"THE SYNTHESIS OF ANTAGONISTS OF γ-AMINOBUTYRIC ACID."

A Thesis

Presented for the Degree of

Doctor of Philosophy

in

The University of Adelaide.

by

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CONTENTS

SUMMARY

Part I of this Thesis is concerned with the development of new synthetic methods for preparing 4- and 6- substituted caprolactams, required for biological evaluation. 4-Allyloxy caprolactams undergo a thermal Claisen rearrangement to give 3- substituted derivatives. The rearrangement of the 4-propargyloxy system proved more complicated and the N-allyl $\Delta^{6,7}$ caprolactam derivatives were unreactive. Alkylation of 4-oxocaprolactam with various allyl halides afforded mixtures of the 3-mono- and the 3,3-di- substituted products. Attempts were made to prepare caprolactams by a photochemical ring enlargement of N-substituted succinimides. Although a limited number of new caprolactams were prepared by this method, the yields were only moderate.

Part II discusses the synthesis of phthalidylphthalazinones, phthalidylcinnolinones, and other analogues of bicuculline. An efficient synthesis of biphthalides was developed and involved the Wittig reaction between phthalic anhydrides and triphenyl (3-phthalidyl) phosphonium bromides. The biphthalides on treatment with hydrazines afforded phthalidylphthalazinones. The synthesis of phthalidylphthalazines by the Reissert reaction is also described. The alkylation of 4-hydroxycinnolines with 3-bromophthalides afforded phthalidylcinnolinones whose structure was confirmed by ^{13}C N.M.R. spectroscopy. The attempted preparation of phthalidylborazanaphthalenes and phthalidylphthalazinones containing boron, is discussed.

Part III describes an efficient synthesis of alkoxy- and carboxyphthalides by the lithiation of alkoxybenzyl alcohols. This provides an efficient entry into the synthesis of phthalideisoquinoline alkaloids. Some interesting mechanistic results emerged during the course of this work. 2'-Substituted papaverines were prepared by the treatment of

2'-bromopapaverine with butyl lithium and an electrophilic species.

The physiological activity of the caprolactams, phthalidyl-phthalazinones, and phthalidylcinnolinones, is detailed in Part IV.

STATEMENT

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

B. A. Mooney

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I wish to express my sincere thanks to my family for their help, patience, and encouragement, during the course of this work. I also wish to thank my friends for their encouragement.

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PART I

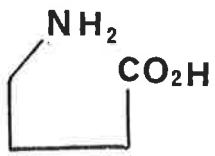
SYNTHESIS

OF

CAPROLACTAMS

CHAPTER 1 : INTRODUCTION

γ-Aminobutyric acid (GABA,1) is a putative neuro transmitter in the mammalian central nervous system (CNS)[1-4] and has a potent inhibitory action against epileptic seizures.[5]



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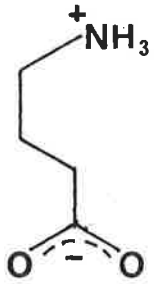
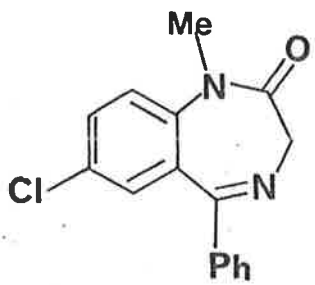


(2)

(3)

A possible explanation for this synaptic activity is its specific rotomer conformation and the resulting distance between zwitterionic centres (2)[6], and indeed many synthetic analogues such as 4-aminotetrolic acid (3) have the same feature[7]. Molecular calculations suggest that GABA assumes a conformation whereby the zwitterionic centres are 5A° and more likely 6A° apart. Similar calculations suggest a distance between 5.5A° and 5.8A° for (3)[7].

The CNS activity of certain cyclic amides was suggestive of anti-GABA activity[8], although physiological activity of the class is by no means homogenous. Examples of active compounds in this group include diazepam (Valium) (4)[9], β-adrenergic blocking agents such as (5)[10], convulsants such as metrazole (6)[11], analgesics (7)[12,13], and hypnotics (8)[14].



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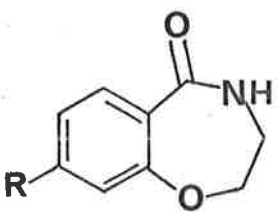

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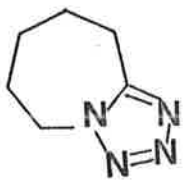

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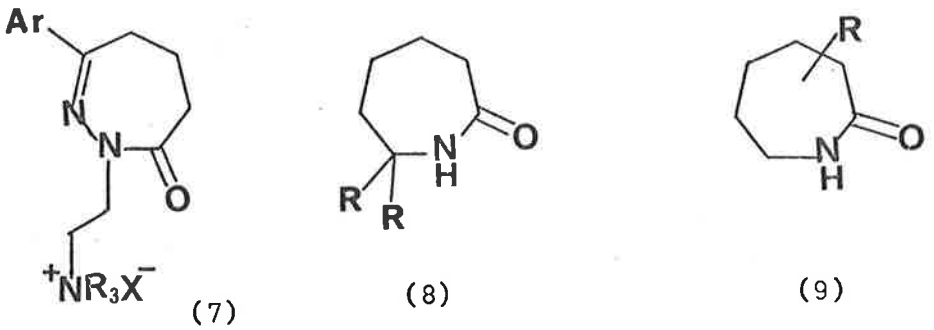


(7) (8) (9)

Caprolactam (hexahydroazepin-2-one) (9,R=H) because of its importance in nylon synthesis, has been a subject of detailed pharmacalogical investigation. It has been shown by Polushkin[15] to produce hypertensive effects in dogs at low doses, but is hypotensive at higher doses. A report by Goldblatt[16] states that caprolactam is an effective convulsant acting on the cortex of the rhinencephalon.

The lipid solubility of a caprolactam is a governing factor in its ability to act as a convulsant[17] and a detailed investigation of the convulsant activity of caprolactams[18,19,20] has shown that the most potent antagonists have substituents on carbons 4 and 6 of the ring. This is exemplified by the four hundred fold increase in convulsant activity of 4,4,6,6-tetramethylcaprolactam, with a CD_{50} of 1.5 mg/Kg, over the parent lactam.[20]

It is apparent that the requirement for biological activity is the amide function, as well as a weak hydrophobic centre at C4 and a stronger one in the region of C6 and C7[21,22]. (Figure 1).

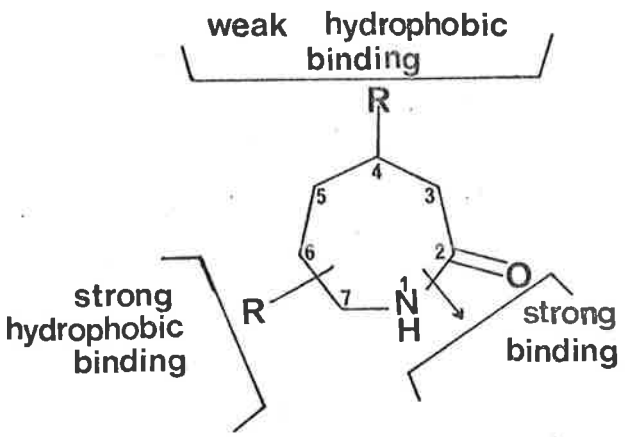
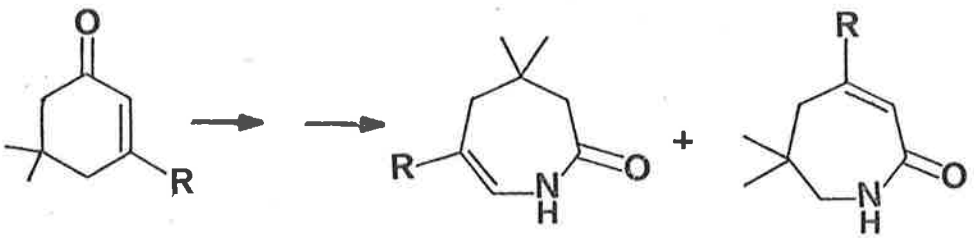


Figure 1.

Thus the most potent antagonists require alkyl substituents in the 6 position or the 4 and 6 position.

The Schmidt reaction or the Beckman rearrangement are two of the most extensively used synthetic methods in caprolactam synthesis[18,19,20,23-25]. These two methods, when applied to 3-alkylcyclohexenones (10), afford mixtures of 4- and 6-alkyltetrahydroazepinones (11) and (12), the former being the predominant isomer and having lower activity[20-22].

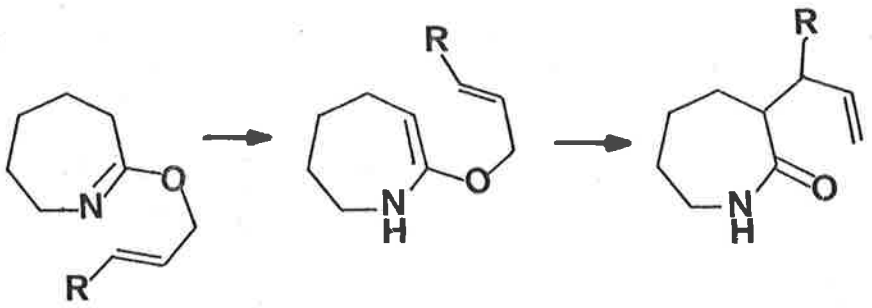


(10) (12) (11)

Furthermore, separation of the isomers is sometimes difficult and tedious. In most cases there does not appear to be a general method for obtaining C6 substitution exclusively although Kanaoka and Hatanaka[26] have achieved C6 and C7 alkyl substitution in yields up to 60%.

In an attempt to elaborate potentially active compounds, the preparation of caprolactams by molecular rearrangement reactions was investigated.

Cope, or more specifically Claisen rearrangements, both [3,3] sigmatropic, have been used extensively in synthetic chemistry and have been well documented.[27-29] Black and Eastwood[30] have shown that a Claisen rearrangement occurs readily on the allyl imino ethers (13; Scheme 1.01) and it was anticipated that a similar type of reaction could be utilised to obtain CNS active caprolactams.



(13)

Scheme 1.01

Another approach to the desired caprolactams utilises the results of Kanaoka and *co workers*[26] who reported that N-substituted succinimides are converted by a photochemical rearrangement process to C6 and/or C7 substituted caprolactams.

CHAPTER 2

RESULTS AND DISCUSSION

2.1 CLAISEN REARRANGEMENT PRODUCTS OF ALLYL VINYL ETHERS OBTAINED FROM CAPROLACTAM DERIVATIVES.

The results of Black and Eastwood *et al.*[30] prompted further investigations of Claisen rearrangements associated with the caprolactam system. It was expected that the allyl vinyl ether (14) would rearrange thermally to afford the C3 substituted derivative (15) with the retention of an activating group at C4. These two classes of compounds retain 6-alkyl groups which are necessary, while varying the C3 and C4

(14)

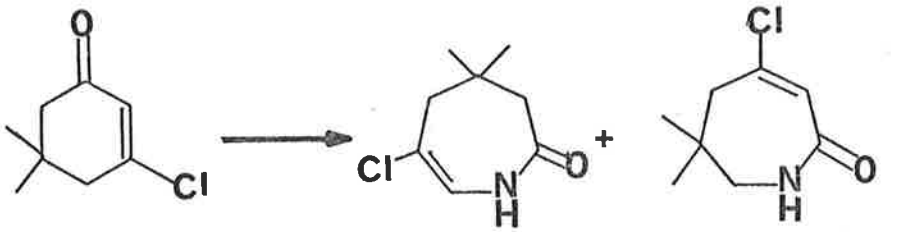
(16) R=H

(15) R= $CH_2CH{=}CH_2$

substituents. Furthermore, such a strategy eliminates O-alkylated-[18] and 3,3-dialkylated- derivatives which accompany 6,6-dimethylhexahydroazepin-2,4-dione (16) in direct alkylation. This Claisen rearrangement could then be extended to other allyl vinyl ethers of the type (14).

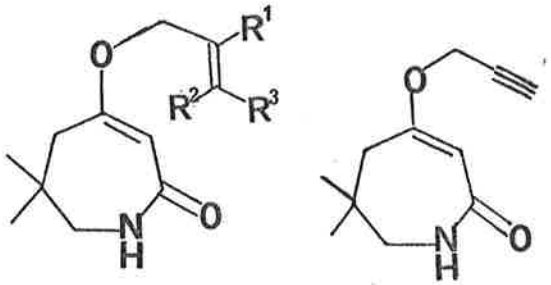
Vinyl substitution by alkoxides on the caprolactam (18; Scheme 1.02), obtained by a Schmidt reaction on the chloro derivative of dimedone (17)[23], is known to proceed quite readily[19]. It was anticipated that a similar strategy, using allyl alcohols and (18), would afford (14) and similar compounds.

