy-2-methyl-4-phenylthio-(2H)-isoquinol-3-one (186).**

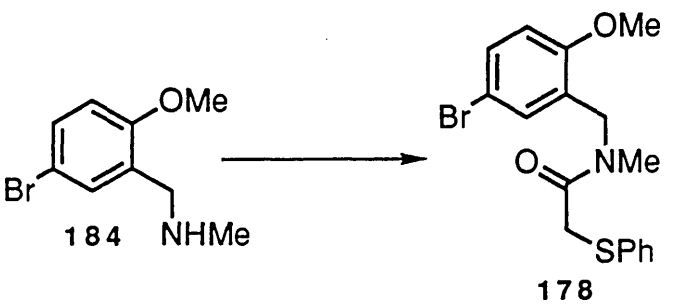



184 186

To a stirred solution of the benzylamine (**184**) (0.055 g, 0.24 mmol) and triethylamine (33 µl) in dry DCM (0.25 ml) at 0 °C was added dropwise a solution of 2-chloro-2-phenylthioacetyl chloride (0.053 g, 0.24 mmol) in dry DCM (0.5 ml). After 20 min tin tetrachloride in DCM (34 µl, 2.226 g / ml, 0.29 mmol) was added in one portion. After a further 1 h the solution was diluted to 10 ml with DCM and poured onto ice. The organic layer was washed with water (2 x 20 ml) and dried over magnesium sulphate. Removal of the solvent *in vacuo* and chromatography on silica (eluting with DCM / ether) gave the *title compound* (62 mg, 69 %) as lemon - green crystals, m.p. 152 - 154 °C (Found: C, 53.8; H, 4.2; N, 3.75; S, 8.8. $C_{17}H_{16}NO_2BrS$ requires C, 54.0; H, 4.2; N, 3.7; S, 8.5 %); $\nu_{max}$ ($CHCl_3$) 1647, 1587, 1457, 1294; $\delta_H$ (250 MHz, $CDCl_3$) 7.42 (1H, d 8.9 Hz), 7.30 - 7.07 (5H, m, $C_6\underline{H}_5S$), 6.55 (1H, d 8.9 Hz), 4.80 (1H, s, C<u>H</u>SPh), 3.96 (1H, d 17.7 Hz, 1/2 C<u>H</u>$_2$NMe), 3.68 (3H, s, OC<u>H</u>$_3$), 3.10 (1H, d 17.7 Hz, 1/2 C<u>H</u>$_2$NMe), 2.85 (3H, s, NC<u>H</u>$_3$); $\delta_C$ (62.9 MHz, $CDCl_3$) 166.63 (s), 154.04 (s), 135.77 (d), 133.43 (s), 132.37 (d), 131.46 (s), 129.11 (d), 128.39 (d), 123.48 (s),

113.88 (s), 110.30 (d), 55.68 (q), 50.75 (d), 47.54 (t), 34.38 (q); *m/z* (200 °C) 379 / 377 ($M^+$, 6 %), 269 / 267 (100 %), 242 / 240 (28 %).

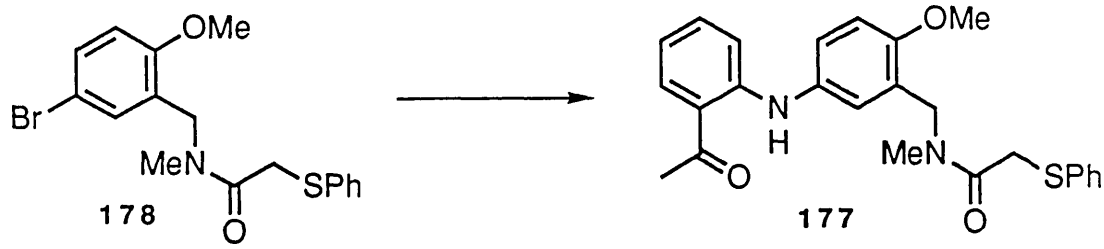
**N-Methyl-N-phenylthioacetyl-5-bromo-2-methoxybenzylamine (178).**




184 178

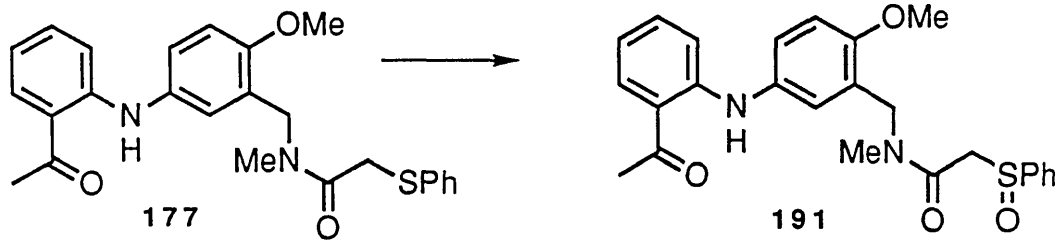
To a stirred solution of the amine (**184**) (16.0 g, 68 mmol) and triethylamine (9 ml) in dry DCM (600 ml) at 0°C under nitrogen was added a solution of phenylthioacetyl chloride (13.0 g, 70 mmol) in dry DCM (150 ml) dropwise over 1 h. The solution was stirred for a further 2 h before being washed with water (3 x 150 ml) and dried over magnesium sulphate. Filtration and removal of the solvent under reduced pressure yielded an oily residue which was crystallised from ethyl acetate - ether to give the *title compound* (25.4 g, 98 %) as white crystals, m.p. 77 - 79 °C (Found: C, 53.6; H, 4.7; N, 3.6; S, 8.65; Br, 20.8. $C_{17}H_{18}BrNSO_2$ requires C, 53.7; H, 4.7; N, 3.7; S, 8.4; Br, 21.0 %); $\nu_{max}$ ($CHCl_3$) 1640, 1350, 1120, 1085, 1022; $\delta_H$(250 MHz, $CDCl_3$) 7.11 - 7.49 (7H, m), 6.73, 6.70 (1H, 2 d 7.5 Hz), 4.55, 4.47 (2H, 2 s, $C\underline{H}_2SPh$), 3.80, 3.78 (2H, 2 s, $C\underline{H}_2NMe$), 3.77, 3.76 (3H, 2 s, $OC\underline{H}_3$), 3.00, 2.90 (3H, 2 s, $NC\underline{H}_3$); *m/z* (170 °C) 381 / 379 ($M^+$, 25 %), 272 / 270 (100 %), 201 / 199 (62 %).

**2'-Acetyl-4-methoxy-3-(N-methylaminomethyl-N-phenylthioacetyl)-diphenylamine (177).**




A mixture of the aryl bromide (**178**) (3.76 g, 9.89 mmol), 2-aminoacetophenone (2 g, 14.81 mmol), sodium carbonate (2 g), copper (56 mg), and nitrobenzene (40 ml) was heated at 210 °C with vigorous stirring for 3 h. After this time the mixture was cooled and the solvent removed under vacuum. The residue was triturated with ether and the black material thus obtained was subjected to flash chromatography on silica (eluting with DCM - ether) to produce the *title compound* (2.58 g, 60 %) as a red oil which solidified on standing, m.p. 108 - 110 °C (Found: C, 68.9; H, 6.0; N, 6.3; S, 7.5. $C_{25}H_{26}N_2SO_3$ requires C,69.1; H, 6.0; N, 6.45; S, 7.4 %); $\nu_{max}$ ($CHCl_3$) 3260 , 1640, 1606, 1571, 954; $\delta_H$ (250 MHz, $CDCl_3$) 10.36 (1H, brs, NH), 7.80 (1H,"t" 7.5 Hz), 6.8 - 7.47 (10H, m), 6.67 (1H,"q" 7.5 Hz), 4.52, 4.62 (2H, 2 s, $C\underline{H}_2SPh$), 3.81, 3.83 (3H, 2 s, $OC\underline{H}_3$), 3.79, 3.87 (2H, 2 s, $ArC\underline{H}_2$), 2.93, 3.04 (3H, 2 s, $NC\underline{H}_3$), 2.64, 2.66 (3H,2 s, $C(O)C\underline{H}_3$); *m/z* (200 °C) 434 ($M^+$, 100 %), 326 (20 %), 283 (38 %), 268 (41 %), 110 (39 %).

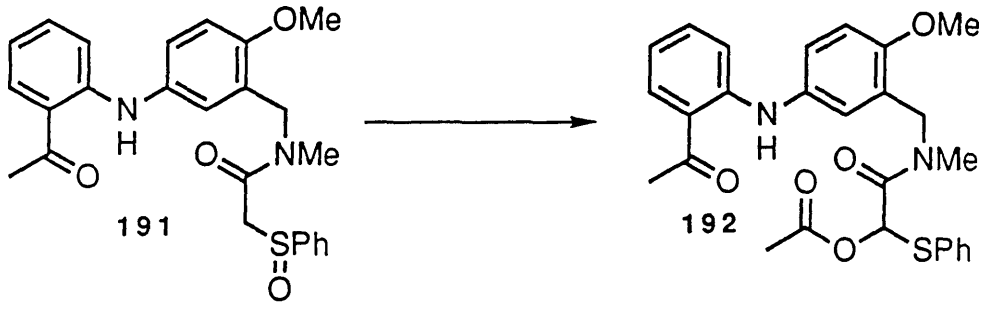
**2'-Acetyl-4-methoxy-3-(N-methylaminomethyl-N-phenylthioacetyl)-diphenylamine-S-oxide (191).**




To a stirred solution of the sulphide (**177**) (2.4 g, 5.55 mmol) in DCM (80 ml) at 0 °C was added 80 % MCPBA (1.2 g, approx. 1 eq.) in portions over 20 min. After 1 h the solution was washed with saturated aqueous sodium bicarbonate (2 x 50 ml), dried over magnesium

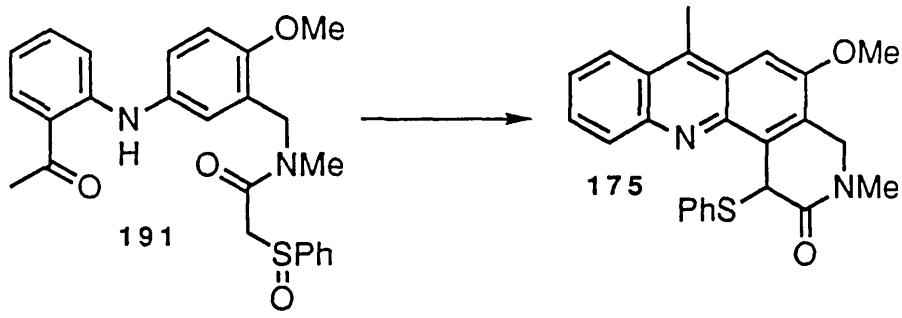
sulphate and the solvent removed *in vacuo*. The resulting red oil was subjected to chromatography on silica (eluting with DCM - ether) to give the *title compound* (2.1728 g, 87 %) as a yellow solid, m.p. 50 - 55 °C $\nu_{max}$ ($CHCl_3$) 3270 (weak), 1637, 1570, 1360, 1163, 1082, 1020, 953, 907; $\delta_H$ (250 MHz, $CDCl_3$) 10.34 (1H, brs, N<u>H</u>), 6.62 - 7.86 (12H, m), 3.82 - 4.70 (4H, m, 2C<u>H</u>$_2$), 3.78, 3.82 (3H, 2 s, OC<u>H</u>$_3$), 2.87, 2.89 (3H, 2 s, NC<u>H</u>$_3$), 2.66 (3H, s, C(O)C<u>H</u>$_3$); *m/z* (200 °C) 450 ($M^+$, 27 %), 434 (100 %), 340 (16 %), 326 (21 %), 283 (65 %), 268 (65 %), 110 (65 %).