Indeed, treatment of an allylic alcohol with sodium, followed by the reaction with (18) proceeded smoothly, resulting in high yields of the required allyl vinyl ethers (14), (20)-(23). A similar result occurred on using propargyl alcohol, to yield (24). Replacement of the allyl



(17) (19) (18)

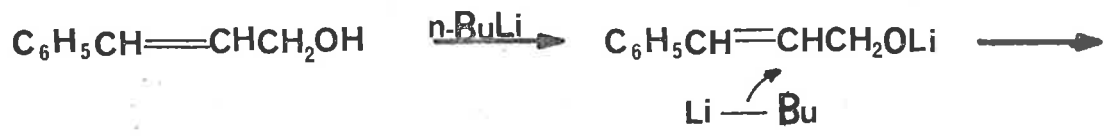
RO^-

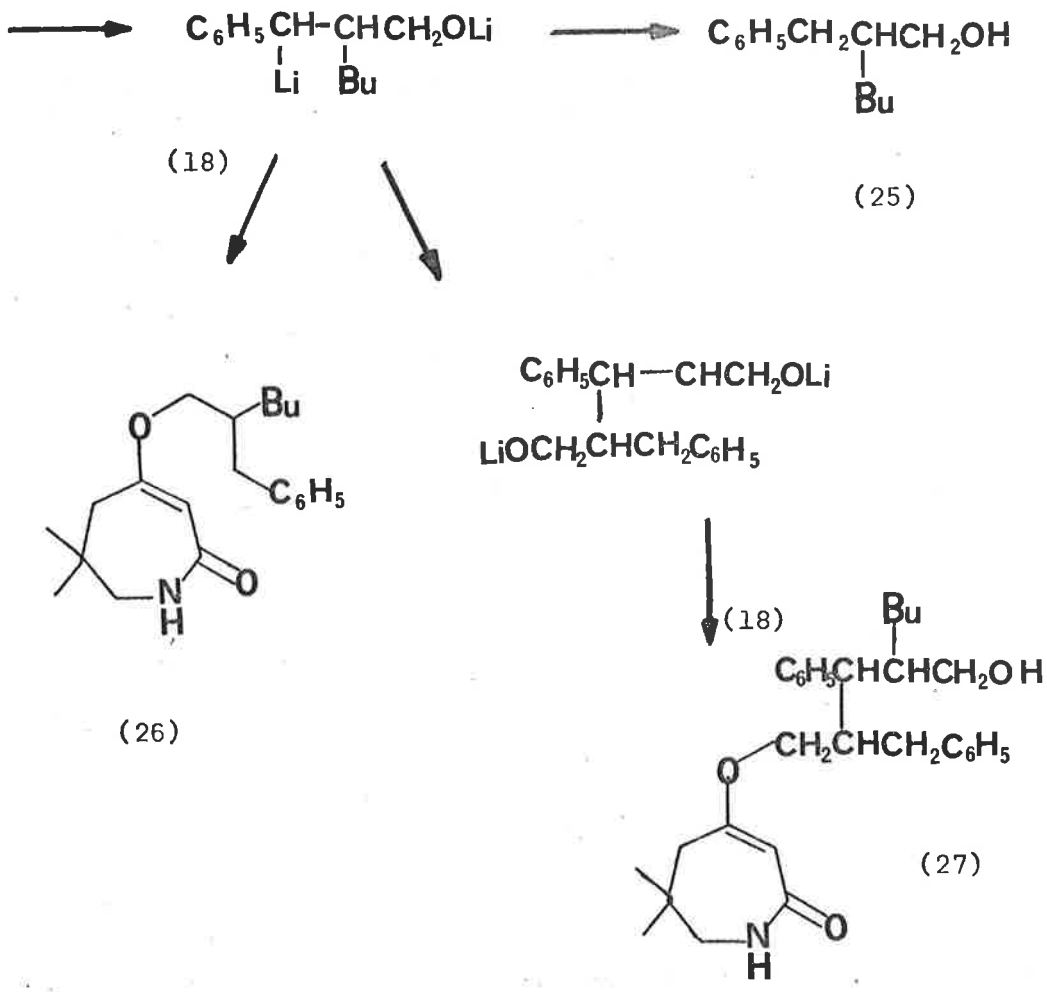


	R^1	R^2	R^3
(20)	H	H	Me
(21)	Me	H	H
(22)	H	Me	Me
(23)	H	H	C_6H_5

(24)

alcohol as solvent by ether, and using one equivalent of alcohol and sodium hydride, followed by the reaction with (18), gave the lactams (20)-(24) in comparable yields, the advantage being the ease of product isolation. Surprisingly, substitution of tetrahydrofuran for ether did not provide the required products. In an attempt to generate the alkoxide of cinnamyl alcohol with butyl lithium instead of sodium hydride, the subsequent reaction with (18) afforded several unexpected products, three of which were identifies as (25), (26), and (27), which are presumed to arise as shown in Scheme 1.03. The structure (27) was consistent with the infrared spectrum which showed absorbances at 3300 and 1680 cm^{-1}, and a molecular weight of 463.





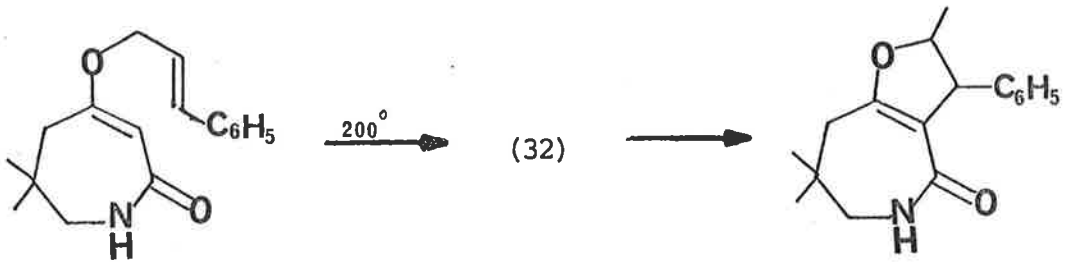
Scheme 1.03

Although the addition of alkyl lithiums to allylic alcohols has been previously reported[31], such reactions with cinnamyl alcohol have not. The Claisen rearrangement products of the readily available allyl vinyl ethers (14), (20)-(24) were subsequently investigated.

Heating the allyl vinyl ethers (14), (20)-(24) at 200° for 30 minutes resulted in their conversion to the 3-substituted compounds (15), (28)-(32). If the caprolactam was subjected to the high temperatures for extended periods of time, a more complex reaction mixture resulted.

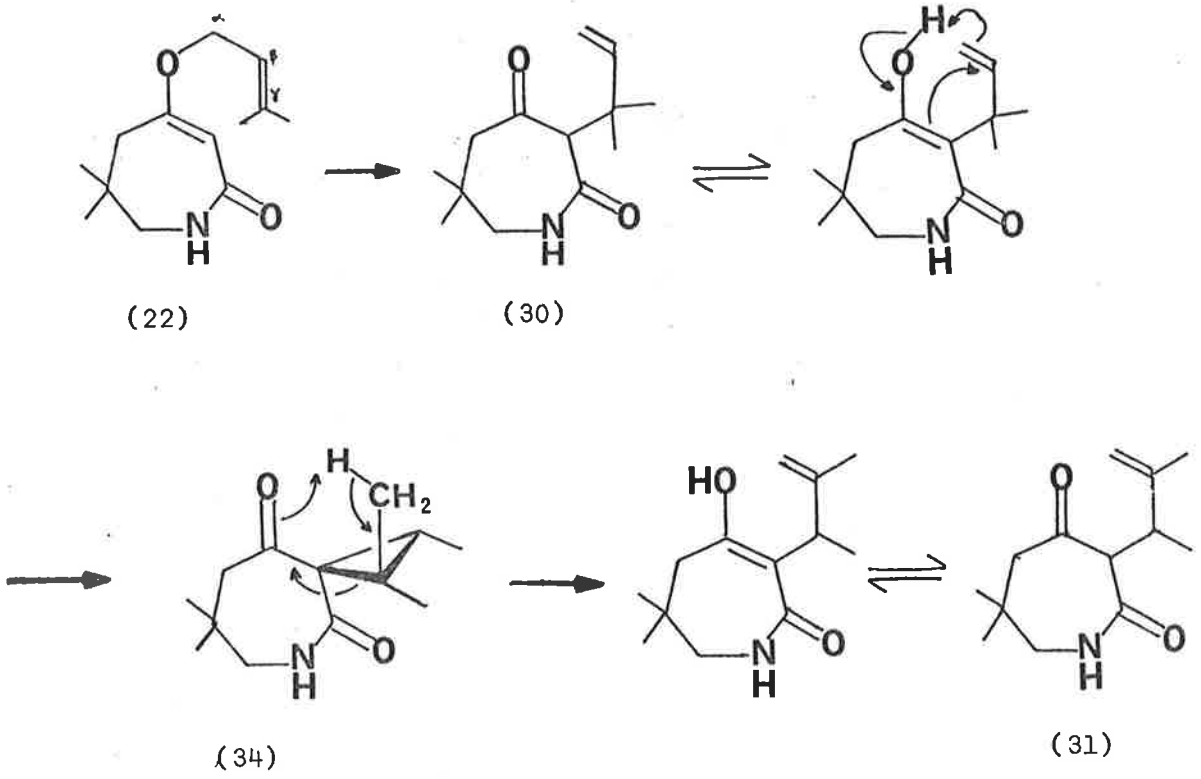
	R^1	R^2	R^3
(15)	H	H	H
(28)	H	H	Me
(29)	Me	H	H
(30)	H	Me	Me
(31)	Me	Me	H
(32)	H	H	C_6H_5

When (23) was heated at 200° for 30 minutes, (32) and the dihydrofuran (33) were isolated. After 15 minutes at 200°, (22) was converted to the



(23) (33)

abnormal Claisen rearrangement product (31). This "abnormal" rearrangement is commonly observed when the allyl ethers bear γ-alkyl substituents on the allyl group.[28] It is in fact produced in a subsequent rearrangement of the normal Claisen product (30), and is believed to be formed through a spirocyclopropyl intermediate (34) which results from a hydrogen transfer from the enolic hydroxyl group to the terminal carbon of the allyl group. Reversal of this process, that is a [1,5] hydrogen shift, but involving the γ-alkyl group, leads to the abnormal product[28] (Scheme 1.04). On decreasing the reaction time to 1.5 minutes at 196°, the normal product could be obtained as a 1:1 mixture of starting material and (30). Longer reaction times or higher temperatures resulted in mixtures of (30) and



Scheme 1.04

(31)* which could not be separated by chromatography or fractional crystallisation.

A characteristic feature of these C3-mono-substituted caprolactams was their p.m.r. spectrum which showed the gem dimethyl groups as two separate singlets in the region δ1.1 and δ1.0. Additionally, the C7 methylene protons and the amidic proton form an ABX system while the C5 protons exhibit an AB system. It is likely that this results from a rapid interconversion of the two pseudo-chair conformers, the spectrum representing the time averaged spectrum but closely approximates the major conformer (Figure 2). All CH groups will be diasterotopic regardless of the rate of inversion of the ring. This interpretation is borne out by analysis of the 3,3-diallyl-derivatives (54)-(57) referred to later.

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* These results are detailed in the experimental section, Part I, Table I.