**2'-Acetyl-4-methoxy-3-(N-methyl-N-(2-acetoxy-2-phenylthioacetyl)-aminomethyl)-diphenylamine (192).**



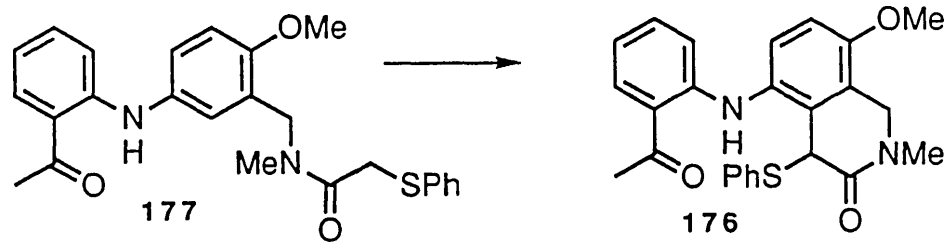

To a homogeneous mixture of commercial PPA (4 ml) and glacial acetic acid (20 ml) at 30 °C was added the sulphoxide (**191**) (90 mg, 0.2 mmol) in glacial acetic acid (2 ml) with stirring. The solution was then stirred for 1 h without heating before being poured onto ice - water (100 ml) and the organic products extracted with DCM (2 x 100 ml). The extracts were dried over magnesium sulphate and the solvent removed *in vacuo*. Chromatography on silica (eluting with DCM - ether) gave the title compound (17.8 mg, 18 %) as a yellow oil; $\delta_H$ (270 MHz, $CDCl_3$) 10.4 (1H, brs, NH), 7.80 (1H,m), 6.62 - 7.50 (11H, m), 6.44, 6.73 (1H, 2 s, C<u>H</u>SPh), 4.46, 4.74, 4.95 (2H, 3 d 16 Hz, C<u>H</u>$_2$), 3.83, 3.86 (3H, 2 s, OC<u>H</u>$_3$), 2.89, 3.15 (3H, 2 s, NC<u>H</u>$_3$), 2.64 (3H, s, C<u>H</u>$_3$COAr), 2.22, 2.28 (3H, 2 s, C<u>H</u>$_3$CO$_2$); *m/z* (70 °C) 492 ($M^+$, 100 %), 434 (10 %), 340 (10 %), 323 (29 %), 110 (16 %).

**3,7-Dimethyl-5-methoxy-2-oxo-1-phenylthio-1,2,3,4-tetrahydro-benzo-[b]-1,8-phenanthroline (175).**



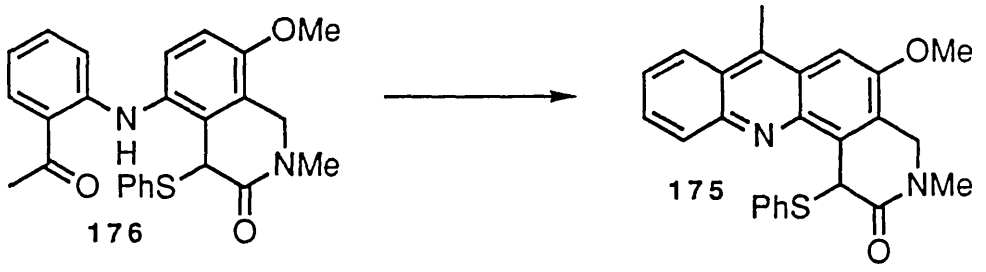

The sulphoxide (**191**) (100 mg, 0.22 mmol) was dissolved in glacial acetic acid (4 ml) and concentrated sulphuric acid (1 ml) in acetic acid (1 ml) added with stirring. The solution was stirred under reflux for 40 min and then allowed to cool. After pouring onto ice (20 g) and concentrated aqueous ammonia (20 ml), the product was extracted with DCM (3 x 20 ml). The organic washings were dried over magnesium sulphate and the solvent removed *in vacuo*. Chromatography on silica (eluting with DCM / ether) followed by crystallisation from DCM / hexane yielded the *title compound* (10 mg, 11 %) as a grey / green solid, m.p. 237 - 241 °C (Found: C, 72.5; H, 5.3; N, 6.7; S, 7.9. $C_{25}H_{22}N_2O_2S$ requires C,72.5; H, 5.3; N, 6.8; S, 7.7 %); $\nu_{max}$ ($CHCl_3$) 1647, 1571, 1466, 1270; $\delta_H$ (250 MHz, $CDCl_3$) 8.14 (2H, t 8.1 Hz, Ar<u>H</u>-5 & 8), 7.68 (1H, t 7.8 Hz, Ar<u>H</u>-6 or 7), 7.52 (1H, t 7.8 Hz, Ar<u>H</u>-7 or 6), 7.39 - 7.13 (5H, m, $C_6\underline{H}_5$), 7.11 (1H, s, Ar<u>H</u>-1), 6.11 (1H, s, C<u>H</u>SPh), 4.09 (1H, dd 18.1, 1.9 Hz, 1/2 $C\underline{H}_2$), 3.93 (3H, s, $OC\underline{H}_3$), 3.20 (1H, dd 18.1, 1.9 Hz, 1/2 $C\underline{H}_2$), 3.07 (6H, "s", $NC\underline{H}_3$ & $ArC\underline{H}_3$); $\delta_C$ (62.9 MHz, $CDCl_3$) 167.52 (s), 152.52 (s), 146.64 (s), 141.45 (s), 138.96 (s), 136.25 (d), 132.76 (s), 132.35 (s), 131.25 (d), 128.91 (d), 128.49 (d), 128.21 (d), 127.36 (s), 125.93 (s), 125.82 (d), 125.49 (s), 123.76 (d), 98.76 (d), 55.50 (q), 48.56 (t), 46.09 (d), 34.45 (q), 13.68 (q); *m/z* (70 °C) 414 ($M^+$, 10 %), 304 (100 %), 233 (38 %).

**5-(2-Acetylanilino)-1,4-dihydro-8-methoxy-2-methyl-4-phenylthio-(2H)-isoquinol-3-one (176).**



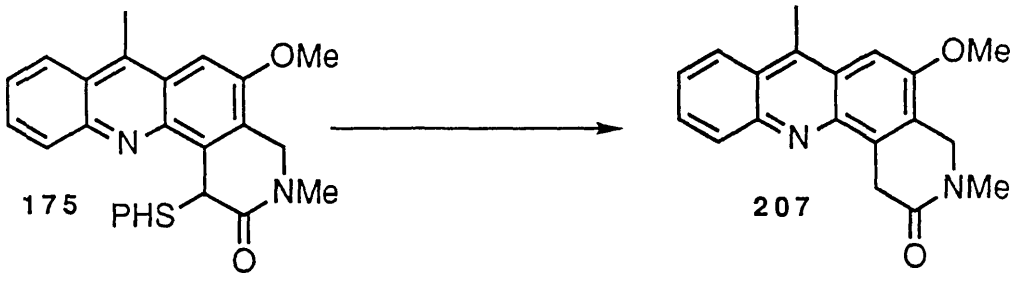

To a stirred solution of the phenylthioacetate (**177**) (4.9 g, 11.3 mmol) in dry tetrachloromethane (150 ml) at 0 °C under argon was added NCS (1.7 g, 12.7 mmol) in one portion. After stirring at room temperature over night the slurry was filtered, and the solids washed well with chilled tetrachloromethane. The solvents were then removed from the combined organic solutions *in vacuo* and the residue redissolved in dry DCM (50 ml) and cooled in an ice bath under argon. To this solution was added dropwise a solution of tin tetrachloride (11.3 ml, 1M in DCM) in DCM (30 ml). After 2 h brine (200 ml) was added with vigorous stirring. After 10 min the aqueous layer was decanted. This process was repeated twice and the organic solution remaining dried over magnesium sulphate. Removal of the solvents *in vacuo* and chromatography on silica (eluting with ether) gave the *title compound* (3.3 g, 68 %) as an unstable yellow solid, m.p. 172 - 174 °C (Found: $M^+$ 432.1507. $C_{25}H_{24}N_2O_3S$ requires M 432.1508); $\nu_{max}$ ($CHCl_3$) 3250 (br), 2960, 2931, 1730, 1667, 1647, 1572, 1270; $\delta_H$ (500 MHz, $CDCl_3$) 10.42 (1H, brs, NH), 7.79 (1H, dd 8.0, 1.5 Hz),7.35 - 7.15 (8H, m), 6.79 (1H, d 8.5 Hz), 6.73 (1H, dd 8.5, 1.0 Hz), 6.69 (1H, td 7.0, 1.0 Hz), 4.72 (1H, s, CHSPh), 4.10 (1H, d 17.0 Hz, 1/2 $CH_2$), 3.81 (3H, s, $OCH_3$), 3.20 (1H, d 17.0 Hz, 1/2 $CH_2$), 2.95 (3H, s, $NCH_3$), 2.65 (3H, s, $C(O)CH_3$); *m/z* (220 °C) 432 ($M^+$, 13 %), 323 (59 %), 305 (58 %), 110 (100 %).

**3,7-Dimethyl-5-methoxy-2-oxo-1-phenylthio-1,2,3,4-tetrahydro-benzo-[b]-1,8-phenanthroline (175).**




To a stirred solution of the aminoacetophenone (**176**) (3.0 g, 6.9 mmol) in glacial acetic acid (100 ml) was added concentrated sulphuric acid (10 ml) diluted in acetic acid (10 ml). This solution was stirred under vigorous reflux for 30 min and then allowed to cool. After neutralising with concentrated aqueous ammonia the product was extracted with DCM (3 x 100 ml). Drying over magnesium sulphate, removal of the solvent *in vacuo*, and chromatography on silica (eluting with chloroform - methanol) gave the title compound, which was crystallised from DCM - light petroleum as a grey - green solid (2.27 g, 79 %) with data as described previously.