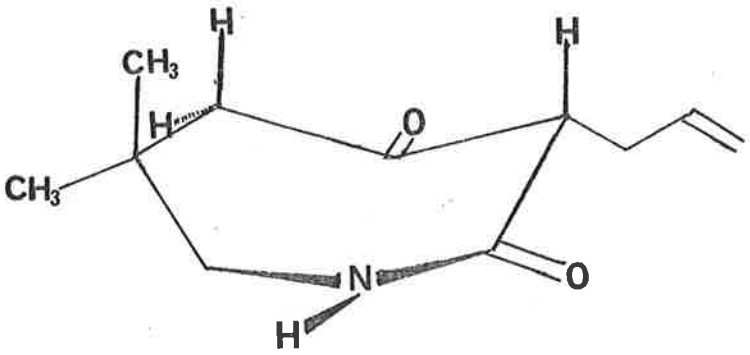
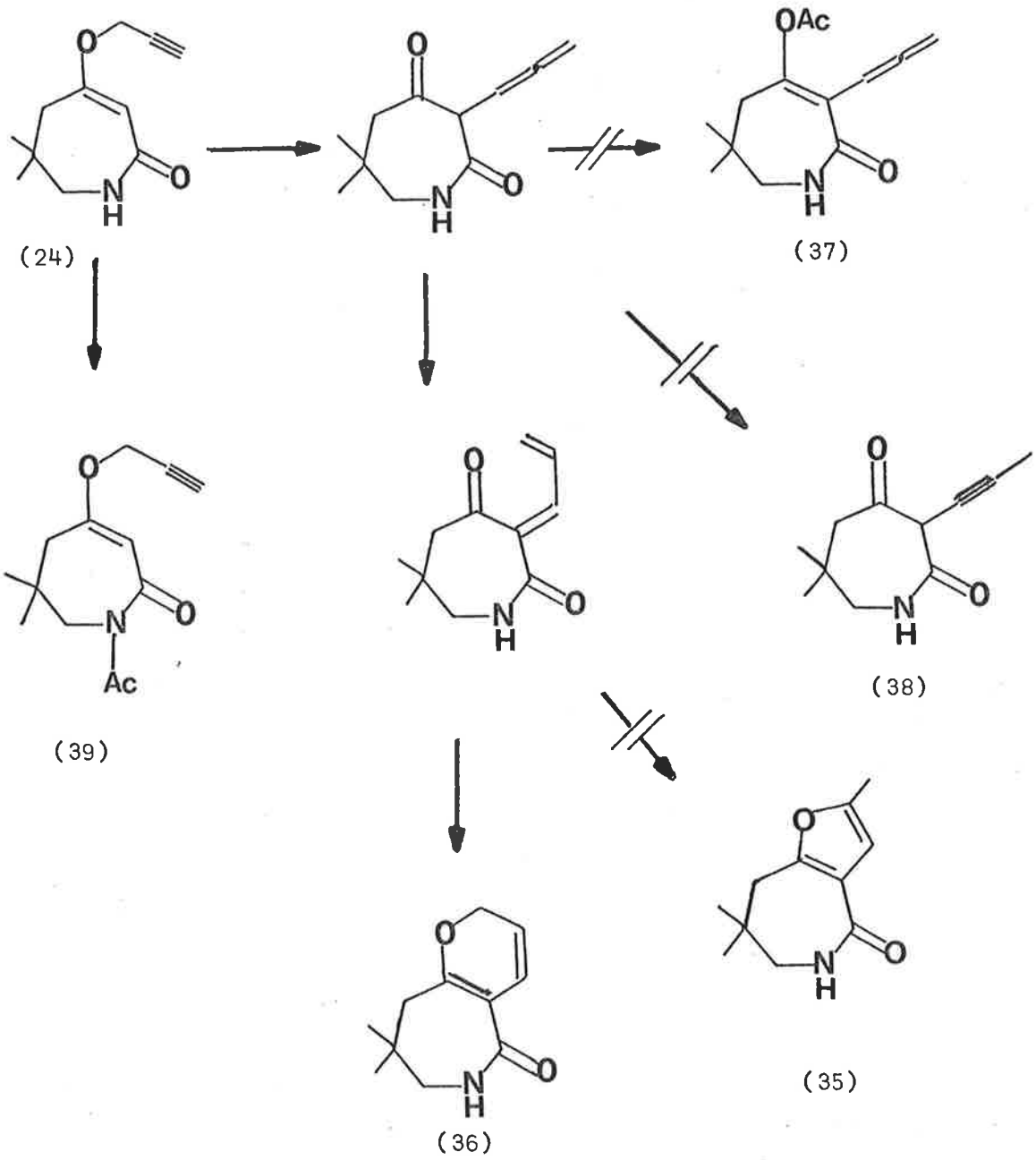


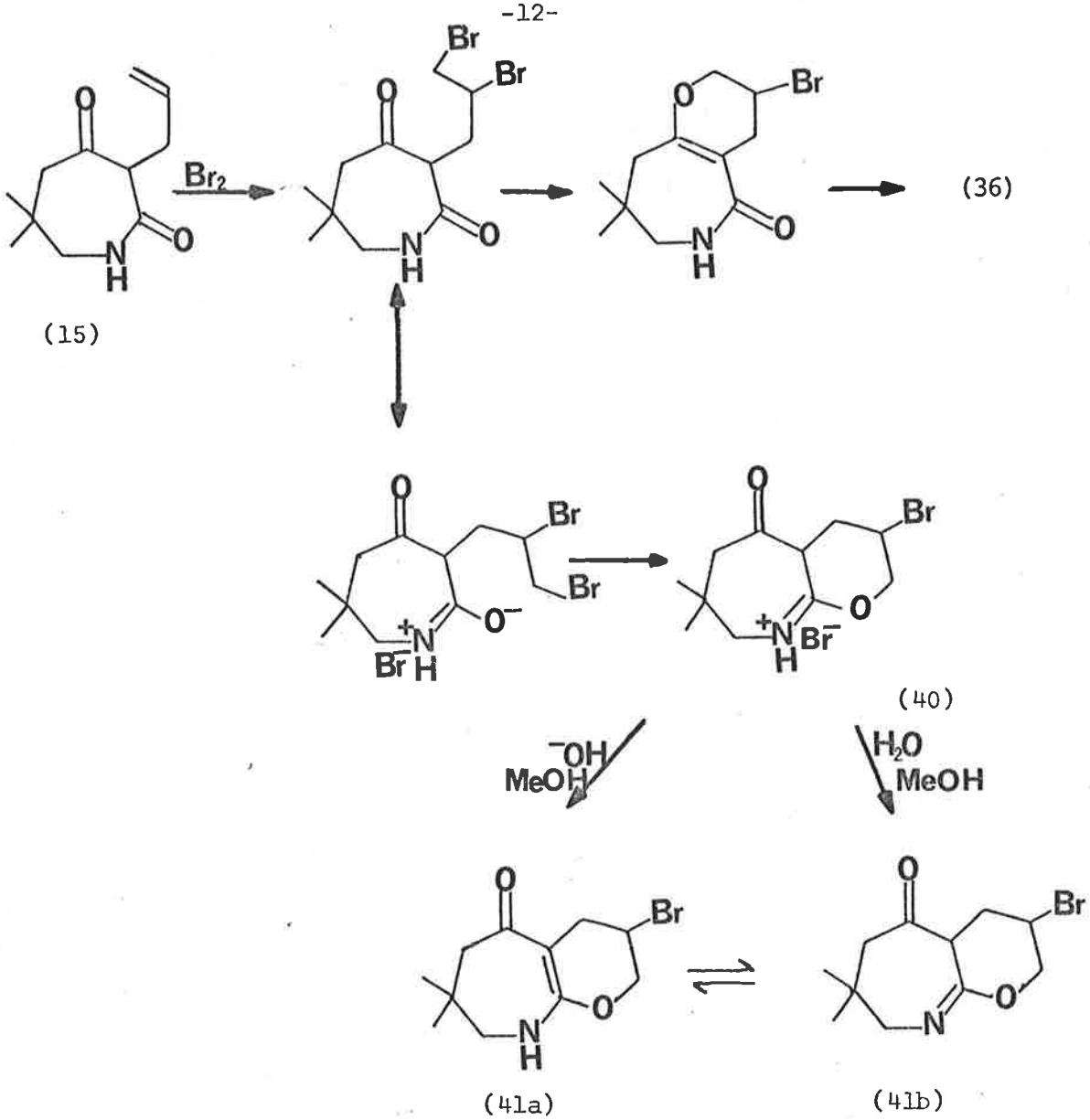
Figure 2.

Propargyl vinyl ethers rearrange readily to form allenic systems[28, 32,33] and Scheme 1.05 shows the expected type of rearrangement (24) should undertake when subjected to thermal rearrangement conditions. Since an allene is so reactive, it is reasonable to expect the formation of either the furan (35) or pyran (36)[34-36]. Alternatively by carrying out the reaction in acetic or butyric anhydride, to minimize the number of side reaction products[37], it could be envisaged that either the allene (37) or the acetylene (38) could be trapped and isolated. In fact, under a variety of reaction conditions only unidentified materials were obtained. Use of acetic anhydride as solvent resulted only in nitrogen acetylation (39) but when the reaction mixture was heated at higher temperatures in diglyme several products were detectable by t.l.c., but none were characterised. Vacuum pyrolysis of (24) at elevated temperatures yielded a glassy solid and although its structure has not been positively identified, the pyran structure (36) appears most likely on the basis of its p.m.r. spectrum which definitely ruled out the furan (35). A possible independent synthesis of the product (36) from vacuum pyrolysis is shown in Scheme 1.06 in which (15) is brominated and the product is cyclised and dehydrobrominated under alkaline conditions. However, on treating (15)

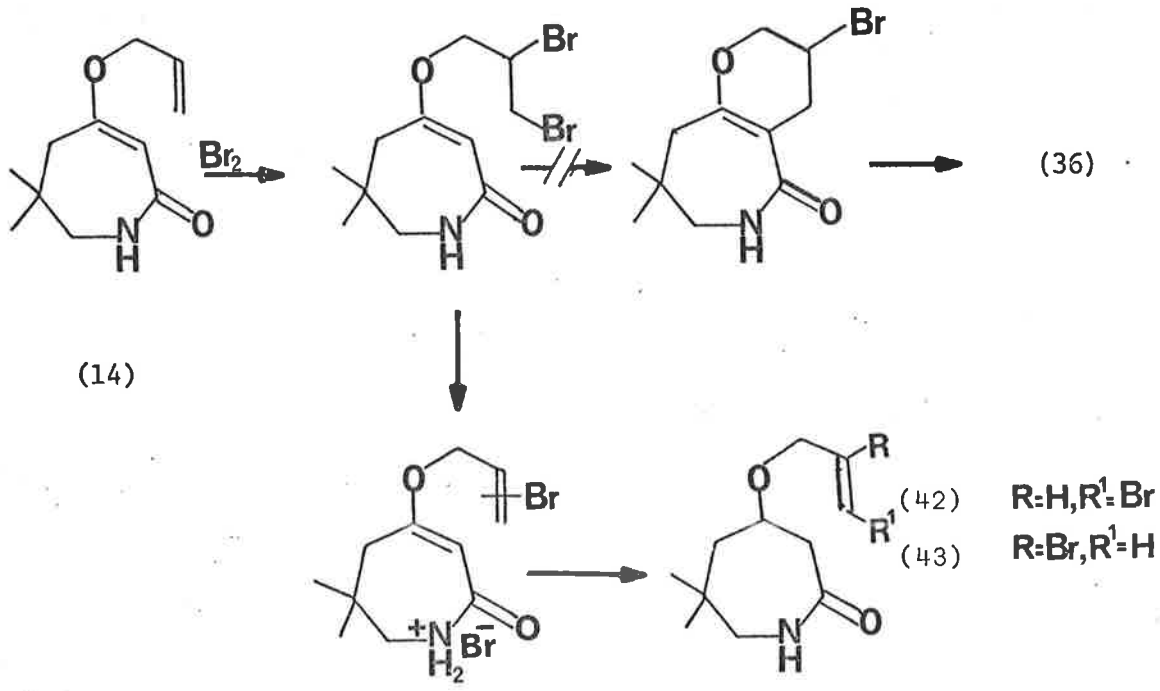


Scheme 1.05

with bromine a white solid was precipitated whose chemistry and analytical data suggested it to be the imino ether hydrobromide (40). This type of cyclisation is similar to the halolactonisation of unsaturated acids[38] and also of iodocyclisations of non-conjugated dienes[39]. Hydrolysis of this hydrobromide (40) afforded a solid, but attempted recrystallisation led to its decomposition. Depending on hydrolysis conditions two products have been isolated. The hydrobromide when treated with water/methanol yielded a product, the p.m.r. spectrum of which was devoid of an NH proton and the methylene protons adjacent to the nitrogen appear as a singlet



Scheme 1.06

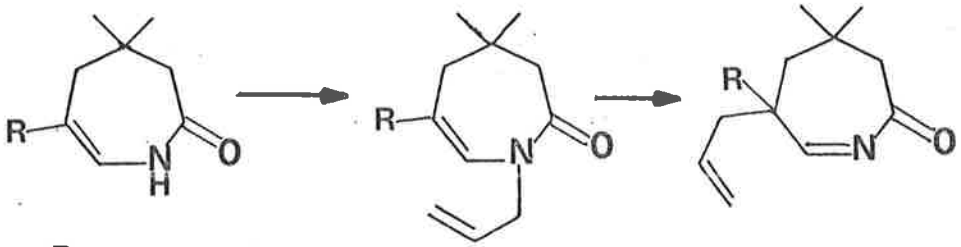


Scheme 1.07

and this was ascribed the structure (41b). The other isomer was isolated from hydroxide/methanol treatment of the hydrobromide and p.m.r. spectroscopy suggested the existance of an NH proton, and the methylene protons adjacent to the nitrogen appeared as a doublet which collapsed to a singlet upon the addition of deuterium oxide. This was ascribed the structure (41a). The i.r. spectrum of the product showed absorptions ascribable to both forms; the absorptions at 3200, 1600 cm^{-1} due to (41a) and 1700, 1645 cm^{-1} due to (41b). The two isomers are able to interconvert quite readily because of the acidic nature of the proton at C4a.