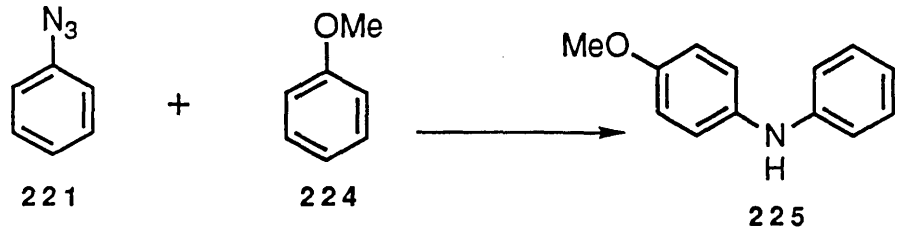
**3,7-Dimethyl-5-methoxy-2-oxo-1,2,3,4-tetrahydro-benzo-[b]-1,8-phenanthroline (207).**




To a stirred solution of the sulphide (**175**) (1.5 g, 3.6 mmol) in glacial acetic acid (190 ml) was added zinc powder (4.45 g, activated by prior acid washing). This slurry was stirred under reflux for 4 h, allowed to cool and diluted with DCM (100 ml). The slurry was filtered, the solids washed well with DCM and the solvents removed *in vacuo*. The residual tar was redissolved in chloroform (150 ml) and this solution washed with saturated sodium bicarbonate solution (3 x 100 ml). The organic solution was dried over potassium carbonate, and ether added to precipitate the title compound (0.75 g, 68 %) as a yellow solid,

m.p. 265 - 270 °C; $\delta_H$ (250 MHz, $CDCl_3$) 8.19 - 8.12 (2H, m, Ar<u>H</u>-5 & 8), 7.70 (1H, td 8.5, 1.3 Hz, Ar<u>H</u>-6 or 7), 7.53 (1H, td 8.5, 1.3 Hz, Ar<u>H</u>-6 or 7), 7.06 (1H, s, Ar<u>H</u>-1), 4.51 (2H, d 9 Hz, C<u>H</u>$_2$), 4.26 (2H, d 9 Hz, C<u>H</u>$_2$), 3.99 (3H, s, OC<u>H</u>$_3$), 3.18 (3H, s, NC<u>H</u>$_3$), 2.95 (3H, s, ArC<u>H</u>$_3$); *m/z* (210 °C) 306($M^+$, 100 %), 264 (26 %).

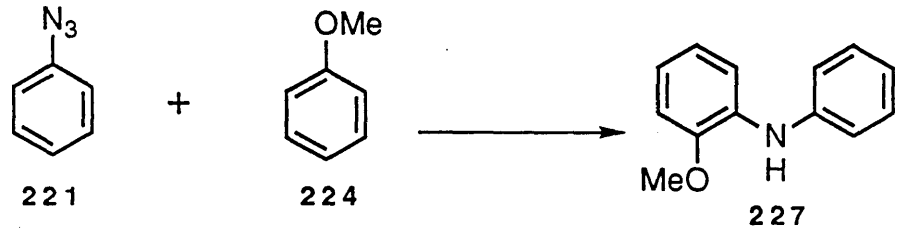
**4-Methoxydiphenylamine (225).**




221 224 225

To a stirred mixture of anisole (**224**) (32.7 ml, 0.3 mol), aluminium trichloride powder (8 g, 0.06 mol) and DCM (90 ml) at -60 °C under argon was added dropwise a solution of phenyl azide (**221**) (3.589 g, 0.03 mol) in DCM (15 ml), followed immediately by phenol (3 g) in DCM (15 ml). After 1 h the reaction mixture was warmed to room temperature, and poured onto excess concentrated hydrochloric acid and ice. Extraction with DCM (3 x 200 ml), drying over sodium sulphate and removal of the solvents *in vacuo* gave a colourless crystalline material which was first distilled (Kugelrohr 0.3-0.5 mbar, 150 - 160 °C), followed by crystallisation from ethanol - hexane (4.775 g, 80 %), m.p. 107 - 108 °C (Lit. 108 - 108.5 °C).[69]

**2-Methoxydiphenylamine (227).**

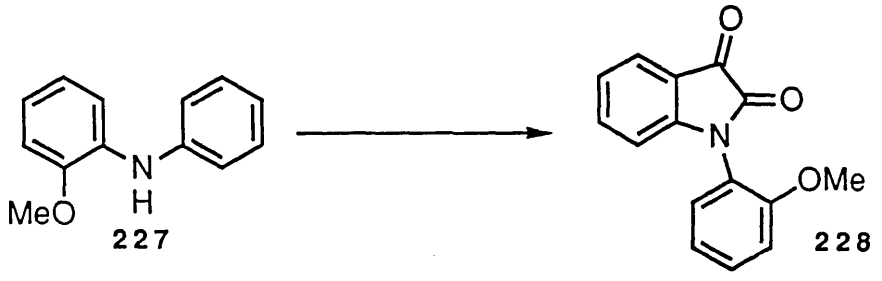



221 224 227

To a stirred mixture of anisole (**224**) (10.8 g, 10.9 ml, 0.1 mol), titanium tetrachloride (2.2 ml, 0.02 mol) and DCM (30 ml) at -78 °C under argon was added dropwise a solution of phenyl azide (**221**) (1.2 g, 0.01 mol) in DCM (5 ml) followed immediately by a solution of

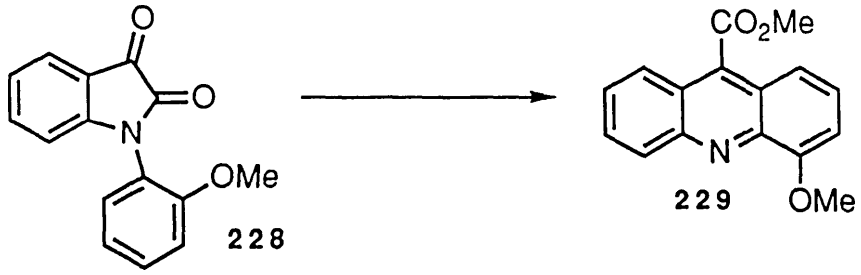
phenol (1 g) in DCM (5 ml). After 1 h the reaction mixture was warmed to room temperature. The product was isolated in the same way as for 4-methoxydiphenylamine as a colourless oil (17.23 g, 87 %), bp 110 °C (15 mmHg) (Lit. 120 °C, 20 mmHg).[69] The compound had identical TLC properties as an authentic sample prepared via a literature route.[69]

**N-(2-Methoxyphenyl)-indolin-2,3-dione (228).**



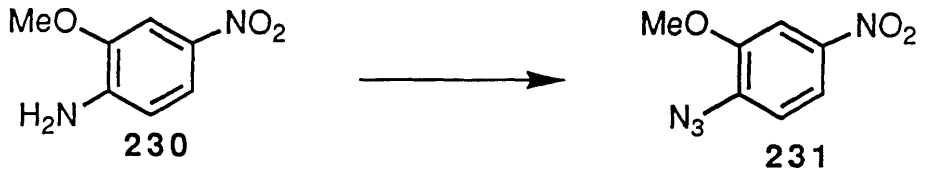

To a stirred refluxing solution of oxalyl chloride (1 ml, 60 mmol) in dry DCM (20 ml) under argon was added dropwise a solution of the amine (**227**) (2.4 g 12 mmol) in dry DCM (15 ml). After 1.5 h the solution was allowed to cool and the solvent and excess of oxalyl chloride were removed under reduced pressure. The remaining oil was redissolved in dry carbon disulphide (35 ml) and fresh powdered aluminium trichloride (2.4 g, 18 mmol) added under argon. The resultant slurry was heated to reflux for 3.5 h before ice (50 ml) and 5N hydrochloric acid (150 ml) were added. The organic material was extracted with DCM (3 x 100 ml), dried over sodium sulphate, and the solvents removed *in vacuo*. Chromatography on neutral alumina (eluting with ether - hexane) gave the *title compound* (77 %) as an orange powder, m.p. 154 -155 °C (Found: C, 71.3; H, 4.3; N, 5.4. $C_{15}H_{11}NO_3$ requires C, 71.15; H, 4.35; N, 5.5 %); $\nu_{max}$ ($CHCl_3$) 3024, 1744, 1613, 1507, 1470, 1371, 1310, 1282, 1554; $\delta_H$ (500 MHz, $CDCl_3$) 7.66 (1H, dd 7.2, 0.9 Hz, Ph<u>H</u>-6), 7.49 (1H, ddd 8.1, 7.5, 1.6 Hz, Ph<u>H</u>-4), 7.46 (1H, ddd 8.1, 8.1, 1.9 Hz, indole <u>H</u>-5 or 6), 7.315 (1H, dd 8.1, 1.9 Hz, indole <u>H</u>-4 or 7), 7.12 (1H, ddd 7.5, 7.2, 0.9 Hz, Ph<u>H</u>-5), 7.095 (1H, ddd 8.1, 7.9, 1.0 Hz, indole <u>H</u>-5 or 6), 7.09 (1H, brd 7.9 Hz, indole <u>H</u>-4 or 7), 6.57 (1H, brd 8.1 Hz, Ph<u>H</u>-3), 3.76 (3H, s, OC<u>H</u>$_3$), (see also COSY 16, Diagram 6 in Appendix B); *m/z* (150 °C) 253 ($M^+$, 73.5 %), 224 (100 %), 196 (62 %).

**Methyl 4-methoxyacridine-9-carboxylate (229).**




The isatin (**228**) (539 mg, 2.12 mmol) was dissolved in 10 % aqueous potassium hydroxide (10 ml) and the solution refluxed for 13 h. After cooling the solution was acidified with concentrated hydrochloric acid and the product extracted with ethyl acetate. The organic phase was dried over sodium sulphate and the solvent removed *in vacuo*. The crude acid was then suspended in methanol (15 ml) and ether (45 ml) and esterified with diazomethane. The resultant solution was filtered through a pad of silica and the solvents removed *in vacuo*.Purification was carried out using chromatography on silica (eluting with ether), and gave the *title compound* (82 %) as a yellow solid, m.p. 162 °C (Found: C, 72.0; H, 5.0; N, 5.5. $C_{15}H_{13}NO_3$ requires C, 71.9; H, 4.9; N, 5.3 %); $\nu_{max}$ ($CHCl_3$) 3025, 2957, 1731, 1603, 1567, 1470; $\delta_H$ (500 MHz, $CDCl_3$ ) 8.41 (1H, brd 7.0 Hz, Ar<u>H</u>-5 or 8), 7.95 (1H, d 8.8 Hz, Ar<u>H</u>-5 or 8), 7.78 (1H, "t" 7.0 Hz, Ar<u>H</u>-6 or 7), 7.60 (1H, dd 8.8, 7.0 Hz, Ar<u>H</u>-6 or 7), 7.57 (1H, d 8.8 Hz, Ar<u>H</u>-1), 7.48 (1H, dd 8.8, 7.0 Hz, Ar<u>H</u>-2), 7.04 (1H, d 7.0 Hz, Ar<u>H</u>-3), 4.20 (3H, s, C<u>H</u>$_3$), 4.17 (3H, s, C<u>H</u>$_3$) (see also COSY 48, Diagram 7 in Appendix B); *m/z* (180 °C) 267 ($M^+$, 100 %), 252 (25 %), 238 (56 %).

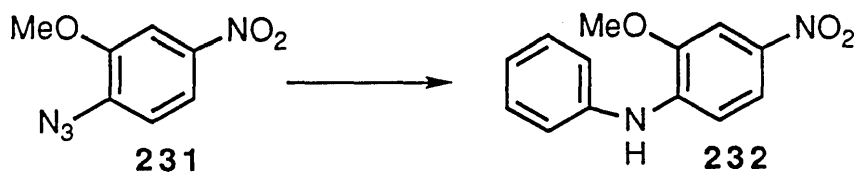
**2-Azido-5-nitroanisole (231).**




To a stirred solution of 5-nitro-2-anisidine (**230**) (6.55 g, 39 mmol) in acetic acid (200 ml) and concentrated sulphuric acid (40 ml) at 5 - 10 °C was added amyl nitrite (7 ml, 58.8 mmol). After 2 h ice - water (500 ml) was added followed by sufficient urea to remove excess nitrous acid. Norite (1 g) was added and the mixture stirred at 5 °C for a further 30

min. This slurry was then rapidly filtered into a cooled vessel and sodium azide (5 g, 77 mmol) in water (100 ml) added in one portion with stirring. After 2 h in the dark the suspension was filtered and the solid washed with 10 % sodium bicarbonate solution (1 l) then water (1 l). The yellow mass was recrystallised from methanol - water and air dried at room temperature in the dark to give the *title compound* (6.33 g, 84 %) as a buff powder, m.p. 78 - 80 °C (Found: C, 43.1; H, 2.85; N, 28.6. $C_7H_6N_4O_3$ requires C, 43.3; H, 3.1; N, 28.9 %); $\nu_{max}$ ($CDCl_3$) 2126, 1525, 1345, 1250; $\delta_H$ (270 MHz, $CDCl_3$ ) 7.859 (1H, dd 8.55, 2.2 Hz, Ar**H**-4), 7.760 (1H, d 2.2 Hz, Ar**H**-6), 7.062 (1H, d 8.55 Hz, Ar**H**-3), 3.987 (3H, s, OC**H**$_3$); *m/z* 194 ($M^+$), 165, 104, 77.

**2-Methoxy-4-nitrodiphenylamine (232).**




**(a) Without phenol.**

To a stirred solution of aluminium trichloride (1.2 g, 8.9 mmol) in benzene (10 ml) and DCM (20 ml) at 0 °C was added a solution of the azide (**231**) (999 mg, 5.95 mmol) in DCM (20 ml) and benzene (5 ml). The solution was allowed to warm and stirred until nitrogen evolution ceased. After a further 1 h the product was partitioned between 2N sodium hydroxide (100 ml) and DCM (2 x 100 ml). The organic layer was dried over sodium sulphate and the solvents removed *in vacuo*. Chromatography on silica (eluting with light petroleum - DCM) gave the title compound (1.1 g, 88 %) as a yellow solid, m.p. 78 - 79 °C (Lit. 77 - 78 °C)[71] (Found: C, 64.0; H, 5.0; N, 11.4. Calc. for $C_{13}H_{12}N_2O_3$ C, 63.9; H, 4.9; N, 11.5 %); $\nu_{max}$ ($CDCl_3$) 3414, 2351, 1585, 1531, 1499, 1327, 1294, 1097; $\delta_H$ (250 MHz, $CDCl_3$ ) 6.9 - 8.0 (8H, m), 6.75 (1H, brs, Ar**H**-3), 4.01 (3H, s, OC**H**$_3$); *m/z* (110 °C) 244 ($M^+$, 100 %), 229 (24 %), 182 (9 %), 154 (19 %).

**(b) With phenol.**

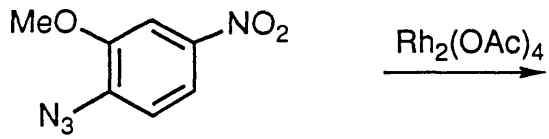
To a stirred solution of aluminium trichloride (232 mg, 1.8 mmol) in benzene (0.6 ml) and DCM (2 ml) at - 80 °C was added a solution of the azide (**231**) (134 mg, 0.69 mmol) in DCM

(0.5 ml) and benzene (0.5 ml). A solution of phenol (98.9 mg, 1 mmol) in DCM (0.5 ml) was added rapidly, and after the initial mild effervescence had subsided, the suspension was allowed to warm to 5 °C over night. The resultant mixture was diluted to 20 ml with DCM and was washed with 2N sodium hydroxide (3 x 100 ml) and brine (2 x 100 ml). The organic layer was dried over sodium sulphate and the solvents removed *in vacuo*. Chromatography on silica (eluting with light petroleum - DCM) gave the title compound (126.5 mg, 75 %), with data as previously.

**(c) With boron trifluoride etherate.**

To a stirred solution of the azide (**231**) (123 mg, 0.63 mmol) in dry benzene (25 ml) at room temperature under argon was added boron trifluoride etherate (200 µl, 1.2 mmol), and the resultant pale yellow solution heated at 60°C for 12 h. After this time the solution had turned green, and was allowed to cool, before being washed with saturated sodium bicarbonate solution (3 x 100 ml), and dried over sodium sulphate. Removal of the solvent *in vacuo*, and chromatography on silica (eluting with light petroleum - DCM) gave the title compound (106 mg, 69 %), with data as previously.

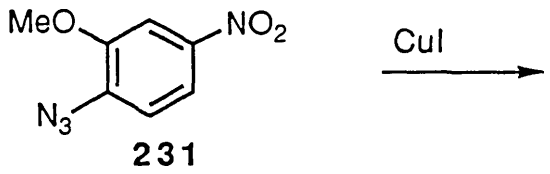
**Treatment of 2-azido-5-nitroanisole (231) with dirhodium tetraacetate.**




**231**

To a solution of the azide (**231**) (33.1 mg, 0.17 mmol) in dry benzene (10 ml) at reflux under argon in the dark was added dirhodium tetraacetate (ca. 2 mg, catalytic), and the solution refluxed for 5 h. After this time TLC showed no products, and the reaction was terminated.

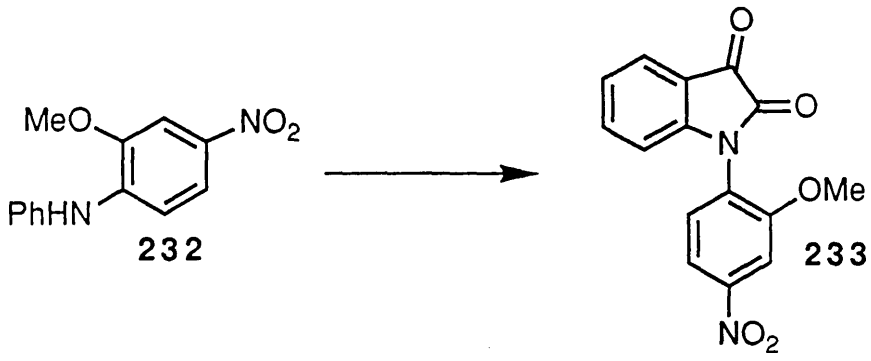
**Treatment of 2-azido-5-nitroanisole (231) with copper (I) iodide.**




231

To a solution of the azide (**231**) (34.7 mg, 0.18 mmol) in dry benzene (10 ml) at reflux under argon in the dark was added anhydrous copper (I) iodide (ca. 2 mg, catalytic), and the solution refluxed for 3 h. After this time TLC showed a large number of polar products not corresponding to the required diarylamine, and the reaction was discontinued.

**N-(2-Methoxy-4-nitrophenyl)-indoline-2,3-dione (233).**

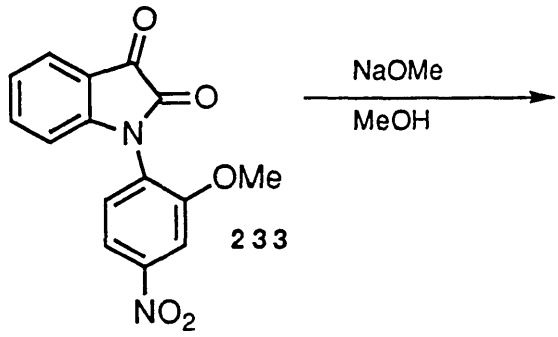



232 233

To a stirred refluxing solution of oxalyl chloride (1 ml, 60 mmol) in dry DCM (19 ml) under argon was added dropwise a solution of the amine (**232**) (2.9 g 12 mmol) in dry DCM (15 ml). After 1.5 h the solution was allowed to cool and the solvent and excess of oxalyl chloride were removed under reduced pressure. The remaining oil was redissolved in dry carbon disulphide (35 ml) and fresh powdered aluminium trichloride (2.4 g, 18 mmol) added under argon. The resultant slurry was heated to reflux for 3.5 h before ice (50 ml) and 5N hydrochloric acid (150 ml) were added. Extraction with DCM (3 x 100 ml), drying over sodium sulphate, and removal of the solvents *in vacuo* gave the *title compound* (3.1 g, 88 %), m.p. 181 - 183 °C (from ethyl acetate - cyclohexane) (Found: C, 60.5; H, 3.3; N, 9.2. $C_{15}H_{10}N_2O_5$ requires C, 60.4; H, 3.4; N, 9.4 %); $\nu_{max}$ ($CDCl_3$) 1745 (sh), 1615, 1533, 1505, 1469, 1416; $\delta_H$ (270 MHz, $CDCl_3$ ) 8.01 (1H, dd 8.6, 2.3 Hz, PhH-5), 7.96 (1H, d 2.3 Hz, PhH-3) 7.72 (1H, d brd 7.6, 0.7 Hz, indole H-4), 7.55 (1H, dt 7.6, 1.2 Hz, indole H-6), 7.54 (1H, d 8.6 Hz, PhH-6), 7.20 (1H, dt 7.6, 0.7 Hz, indole H-5), 6.58 (1H, brd 7.6 Hz, indole H-7), 3.93 (3H,

s, $OCH_3$); $\delta_C$ (62.9 MHz, $CDCl_3$ ) 56.6, 107.9, 111.5, 116.5, 117.7, 124.6, 125.7, 127.3, 129.9, 138.5, 149.2, 151.0, 155.7, 157.2, 181.9; *m/z* (180 °C) 298 ($M^+$, 71 %), 270 (100 %), 196 (43 %), 194 (50 %).