An alternative strategy to synthesise (36) is seen in Scheme 1.07 in which (14) is brominated, the product cyclised and then dehydrobrominated, but this too proved unsuccessful. The product from the bromination of (14) failed to react with a variety of bases. The p.m.r. spectrum of the product suggests it to be a mixture of two compounds which were postulated as being the two allyl ethers (42) and (43).

Although there appears to be only little information available on Claisen rearrangements involving migration of allyl groups from nitrogen, it is known that the successful ones have required either high temperatures[27,40], nitrogen quaternisation[41], the nitrogen to be part of an aromatic heterocycle[42], or the use of a Lewis acid[43-45]. A brief investigation of the possibility of alkylating the C6 position via an Aza-Claisen rearrangement was made.



(44) R:H
(19) R:Cl

(45) R:H
(46) R:Cl

With allyl bromide in the presence of sodium hydride[18], the lactams (44) and (19) gave (45) and (46) respectively, in high yield. Thermally induced rearrangement in the presence of triethylamine (to trap any HCl formed) at high temperatures, resulted in the formation of unidentified compounds. In the absence of a Lewis acid catalyst the lactam was recovered unchanged, while treatment of (45) with zinc chloride[43,44] at high temperatures resulted in the recovery of starting material, together with a small amount of unidentified material.

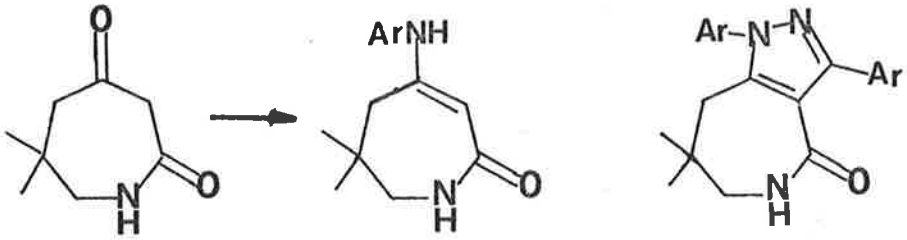
Two possible geometries have been considered for the cyclic transition state associated with the Claisen and Cope rearrangements[28,40], the four centred or chair-like arrangement (Figure 3) and the six centred or boat-like arrangement (Figure 4)

Figure 3

Figure 4

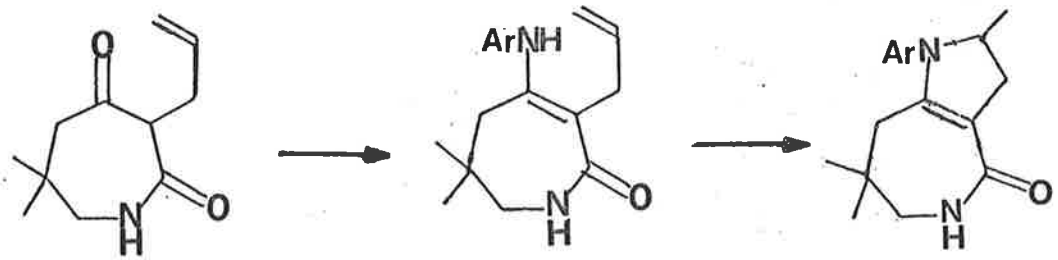
Examination of a model of the N-allyl species (45) and (46) indicates there is a large distance between the developing bond carbons, so that both possible arrangements are highly unfavourable causing severe structural strain. Thus the likelihood of the rearrangement proceeding smoothly is severely reduced.

A series of 4-arylamino caprolactams (47) have been prepared and their physiological properties tested[19], and the caprolactam (48) has been shown to be toxic (LD_{50}, 6mg/Kg)[46] and in fact is a strong convulsant[47]. These results prompted a brief investigation into the preparation



(16) (47) (48)

of caprolactams of the type (49). Condensation of an arylamine with (15), followed by thermal cyclisation should provide the desired product (49; Scheme 1.08). Although the p.m.r. spectrum of the crude condensation

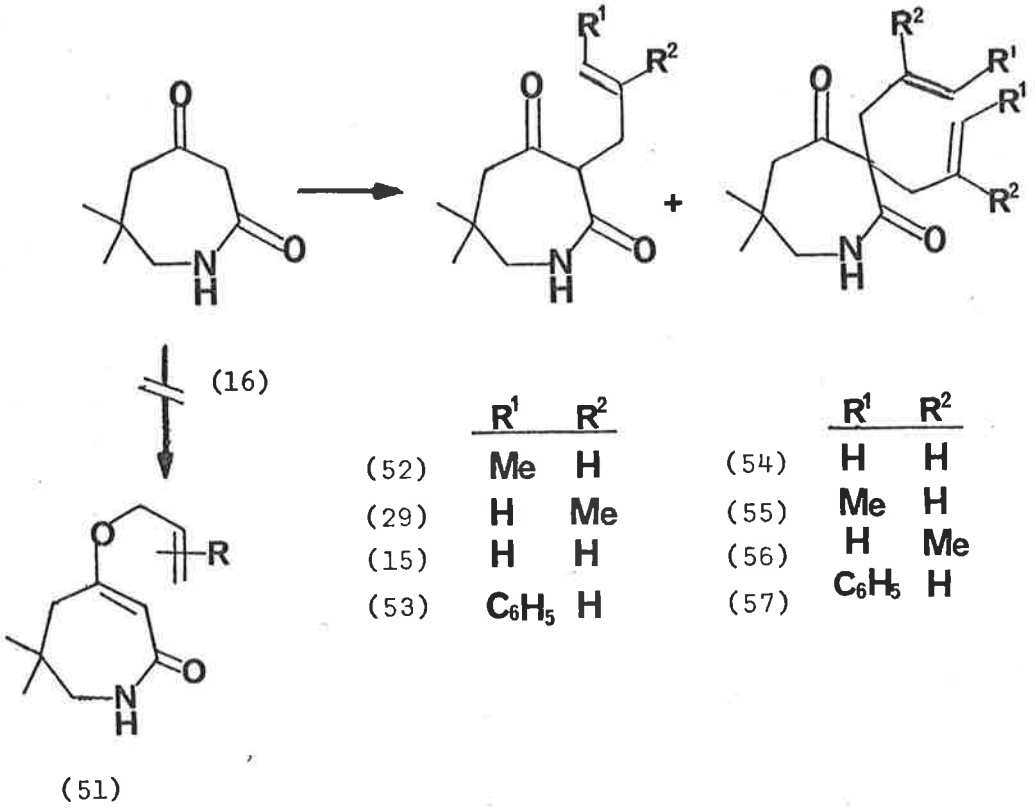


(15) (50) (49)

Scheme 1.08

product from the reaction of (15) with aniline suggested the 4-arylamino caprolactam (50) to be present, attempted isolation resulted in the recovery of (15) and it appears that hydrolysis occurs during the isolation procedure. Because of the ease of hydrolysis and the fact that the furan analogue (33) was not an extremely active compound no further work was undertaken in this area.

Because of the unusual p.m.r. spectrum of (15), an independent synthesis was undertaken to confirm that it was the required caprolactam.

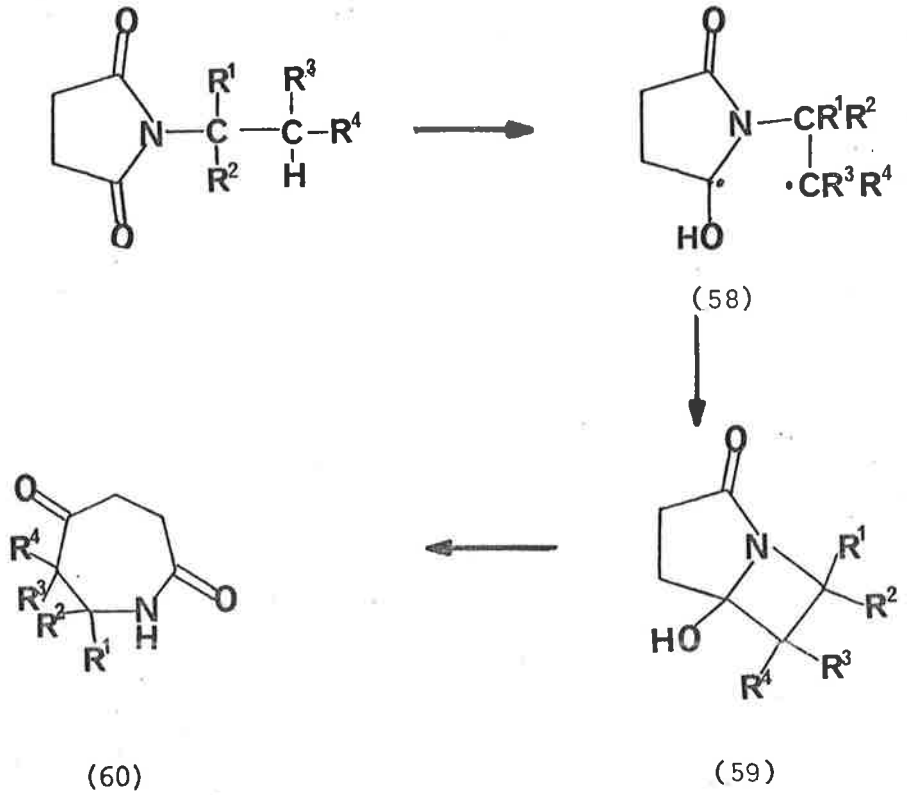


Thus, the keto caprolactam (16), derived from dimedone using known methods[19], when alkylated with allyl bromide, afforded both (15) and the 3,3-dialkylated product (54). The product (15) obtained by alkylation of (16) was identical to the compound obtained by the Claisen rearrangement of (14).

Because (54) showed convulsant activity in preliminary screenings, a series of 3,3-dialkylated caprolactams were prepared. Thus, alkylation of (16) with an allyl halide gave the 3-mono- and 3,3-dialkylated product. Examination of the p.m.r. spectrum before purification did not indicate the presence of any O-alkylated lactam (51); O-alkylation was a major pathway in previous alkylations[18]. The caprolactams (54)-(57) did not exhibit the complex p.m.r. spectra shown by the 3-mono-alkylated caprolactams. This shows that rapid ring equilibration is occurring, otherwise the methylene protons at C5 and C7 would be non-equivalent.

2.2 THE SYNTHESIS OF CAPROLACTAMS BY A PHOTOCHEMICAL REARRANGEMENT REACTION.

There has been a great deal of interest recently in the photochemistry of cyclic imides. A variety of N-arylphthalimides was found to be valuable in the synthesis of isoindoloindole and other hetocyclic systems by a photocyclisation process[48,49]. The formation of benzazepinone lactams by photochemical processes is well known[50-56] and in a number of cases the lactam results by a Norish type II process[53-55]. This Norish type II process was found to occur in a series of N-alkyl substituted succinimides[26,57] and glutarimides[26]. The two carbon ring enlargement process of the succinimides was of particular interest to us as it provides caprolactams with alkyl substituents at C6 and C7. The proposed mechanism (Norish type II) occurs via an initially formed biradical (58)[26]. This biradical can undergo an elimination reaction[26],



(58) (59) (60)

Scheme 1.09

or alternatively, cyclise to give the bicyclic system (59) followed by a retrotransannular ring opening leading to the ring enlarged product (60; Scheme 1.09)[26].

Clearly, this rearrangement reaction, besides providing caprolactams with alkyl substituents at C6 and C7, allows potentially, the preparation of caprolactams with activating groups, such as carboxy, nitrile, phenyl, or hydroxy, at C6. These substituents thus provide a means whereby modification at C6 may be easily effected. We were initially interested in obtaining caprolactams with alkyl groups at C6. The succinimides(61) required for these photorearrangement reactions are readily available[58].