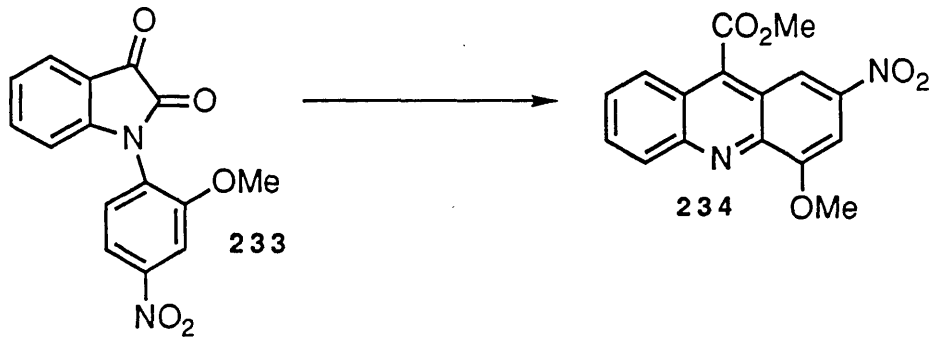
**Reaction of N-(2-methoxy-4-nitrophenyl)-indoline-2,3-dione (233) with sodium methoxide in methanol.**




233

To a solution of sodium (280 mg, 12 mmol) in dry methanol (40 ml) was added the isatin (233) (293 mg, 0.98 mmol), and the solution refluxed under argon for 48 h. TLC after this time showed no starting material, but instead an intensely fluorescent baseline. Continued reflux produced no change in the TLC and the reaction was abandoned.

**Methyl 2-nitro-4-methoxyacridine-9-carboxylate (234).**




233 234

**(a) By reaction of the isatin (233) with potassium hydroxide followed by esterification.**

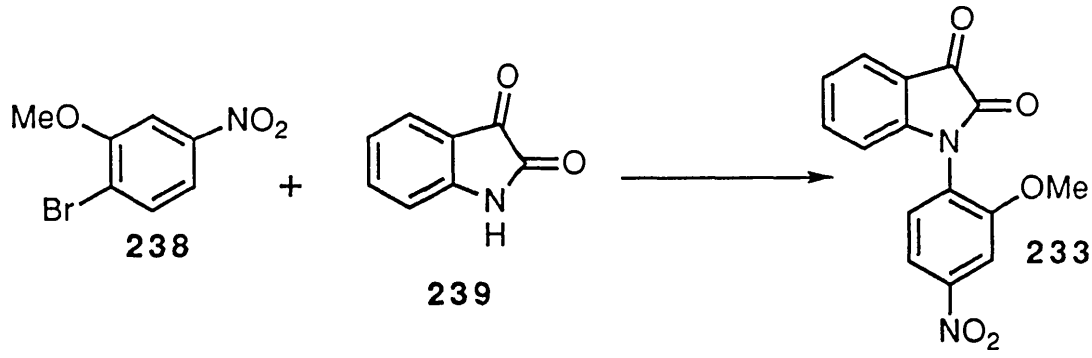
The isatin (233) (635 mg, 2.13 mmol) was dissolved in 10 % aqueous potassium hydroxide (10 ml) and the solution refluxed for 15 h. After cooling the solution was acidified with concentrated hydrochloric acid and the product extracted with ethyl acetate. The organic

phase was dried over sodium sulphate and the solvent removed *in vacuo*. The crude acid was then suspended in methanol (15 ml) and ether (45 ml) and esterified with diazomethane. The solution was filtered through a pad of silica and the solvents removed *in vacuo* to give the *title compound* (113 mg, 17 %) as a yellow solid, m.p. 235 - 237 °C (Found: $M^+$ 312.07400. $C_{16}H_{12}N_2O_5$ requires M 312.07462); $\nu_{max}$ ($CDCl_3$) 1735, 1615, 1521, 1341, 1160, 1090; $\delta_H$ (270 MHz, $CDCl_3$ ) 8.63 (1H, d 2.2 Hz, Ar<u>H</u>-1), 8.46 (1H, ddd 8.8, 1.5, 0.7 Hz), 8.07 (1H, ddd 8.5, 1.2, 0.7 Hz), 7.93 (1H, ddd 8.8, 6.8, 1.5 Hz), 7.81 (1H, d 2.2 Hz, Ar<u>H</u>-3), 7.73 (1H, ddd 8.5, 6.8, 1.2 Hz), 4.29 (3H, s, C<u>H</u>$_3$), 4.28 (3H, s, C<u>H</u>$_3$); *m/z* (220 °C) 312 ($M^+$, 100 %), 297 (2 %), 283 (26 %), 266 (34 %), 250 (53 %), 236 (32 %).

**(b) By reaction of the isatin (233) with sodium methoxide.**

The isatin (**233**) (150 mg, 0.5 mmol) was dissolved in dry 1,4-dioxane (10 ml). To this solution was added fresh sodium methoxide [prepared by removal of excess methanol from a solution of sodium (499 mg, 42 eq.) in methanol (8 ml)], and the resultant solution refluxed for 36 h. After cooling the solution was diluted with water (25 ml), acidified with excess ammonium chloride and the product extracted with ethyl acetate. The organic phase was dried over sodium sulphate and the solvent removed *in vacuo*. Chromatography first on alumina (eluting with chloroform) to remove the predominant yellow baseline material, and then silica (eluting with chloroform) gave the title compound (14.0 mg, 9 %) with data as above. The yellow material remaining on the alumina during chromatography was isolated by eluting with methanol and removing the solvent *in vacuo*. This material was then treated with diazomethane in the normal way and the product purified by chromatography on silica (eluting with chloroform) to give the ester (**234**) (26.4 mg, 17 %) as previously described.

**N-(2-Methoxy-4-nitrophenyl)-indoline-2,3-dione (233).**




A mixture of the bromobenzene (**238**) [70] (2 g, 8.6 mmol), isatin (**239**) (0.89 g, 6.0 mmol) and copper (II) oxide (1.0 g, 12.0 mmol) in DMF (15 ml) was refluxed for 18 h, and then filtered hot. The solid residues were washed with more DMF, and the filtrate poured into water (200 ml). The precipitate was filtered and recrystallised three times from hot methanol to give the title compound as a yellow solid (1.0 g, 40 %) with data as described previously.

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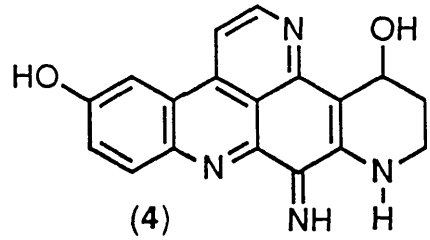
# 6 APPENDIX A.

## A list of the pyridoacridine alkaloids.

**The pyridoacridine marine alkaloids:**

an alphabetical list in three sections, corresponding to the animal sources: sea anemones; sponges; tunicates (and its subgroup ascidians).

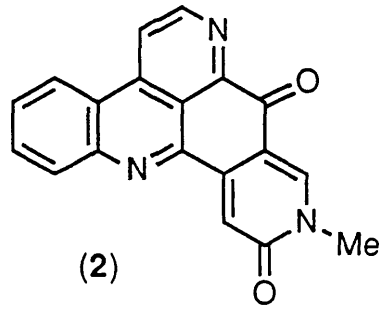
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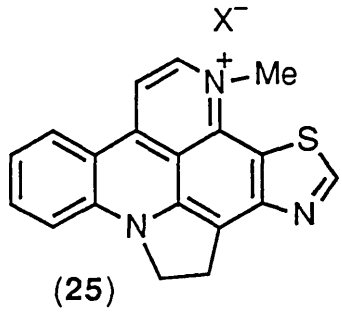
calliactine.

## SPONGES.



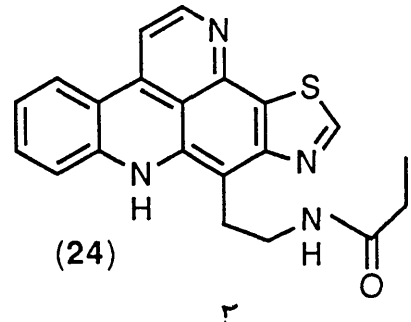

(2)

amphimedine.



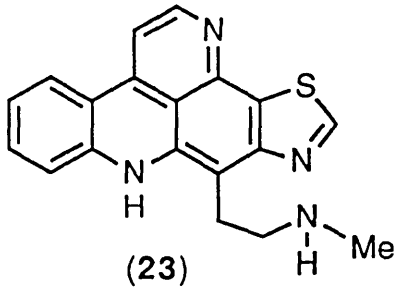

(25)

cyclodercitin



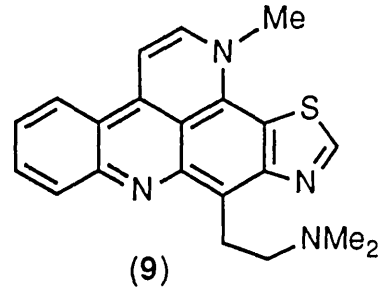

(24)

decitamide



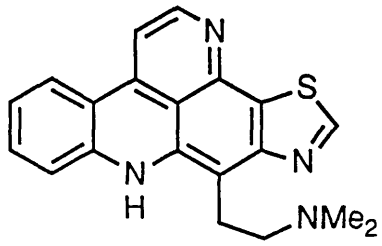
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dercitamine



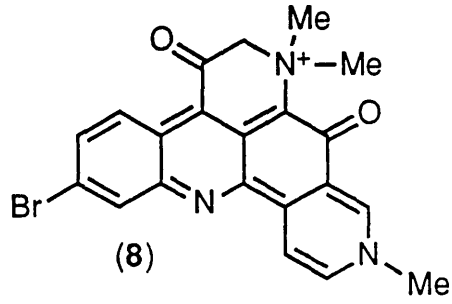
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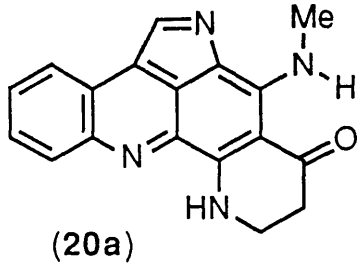
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nordercitin



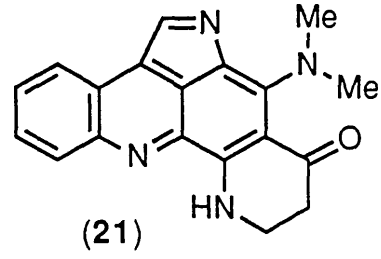
(8)

petrosamine



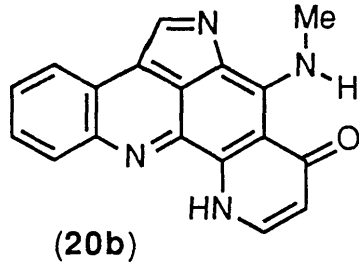
(20a)

plakinidine A



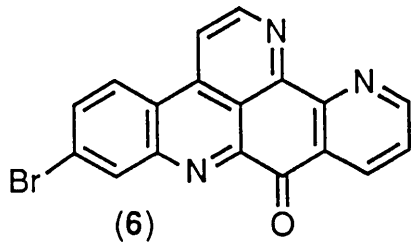
(21)

plakinidine B



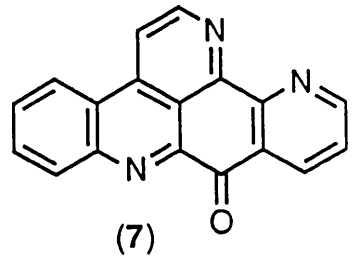
(20b)

plakinidine C



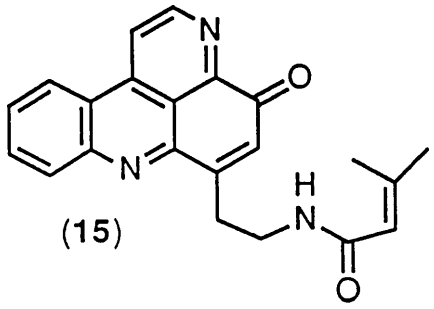

(6)

2-bromoleptoclinidinone



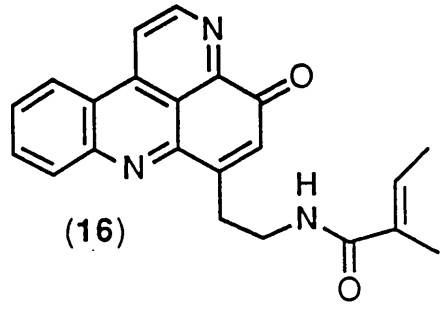

(7)

ascididemin



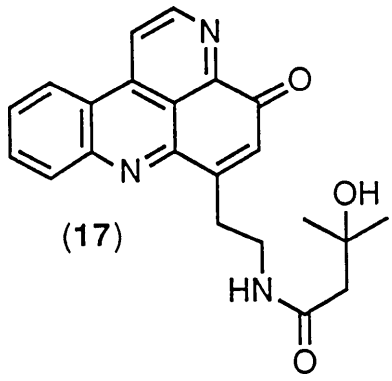

(15)

cystodytin A



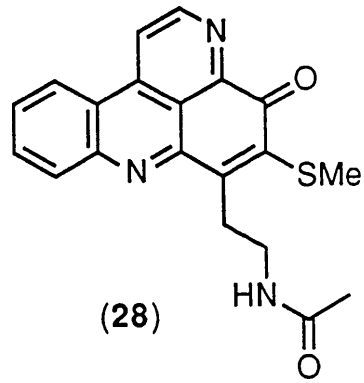

(16)

cystodytin B



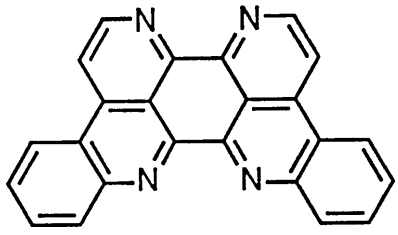

(17)

cystodytin C



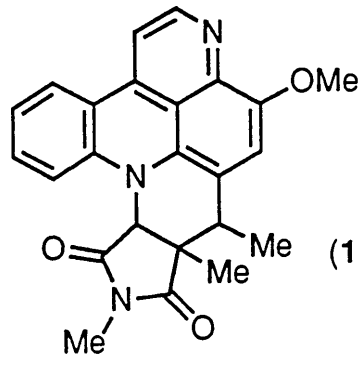

(28)

diplamine



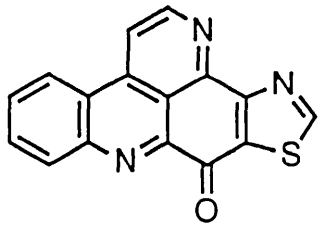

(14)

eilatin



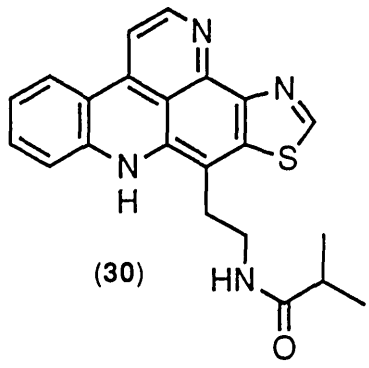

(12)

isosegoline A



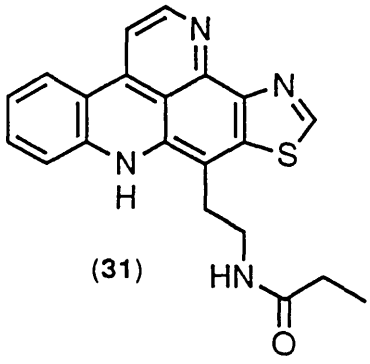
(29)

kaunoniamine A



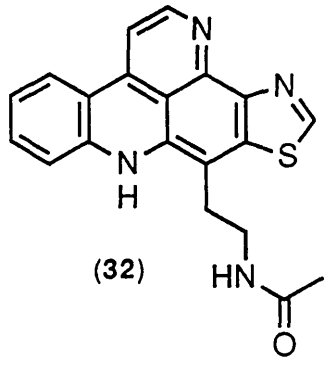
(30)

kaunoniamine B



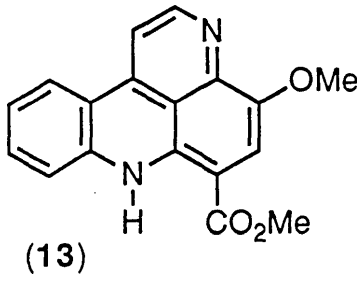
(31)

kaunoniamine C



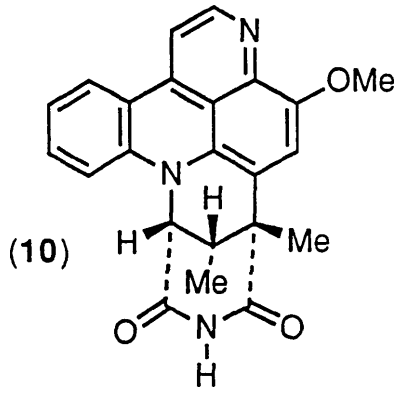
(32)

kaunoniamine D



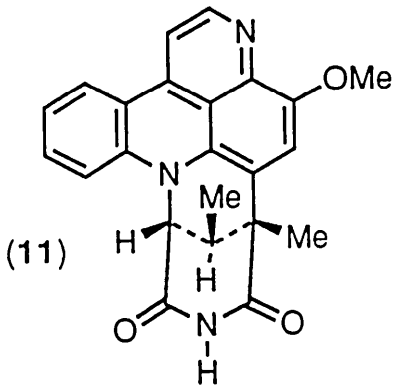
(13)

nor-segoline



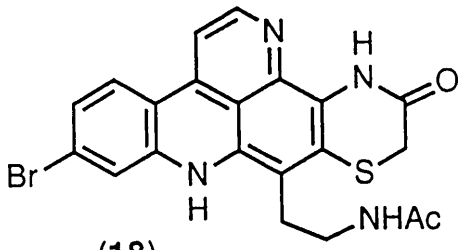
(10)

segoline A



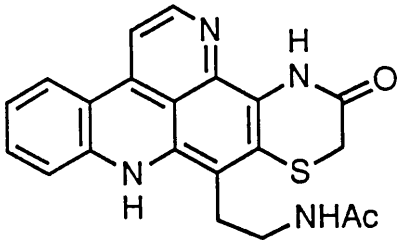

(11)

segoline B



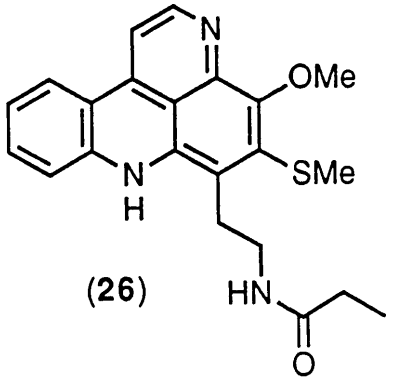

(18)

shermilamine A



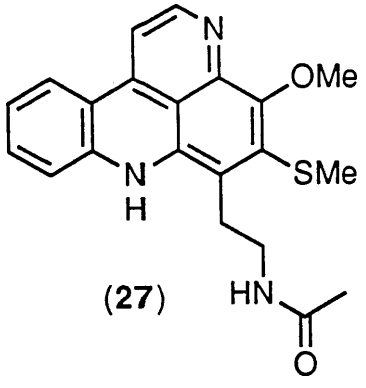

(19)

shermilamine B




(26)

varamine A




(27)