(61) (a) R=H (b) R=Me (c) R=Et (d) R=nBu (62)

Although we were able to repeat the work of Kanaoka[26] and convert (61; a-c) to(62; a-c) our yields never approached those quoted. Some interesting side reactions were also observed in these photolysis reactions. When (61b) was irradiated*, besides isolating (62b), succinimide (63) was also isolated and presumably arises by a fragmentation reaction (Scheme 1.10). When (61c) was irradiated, the required caprolactam was

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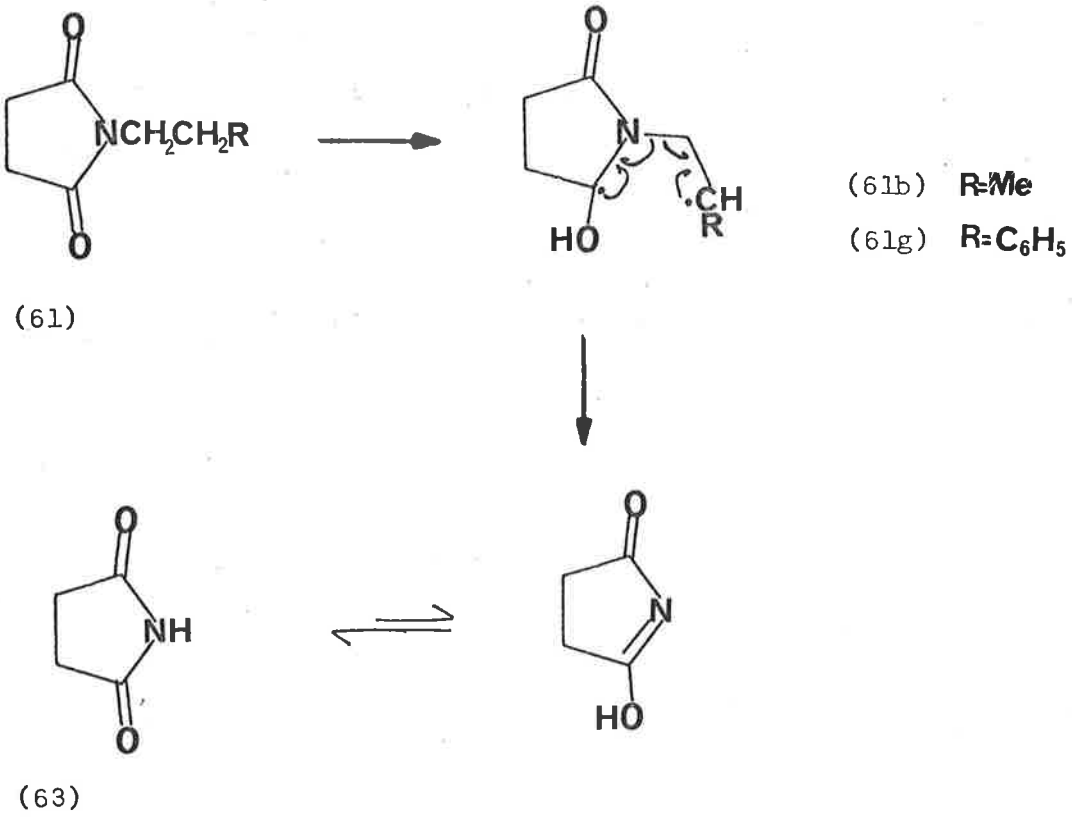
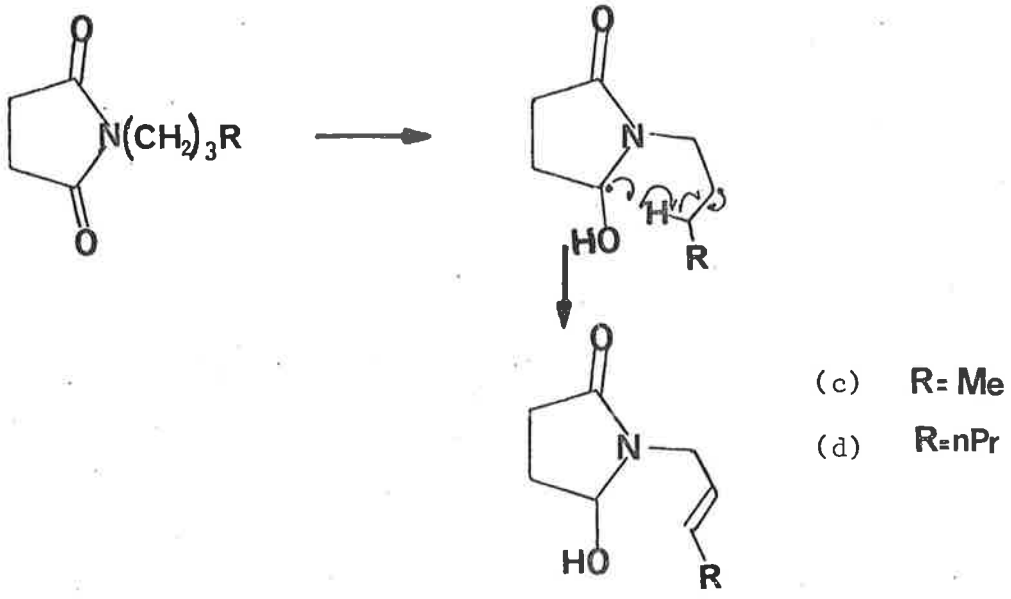
* These photolyses were performed in acetonitrile using light with a wavelength of 254nm.



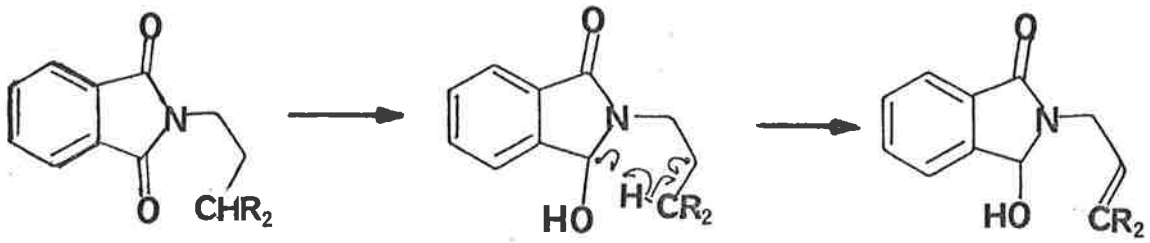
Scheme 1.10

isolated, as well as a compound which exhibited olefinic protons in the p.m.r. spectrum. Similarly, irradiation of (61d) afforded (62d) and a product possessing olefinic protons as suggested by p.m.r. spectroscopy. These dihydrosuccinimides (64) were formed in only low yields, and presumably arise by the mechanism shown in Scheme 1.11. Similar results



Scheme 1.11

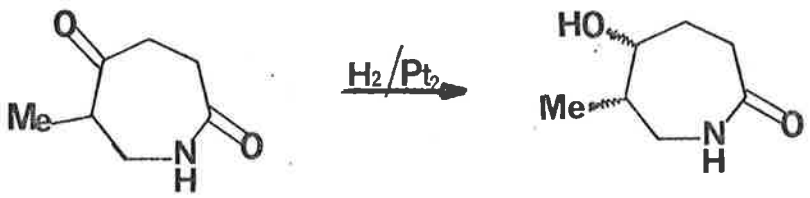
have been observed in the photocyclisation of N-alkylphthalimides in which the dihydro product results by way of a δ hydrogen abstraction (Scheme 1.12)[50]. Cyclopenteneone systems when irradiated also undergo



Scheme 1.12

intramolecular disproportionation reactions[59,60].

In an attempt to obtain molecules of greater water solubility than (62b) and therefore potentially with increased physiological activity, (62b) was reduced to 5-hydroxy-6-methylcaprolactam (65).

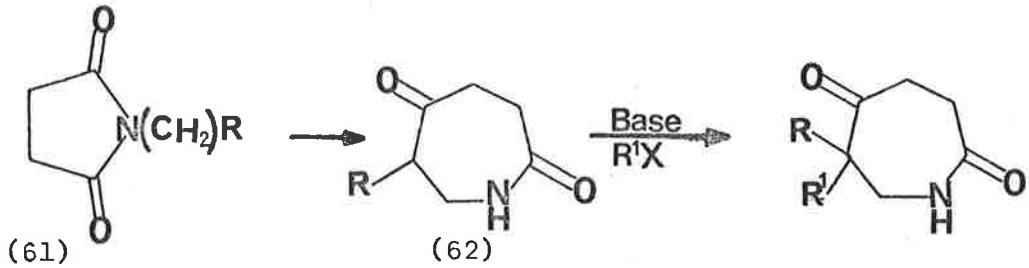


(62b) (65)

The diastereoisomers were not separated because the mixture was insufficiently active to warrant the isolation of each isomer and the determination of which isomer was the more active.

Although N-alkyl succinimides undergo photochemical ring enlargements readily, there was no suggestion in the literature that it could be logically extended to the succinimides (61; e-h). We therefore

investigated the possibility of converting succinimides (61; e-h) to caprolactams (62;e-h). The caprolactams (62e) and (62f) were desirable as they should be readily alkylated at C6 (Scheme 1.13) because of the



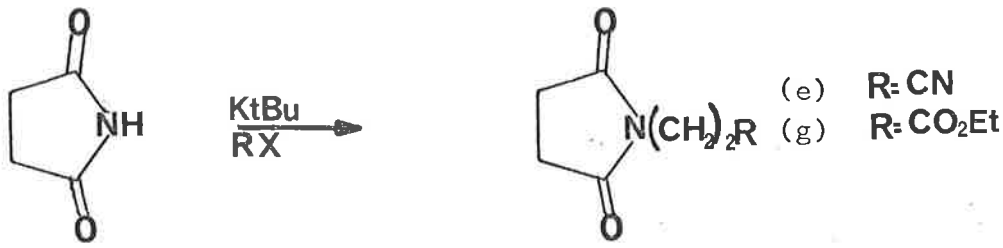
(61) (62)

(e) R=CN
(f) R=CO_2Et
(g) R=C_6H_5
(h) R=OH

R^1=alkyl

Scheme 1.13

activating ability of the nitrile and carboxy substituents. The succinimides (61; g,h) are readily available[61,62] and (61; e,f) were prepared by the alkylation of succinimide (Scheme 1.14).

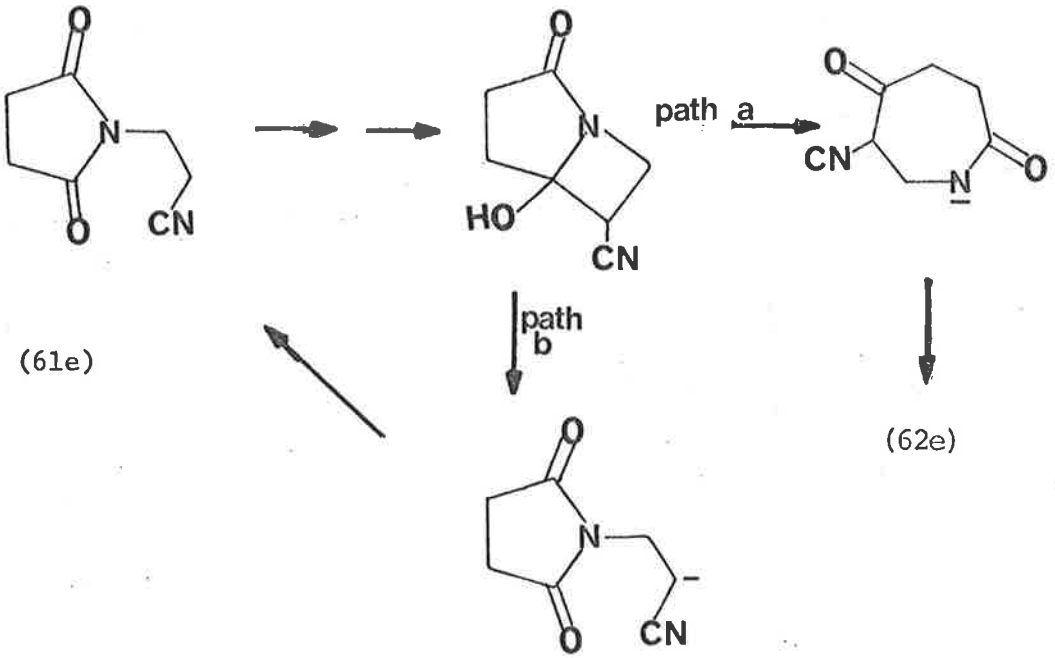


(61)

Scheme 1.14

It was disappointing that, although irradiation of (61; g,h) afforded the corresponding caprolactam (62; g,h), the yields were very low.