varamine B

# 7 APPENDIX B.

## NMR SPECTRA.

**Diagram 2** NMR spectrum of ascididemin (7).

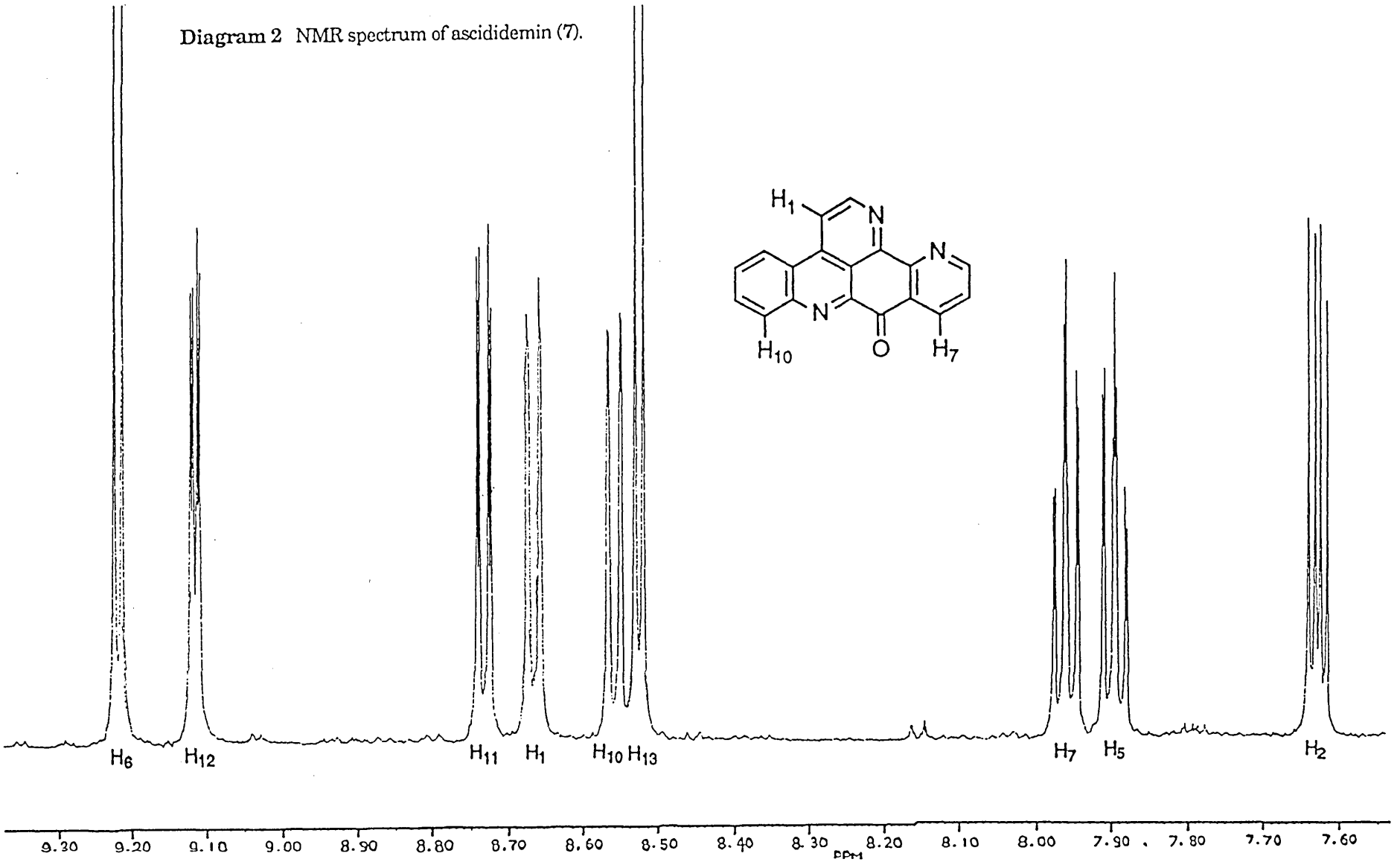
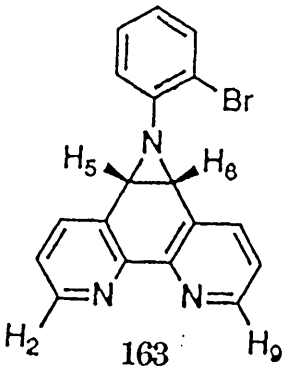


Diagram 3 NMR spectrum of the reaction products of the Mitsunobu reaction of (155), clearly showing the phenanthroline protons of the aziridine product




163

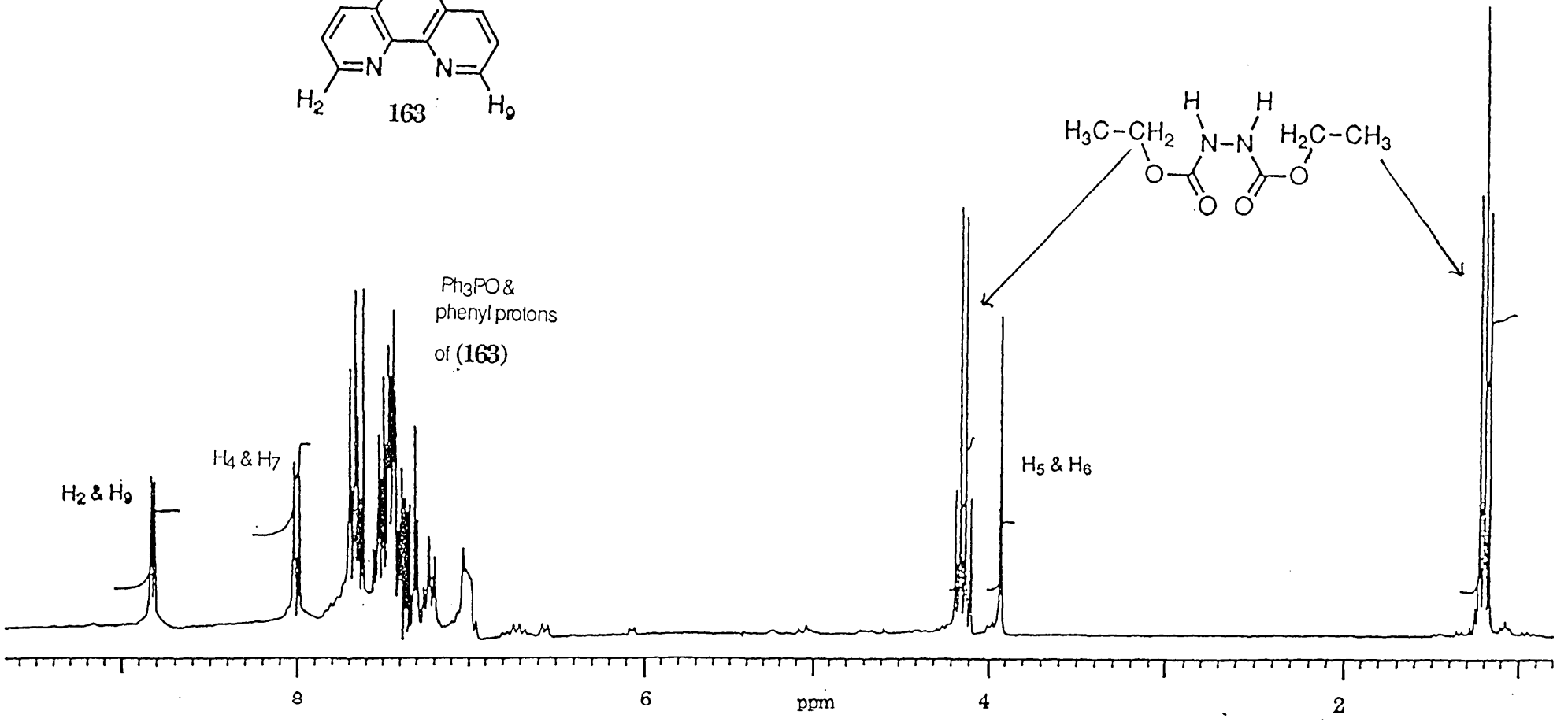


Diagram 4 $^1H$ decoupling of the quinoneimine (121 X = H).
The lower trace shows the normal spectrum of this compound.
The two upper traces show decoupling caused by the separate irradiation of the phenanthroline 4 and 7 protons. This experiment clearly shows the two different 3 - spin systems of the phenanthroline.

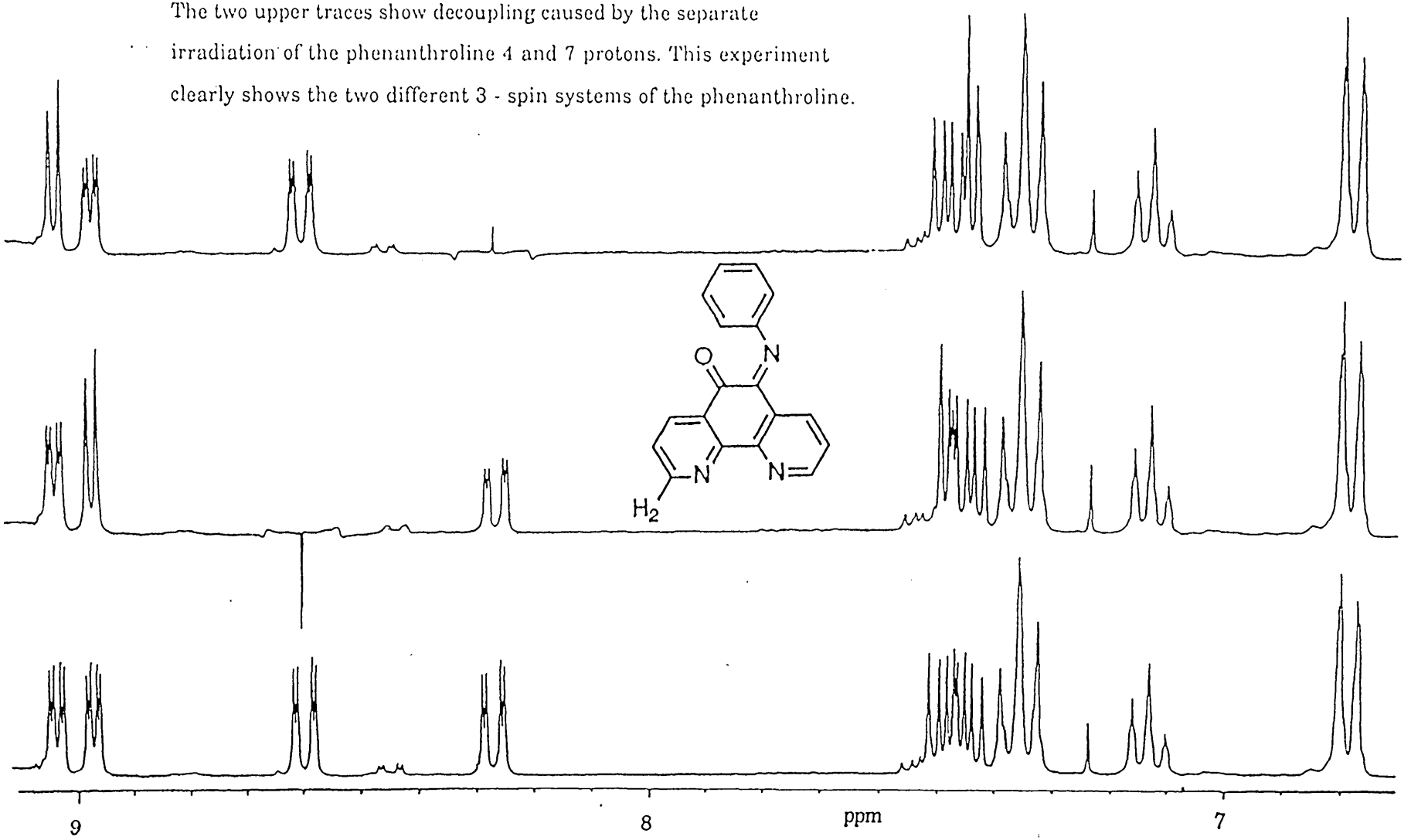


**Diagram 5a** (this page) and **diagram 5b** (next page) show the results of nOe experiments carried out on the quinoneimine **(121 X = H)** Each diagram depicts the irradiation of protons on only one of the pyridine rings of the phenanthroline. In each diagram the lowest scans are normal spectra, the central scan shows irradiation of the pyridine - 2 type proton, and the top scan shows irradiation of the pyridine - 4 type proton.