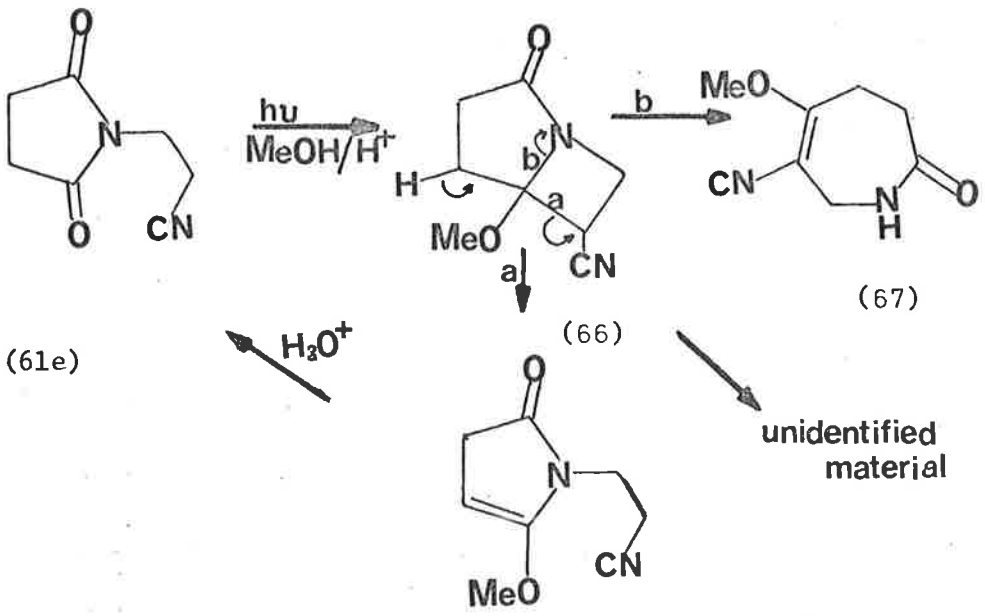
These low yields may in part, be due to alternative reaction pathways that the biradical species (58) can take. These by-products were particularly prevalent when (61g) was irradiated; besides (62g), succinimide was also isolated and presumably arises by the mechanism shown in Scheme 1.10. The photochemically induced ring enlargement of (61e) was not expected to prove difficult as there is no obvious reason why the nitrile group should interfere with the rearrangement reaction, as the earlier reactions were performed in acetonitrile. Irradiation of (61e), however, resulted in the recovery of starting material. Similarly (61f) was recovered unchanged after irradiation. It was believed initially that the problem was associated with the retrotransannular reaction which had two available pathways (Scheme 1.15). Pathway *a* leads to the



Scheme 1.15

required product but pathway *b* also leads to a stabilised anion and it appeared possible that this was the preferred pathway. This hypothesis is capable of testing. Thus, if the reaction was performed in the

presence of deuterium oxide, deuterium incorporation should be observed, but in fact this was not the case. It appeared that in fact the failure to observe the desired reaction was a solvent effect, because a report by Mariayama[63] stated that N-2-alkenyl alicyclic succinimides underwent ring enlargement by two carbons when the photolysis was performed in acidified methanol, but the same photolysis in acetonitrile gave an oxetane which reverted to starting material on heating. He also reported that irradiation of N-allyl succinimide in acetonitrile failed to give any detectable products. Therefore we investigated the photolysis of (61e) in acidified methanol. Irradiation of (61e) in acidified methanol afforded a complex mixture which had no starting material remaining as evidenced by the p.m.r. spectrum, but on attempted separation by column chromatography, starting material was recovered. Further attempts at purification by preparative t.l.c. led to the recovery of more starting material. A plausible explanation is the formation of the oxetane (66) which then converts to the starting material, a small amount of the caprolactam (67) and several other compounds which were not characterised (Scheme 1.16). Identical results were obtained when (61f) was photolysed



Scheme 1.16

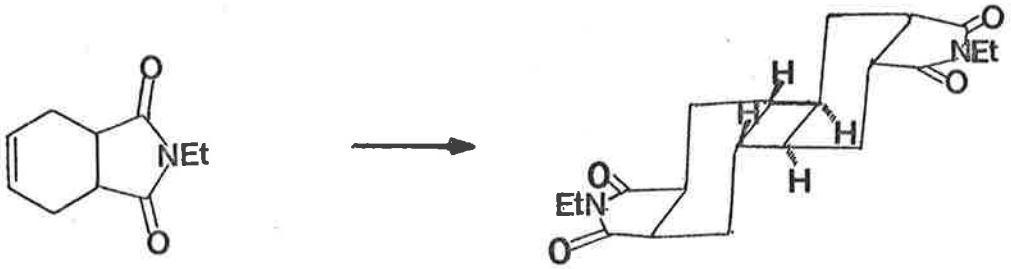
in acidified methanol. Due to the lack of success, further work in this area was abandoned.

Although there has been a great deal of photochemical research associated with phthalimides, the tetrahydro- and hexahydrophthalimides have not received similar detailed investigation. It was anticipated that the imides (68) and (69) would rearrange photochemically, in a

(68) (70)

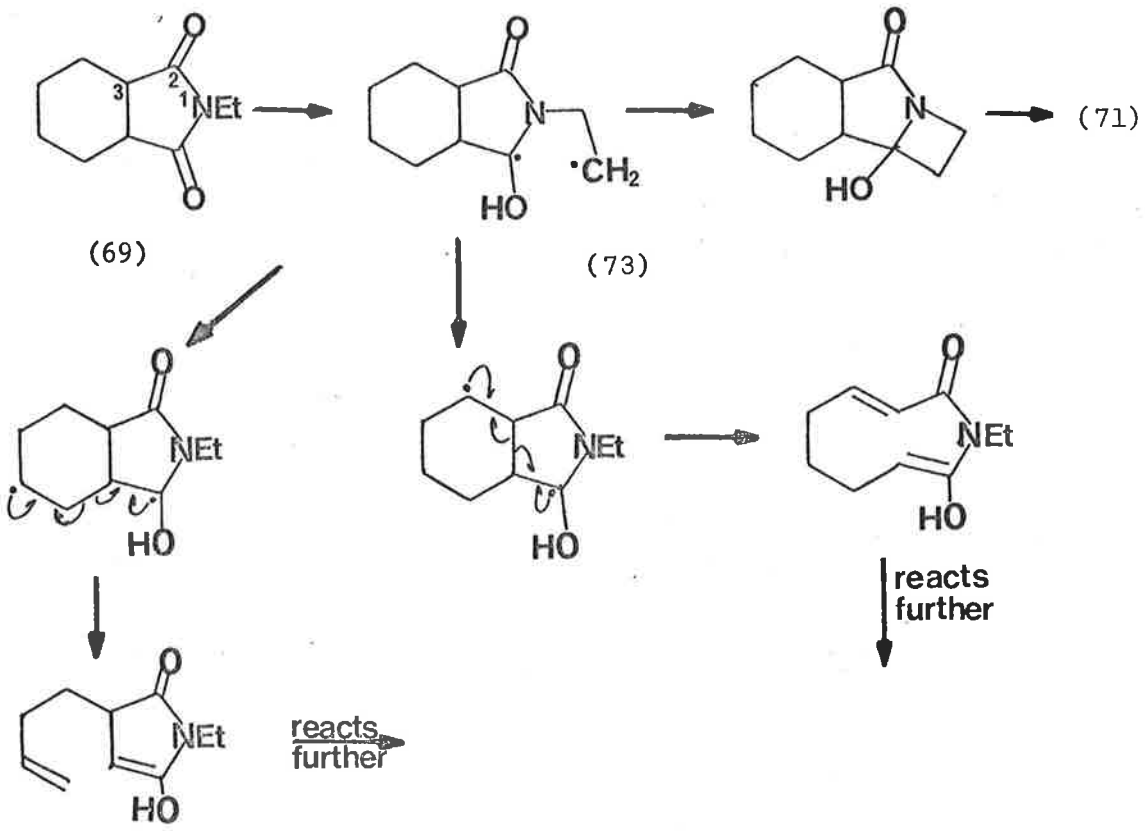
(69) (71)

similar manner to the phthalimides, and therefore yield the caprolactams (70) and (71) respectively. Unfortunately this was not the case, as irradiation of (68) resulted in the formation of a dimer, assigned the structure (72), although relative stereochemistry can not be stated with certainty. This dimerization is not totally unexpected as photodimerization processes are known to occur in both cyclic olefins and conjugated carbonyl systems[64-67]. Irradiation of (69), under varying conditions, afforded complex mixtures of products, none of which could be isolated



(68) (72)

and characterised.* Examination of the possible pathways that the initially formed biradical species (73) can take (Scheme 1.17) suggests,



Scheme 1.17

* While we were investigating these photochemical ring enlargement processes, Kanaoka[68,69] reported the successful ring enlargement of (69) and similar compounds, although in relatively poor yields. It was also reported that similar systems undergo α-cleavage of the C2-C3 bond[70,71]. Clearly, the reaction conditions determine the reaction pathway.

in fact, that a variety of products are possible. Besides the desired caprolactam being formed, hydrogen abstraction at C4 and C6 results in other biradical species which can lead to a variety of compounds.

The results obtained in the photolysis of the succinimides suggest that a detailed investigation may further elucidate some interesting mechanistic aspects of these rearrangement reactions, but that the usefulness of the reaction for the synthesis of 6- substituted caprolactams is severely limited.

PART II

SYNTHESIS

OF

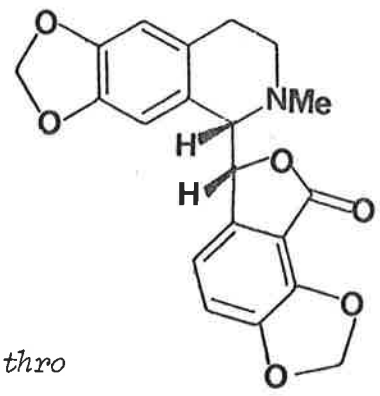
ANALOGUES

OF

BICUCULLINE

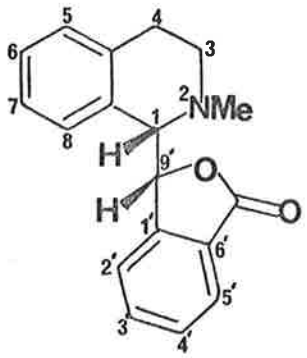
CHAPTER I : INTRODUCTION

(+)-Bicuculline (1) and other related naturally occurring alkaloids[1-3] are formally derived from the parent compound (2) by the substitution of hydroxyl or alkoxyl groups at C-6,7,8,4' and 5'. These



erythro
1S,9R

(1)



(2)

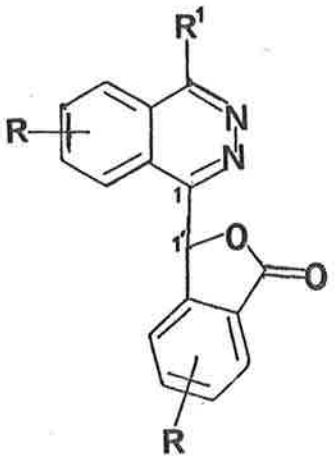
naturally occuring phthalideisoquinolines are found with either *erythro* or *threo* centres at C1 and C9'.

(+)-Bicuculline is isolated from plants of the genera *Corydalis* and *Dicentra*[4-6]. This phthalideisoquinoline shows convulsant activity in vertebrates[7-9] due to antagonism of γ-aminobutyric acid (GABA), a known synoptic inhibitory transmitter[10-13] (described in Part I). Because of the physiological effect of these alkaloids, significant interest has been shown in their application as therapeutic agents.[14]

By increasing the ability of compounds to reach the neurons in the central nervous system, more effective GABA antagonism should result.[15] Compounds possessing this ability may be those with adequate solubility in lipid phases as well as in aqueous media, the former being necessary to cross the blood brain barrier, the latter to allow transport in the body fluids. We were thus interested in the preparation of bicuculline

analogues, which may be useful therapeutics.

Since there was some indication[16] that the lactone ring was necessary for physiological activity, the phthalideisoquinoline analogues to be discussed in this Thesis concentrate on varying the isoquinoline part of the molecule. The Phthalidylphthalazines (3)*, Phthalidylcinnolinones (4) and Phthalidylborazanaphthalenes (5) were seen as providing these variations.



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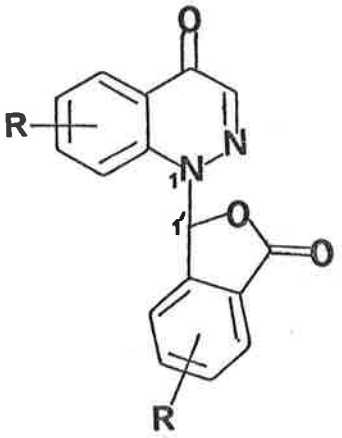

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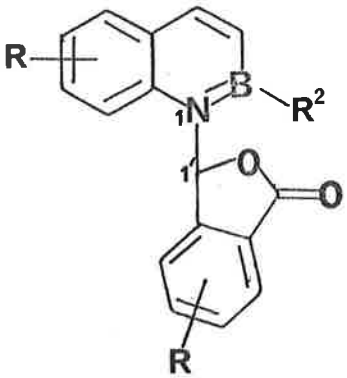

(5)

It has been shown that CNS activity is greatest with those phthalideisoquinolines with the *erythro* stereochemistry[16]. The structural types (3)-(5) would not exist as *erythro* or *threo* isomers, therefore the stereochemical restraints of the phthalideisoquinolines, and the additional oxygen, nitrogen, and boron atoms, should confer greater water solubility, a major problem in the chemical use of alkaloids†. On the

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* For simplicity the term phthalidyl will be substituted for "3-oxo-1,3-dihydroisobenzofuran-1-yl" throughout this text.

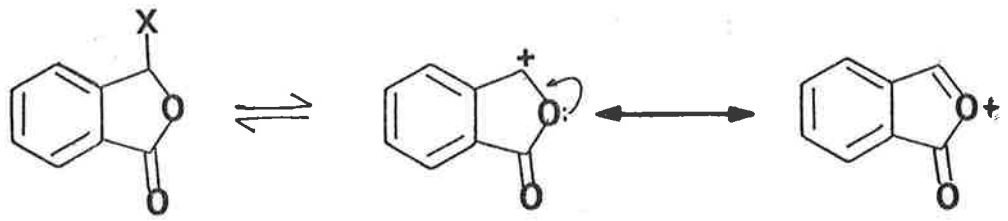
† This expectation has not actually been realised; the non basic nature of most of the analogues of type (3)-(5) has resulted in a decrease in general solubility.

other hand, the compounds (3)-(5) would be less basic than the naturally occurring compounds. Since the naturally occurring phthalideisoquinolines all have oxygenated functions at the 6,7 and 3',4',5' positions, it was clearly desirable to have these substituents present on our compounds.

Of the synthetic schemes available for the synthesis of phthalideisoquinolines, the most general involve the formation of the (1-9) bond in the key step.[16] It was obvious that a similar strategy could be used in the preparation of the compounds (3)-(5) as an examination of the literature suggests that (1-1') bond forming reactions for these systems were available. Thus the reaction of a nucleophile with an electrophilic phthalide species, or alternatively, the reaction of a nucleophilic phthalide substrate with an electrophilic species, would yield the desired products. Either pathway requires substituted phthalides, and there are a large number of suitable syntheses available for these systems. For example, 4-methoxy[18], 5-methoxy[19], 6-methoxy[20], 7-methoxy[21], 4,5-dimethoxy[22], 5,6-dimethoxy[22], 6,7-dimethoxy[22], 4,5-methylenedioxy[23], 5,6-methylenedioxy[24,25], and 6,7-methylenedioxy[26] phthalides are known. Many of these involve the acylation of a substituted benzoic acid derivative with formaldehyde and in some cases the yields are low[18,20,22,26]. Recent work making use of the metallation of a suitably substituted aromatic system affords directly, either the phthalide or the corresponding phthalaldehydic acid[27-30]. Part III of this Thesis discusses the efficient preparation of meconine, an important precursor in alkaloid synthesis, via a metallation reaction.

In order to achieve the synthetic targets, one approach necessitated an electrophilic phthalide substrate. The preparation of an electrophilic phthalide system can be achieved by radical substitution which provides 3-substituted phthalides. These compounds are powerful electro-

philes due to their having a potential leaving group at a position which is both benzylic and activated by an ester group (Scheme 2.01). Phthal-



(6) X=OH

(7) X= Br

Scheme 2.01

aldehydic acid (6) readily undergoes uncatalysed* nucleophilic substitution by a series of nucleophiles which include alcohols, amides, amines, and thiols, to afford the corresponding 3-substituted phthalide[31]. An alternative suitable electrophile was 3-bromophthalide (7), though this was not the preferred species as there is only one report of 3-bromophthalides being used successfully as alkylating agents[32].

The nucleophilic phthalidyl anion (8) can be generated reversibly by either sodium methoxide or potassium tertiary butoxide[16] and irreversibly by lithium diisopropylamide[33,34].

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* Probably general acid catalysis using the proton of phthalaldehydic acid ($K_a = 2.76 \times 10^{-5}$, 25°)[31].

(9) (8)

Base = LDA, NaMeO, or KtBuO

Phthalidylphthalazinones and Phthalidylphthalazines

Mustafa and *co-workers*[35] observed that phthalazine (10) undergoes 1,2-addition of phenylmagnesium bromide, followed by autooxidation to afford 1-phenylphthalazine (11). Similarly, other organometallic reagents have also been successfully reacted with (10) to give 1-alkylphthalazines (12)[36,37].

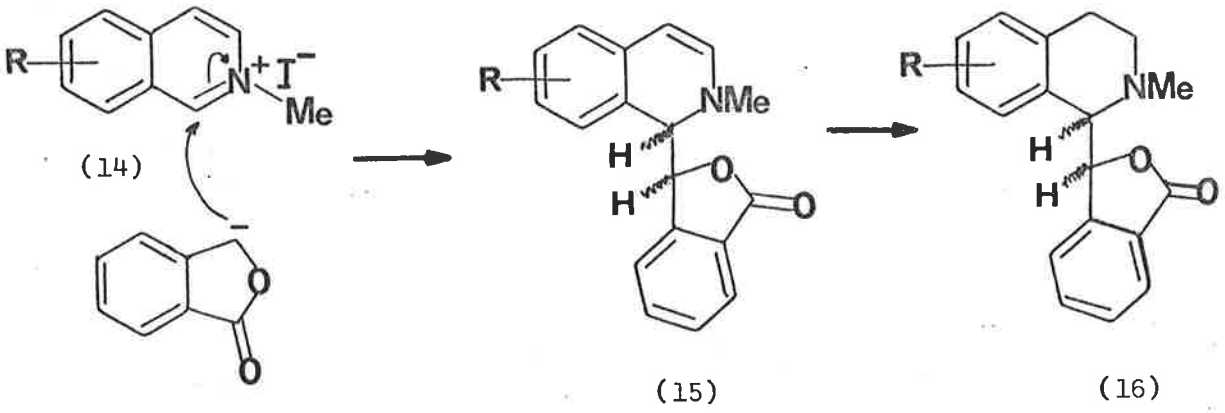
(10) **X=H** (11) **R= C_6H_5**

(13) **X=Cl** (12) **R= alkyl**

1-Chlorophthalazine (13) and substituted 1-chlorophthalazines are very reactive towards nucleophilic species and there are many examples of nucleophilic substitution by alkoxides[38-41], amines[42,43] and hydrazines[43]. The most commonly used method for the preparation of 4-substituted

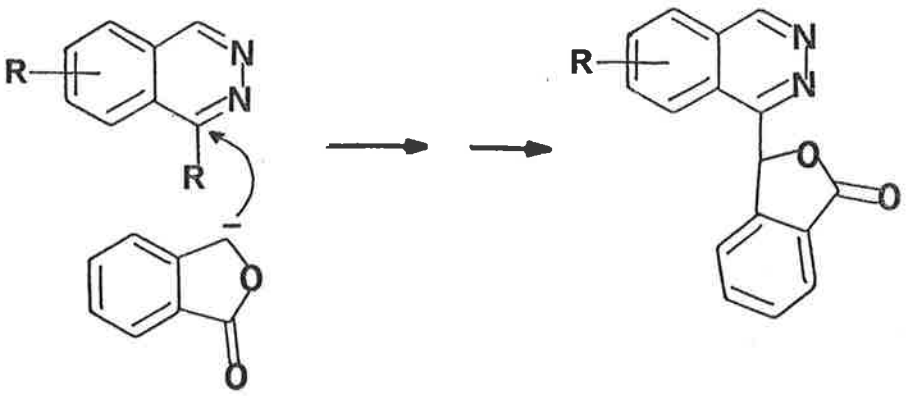
phthalazinones is to condense correctly substituted acyl benzoic acids or alkylidenephthalides with hydrazines[43].

The synthesis of phthalidylphthalazines could thus be achieved by nucleophilic substitution on a suitably substituted phthalazine, while the phthalidylphthalazinones could be prepared by treating correctly substituted phthalide species with hydrazine. The key step in the nucleophilic substitution reaction was the formation of the Cl-Cl' bond and it was clear that a phthalidyl anion was necessary. Tippett[16] has successfully effected nucleophilic attack of the phthalidyl anion (8) on the isoquinoline methiodide (14) to yield a diastereoisomeric mixture of the dihydroisoquinolines (15) which were catalytically hydrogenated to give (16; Scheme 2.02).



Scheme 2.02

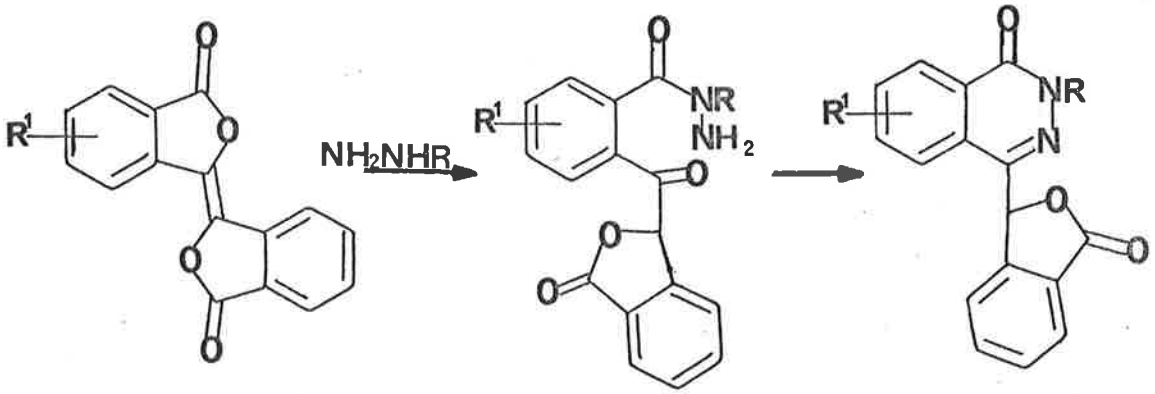
It was envisaged that similar nucleophilic substitution on either substituted phthalazines (Scheme 2.03) should provide the required phthalidylphthalazines (17).



(17)

Scheme 2.03

Alternatively, the reaction between suitably substituted biphthalides (18) and either hydrazine or alkyl hydrazine would yield the corresponding 4-phthalidylphthalazinone (19) (Scheme 2.04). This



(18)

(19)

R=H or alkyl

Scheme 2.04

also provides a method for obtaining 2-alkylated products[43], due to the greater nucleophilicity of the secondary nitrogen atom in the reacting

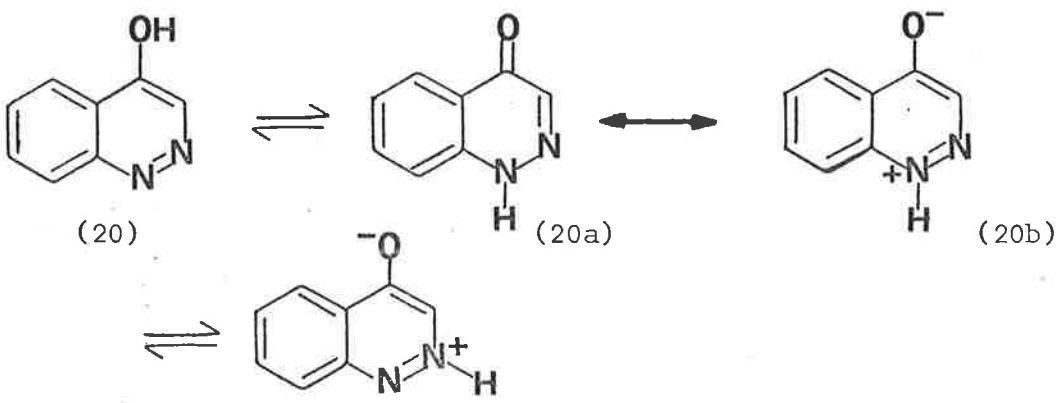
hydrazine[44]. The non-alkylated phthalidylphthalazinones could, in principle, be reduced to the corresponding phthalidylphthalazine.

Phthalidylcinnolinones

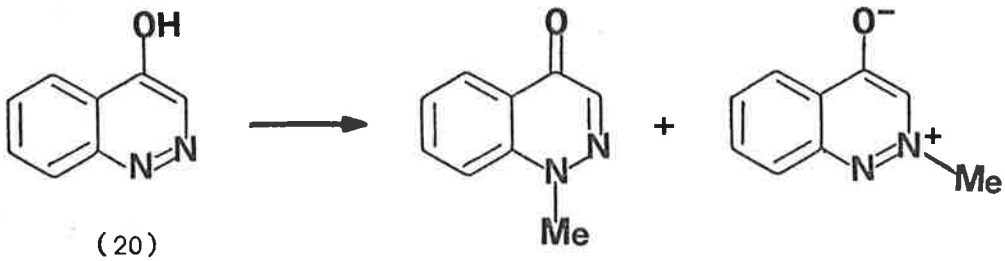
Although only a few alkyl or aryl cinnolines have been examined for pharmacological activity, some are claimed to have therapeutic benefits to ulcer sufferers as well as being anti inflammatory agents. In addition, they have shown activity as appetite inhibitors and central nervous system stimulants[43].

The formation of a C1-C1' bond between the cinnolinone (20) and an electrophilic phthalide appeared an attractive approach, firstly because (20) should be readily alkylated at N1 and secondly because either (6) or (7) is readily substituted at C3.

Under basic conditions, generation of an amide anion results in N-alkylated products[45-47], whereas the alkylation of the corresponding silver salt results in O-alkylated products[48,49]. 4-Hydroxycinnoline (20), the weakest acid (pKa 9.27 in water) of the hydroxycinnolines[50], exists principally in the amide form (20a) both in the solid state and in solution, the form (20a)↔(20b) with hydrogen at N1 being preferred to the tautomeric structure (20c) with hydrogen at N2[51]. Treatment of (20) with a strong base should yield an amide anion which should alkylate at N1.