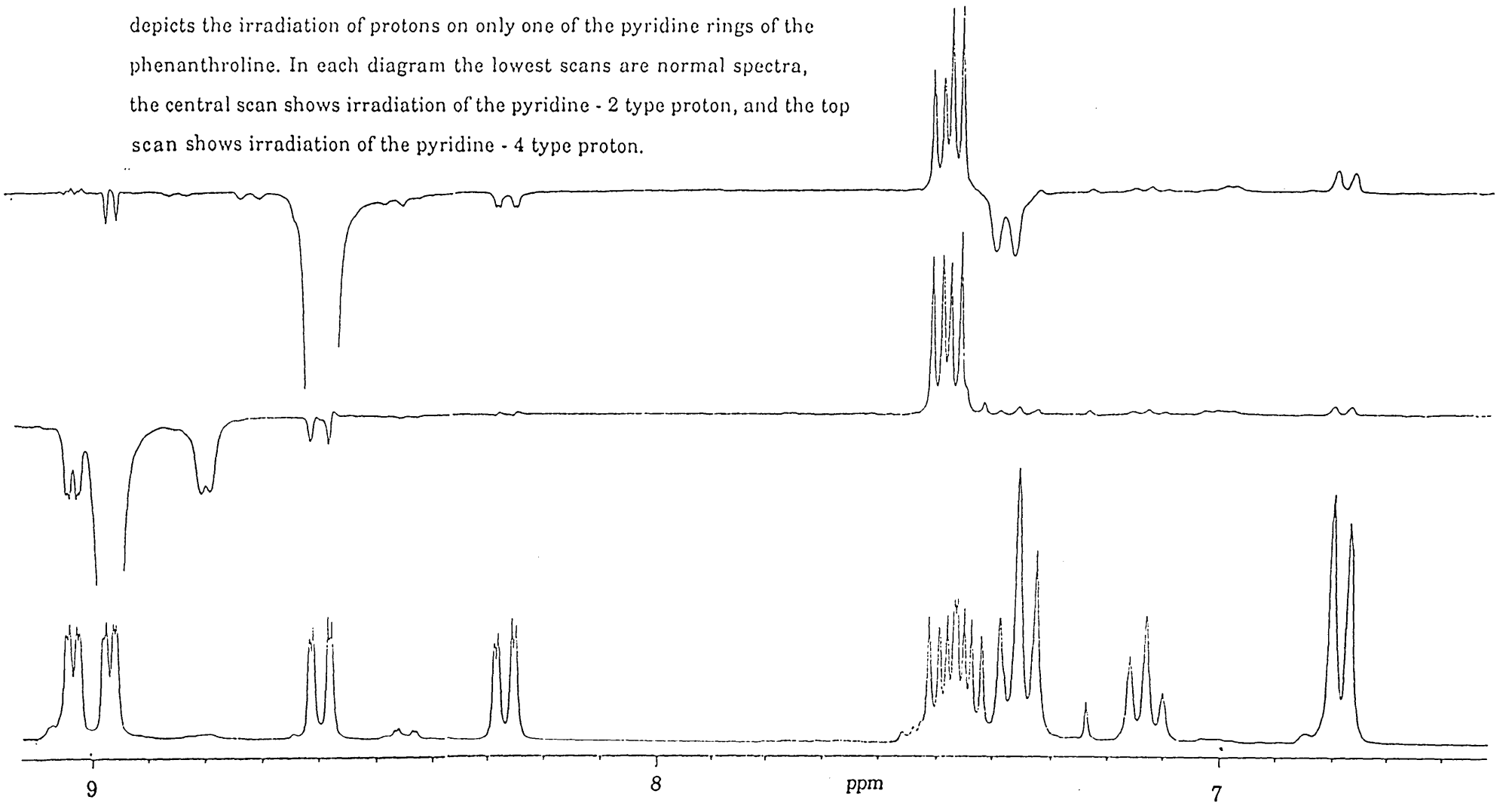


Diagram 5b

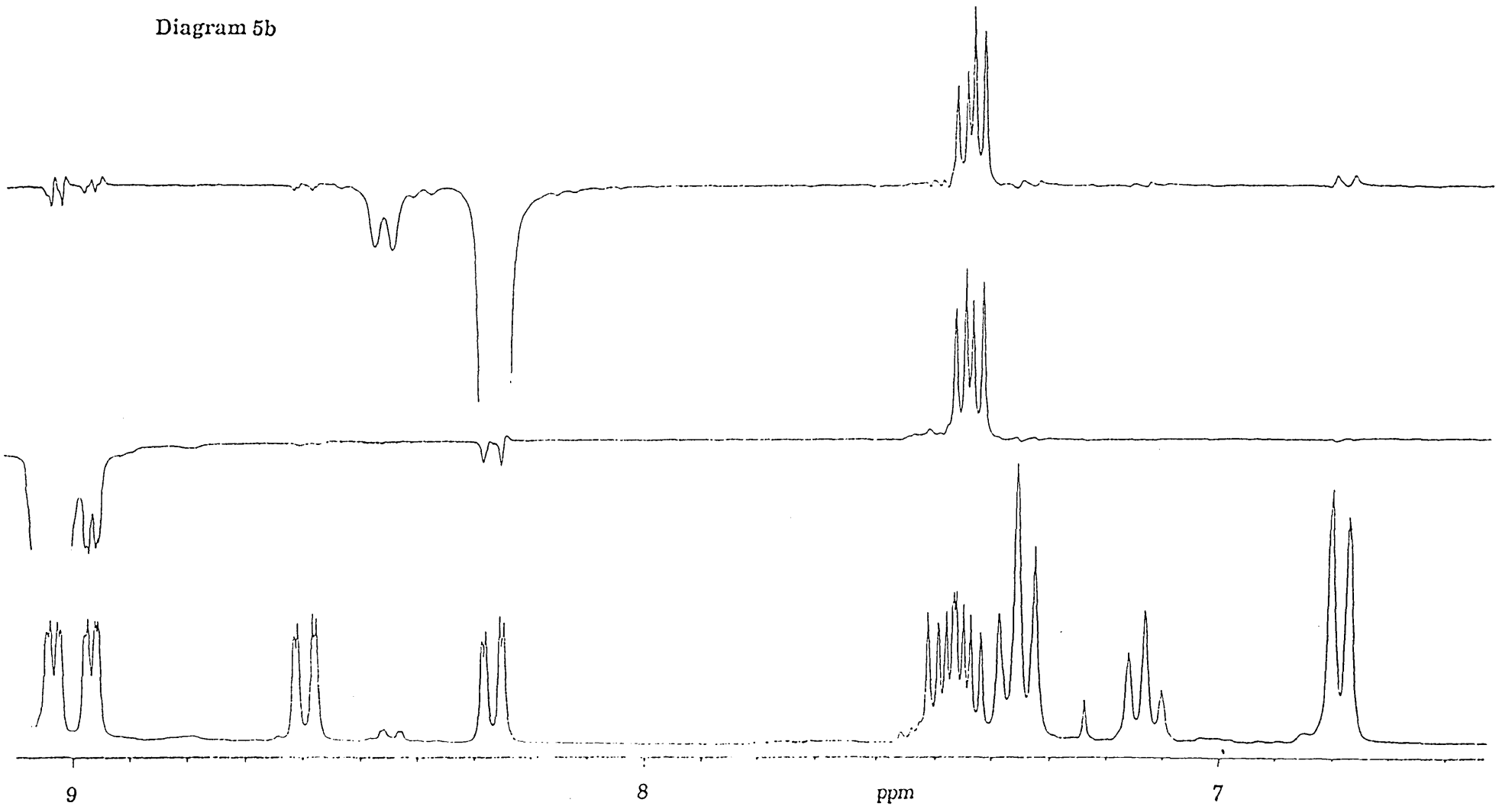
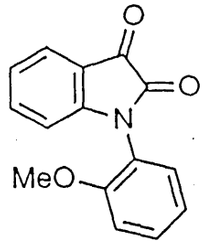


**Diagram 6** COSY 16 spectrum of (228).



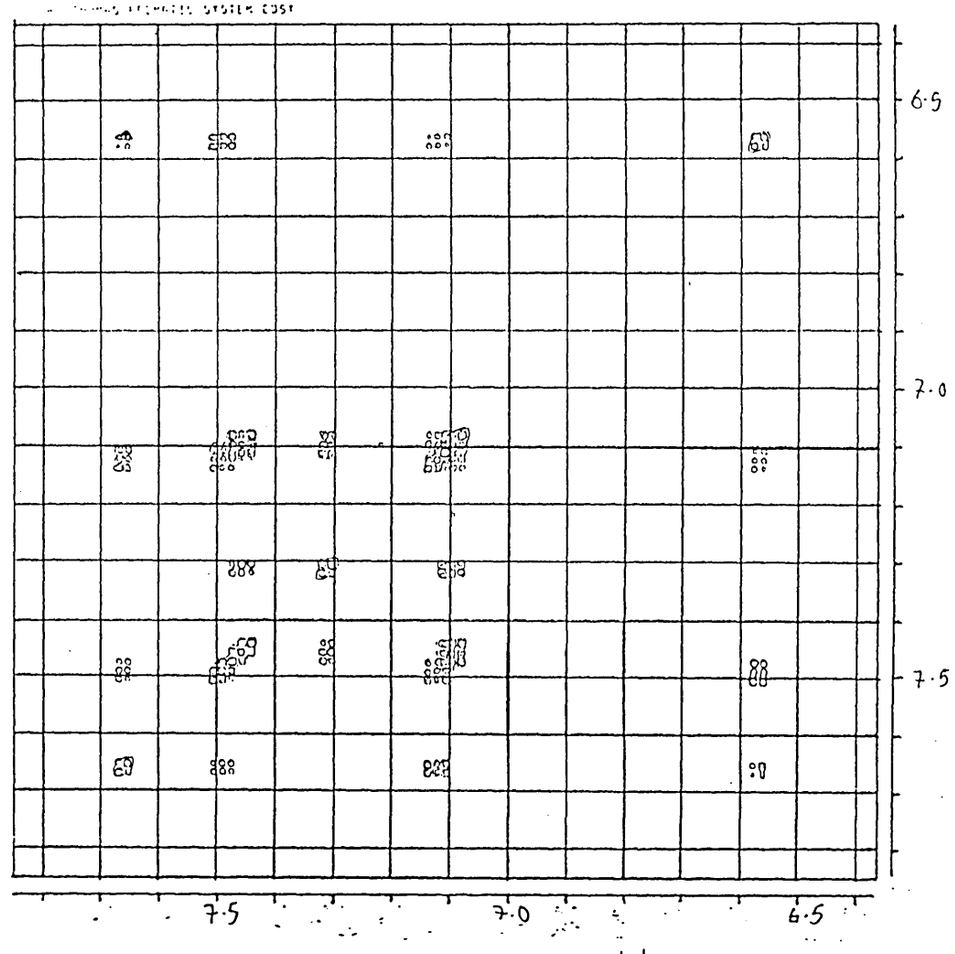



Diagram 7 COSY 48 spectrum of (229).

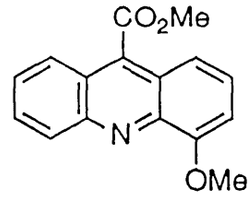


**Diagram 8** Heteronuclear Shift Correlation spectrum of (154) with heteronuclear decoupling in both dimensions.