The methylation of 4-hydroxycinnoline (and some substituted derivatives) with dimethylsulfate, diazomethane, or methyl iodide, gives principally the anhydro base 2-methyl-4-hydroxycinnoline (21) together with a small amount of 1-methyl-4-cinnolinone (22)[52-54]. A variety of

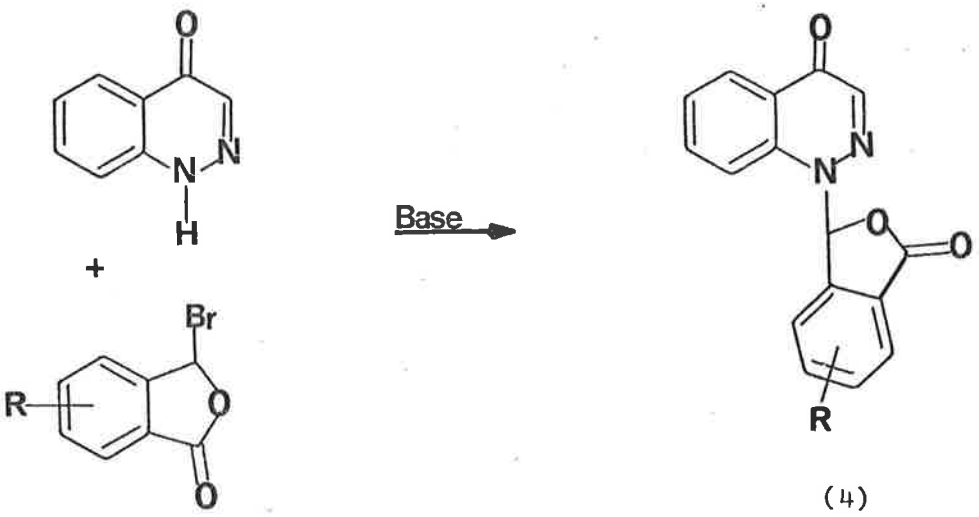


(20) (22) (21)

other alkylating agents including ethyl iodide, isopropyl bromide and benzyl chloride also lead predominantly to the N2-alkylated products[53,54]. Several examples have shown that C3 substituted hydroxycinnolines form 1-alkyl derivatives[53,55,56], whereas 4-hydroxycinnolines with a substituent at C8 alkylate predominantly at N2[56,57], suggesting that the process is controlled mainly by steric rather than electronic factors[53,56].

In contrast with these results, cyanoethylation of (20) with acrylonitrile in the presence of Triton B gives exclusively 1-cyanoethyl-4-cinnolinone and this result has been attributed to the base catalysed cyanoethylation which leads to the most stable product[53]. Acetylation of (20) using acetic anhydride occurs exclusively at the 1-position[58].

Since (6) is so reactive towards nucleophiles, it was anticipated that (6) would react in a similar manner to acetic anhydride with 4-hydroxycinnoline and form the N1-alkylated product. 3-Bromophthalides have not been used extensively as alkylating agents, due possibly to their high reactivity, and it was felt that the alkylation reaction outlined in Scheme 2.05 was a less likely approach to compounds of type (4).



(4)

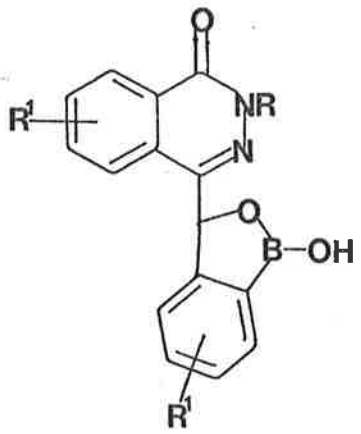
Scheme 2.05

Phthalidylborazanaphthalenes

Boron analogues of amino acids have shown in preliminary animal tests, beneficial effects for arthritis, high blood cholesterol levels and certain cancers[17]. Some derivatives of phenylboronic acid have been tested for their action upon bacteria; however only nitro and bromo substituted boronic acids showed any bacteriostatic action[59]. Dewar has studied the water soluble derivatives of 10,9-borazaphenanthracenes and 2,1-borazanaphthalenes as potential agents for neutron capture therapy of cancer[60]. The preliminary tests showed little or no anti-bacterial activity and the use of these compounds as possible agents for neutron capture therapy was disappointing. The compounds were in fact very toxic and were selectively concentrated in the brain of cancerous mice rather than in brain tumors[60]. Similar compounds modelled more closely on natural products may be effective. The field of borazaromatic chemistry is, however, only a little over 20 years old and there has been only a limited amount of screening of these compounds for biochemical activity.[61]

The phthalidylborazanaphthalenes (5) appeared attractive target compounds for screening as they retained the γ-lactone ring necessary for CNS activity[16] and possessed the 2,1-borazanapthalene ring which exhibited very toxic behaviour in mice[60].

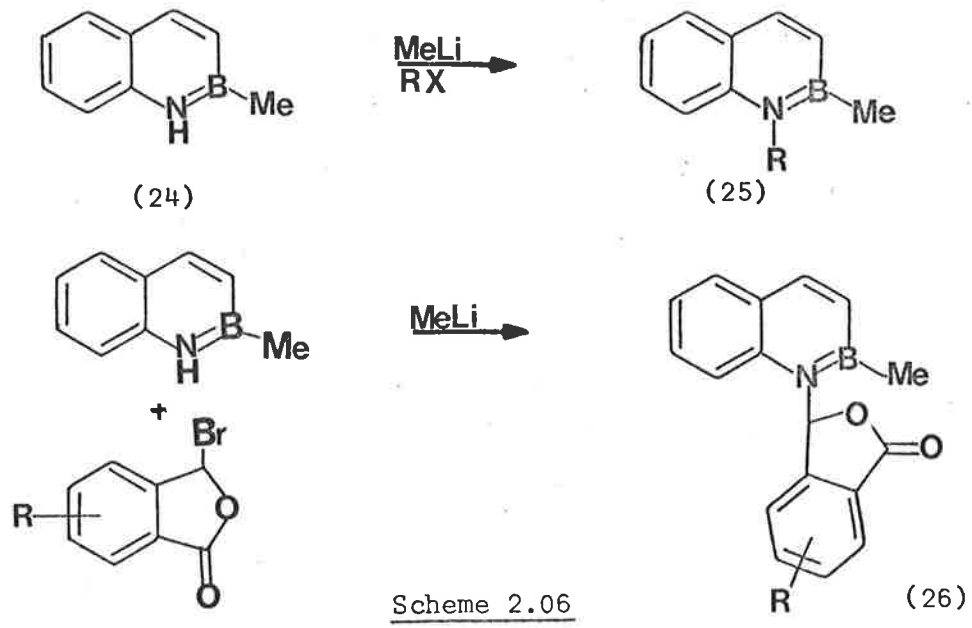
Alternative bicuculline analogues containing boron to be considered include (23). This retains the phthalazinone ring of earlier compounds which were shown to have limited pharmacalogical activity, but



(23)

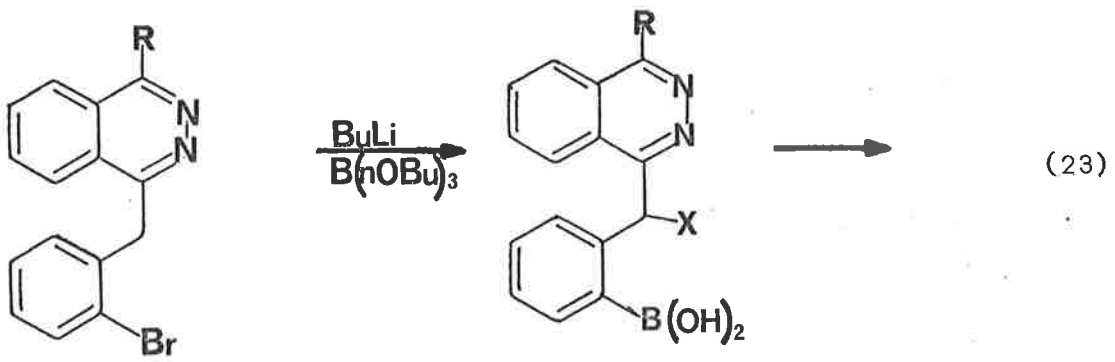
introduces an isoelectronic BOH group for the lactone carbonyl, a change which was expected to increase the water solubility, thus increasing the activity.

Clearly, the most obvious method for assembling compounds of the type (5) was by the formation of the N-Cl' bond in a method similar to the preparation of the phthalidylcinnolinones. This seemed an attractive and promising pathway as 2-methyl-2,1-borazanaphthalene (24) is readily alkylated[60] to yield (25; Scheme 2.06). Thus, the N-lithio derivative of (24) on reaction with 3-bromophthalides should afford (26).



Scheme 2.06

Lastly, it was anticipated that transmetallation of (27) with butyl lithium, followed by the reaction with tributyl borate, or similar electrophiles, would yield (28). Bromination of (28) would yield (29) which on hydrolysis would result in the formation of compounds of the type (23; Scheme 2.07).



(28) X=H

(29) X=Br

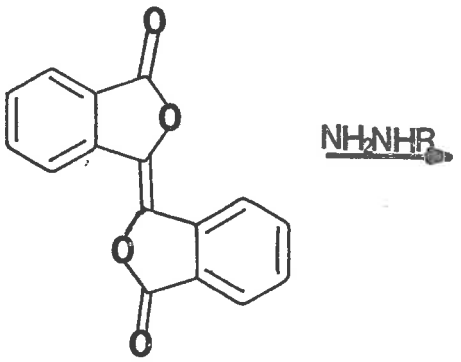
Scheme 2.07

CHAPTER 2

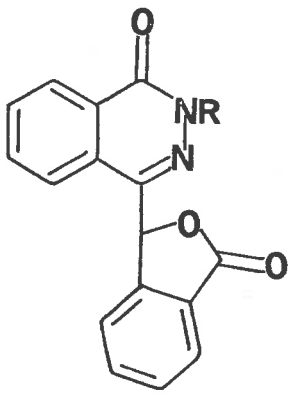
RESULTS AND DISCUSSION

2.1 SYNTHESIS OF PHTHALIDYLPHTHALAZINONES AND PHTHALIDYLPHTHALAZINES.

The synthesis of phthalidylphthalazinones (19) depends on the successful condensation reaction of hydrazine with biphthalide (30); the synthesis could then be logically extended to the oxygenated derivatives. Accordingly, the reaction between hydrazine and (30) was investigated. The treatment of biphthalide[62] with hydrazine in refluxing



(30)

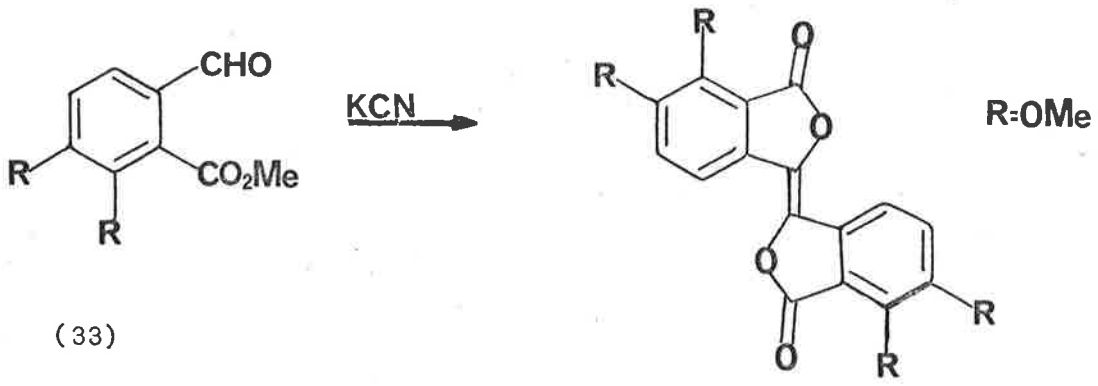


(31) R=H

(32) R=Me

ethanol afforded (31) in high yield and treatment of (30) with methylhydrazine gave the expected 2-methyl derivative (32) was obtained in high yield.

Thus, to extend this series of phthalidylphthalazinones, substituted biphthalides were required. However, only a limited number of procedures have been reported for preparing biphthalides. For example, the fusion of phthalic anhydride and substituted phthalides in the presence of sodium acetate affords biphthalides in low yields[63]. The reaction of 3-alkoxyphthalides with potassium cyanide has also been used to prepare biphthalides[64,65]. Chatterjea *et al.*[66] has prepared biphthalides by the treatment of methyl-2-formylbenzoates with potassium cyanide, for example (33) was converted to (34, Scheme 2.08).



(33) (34)

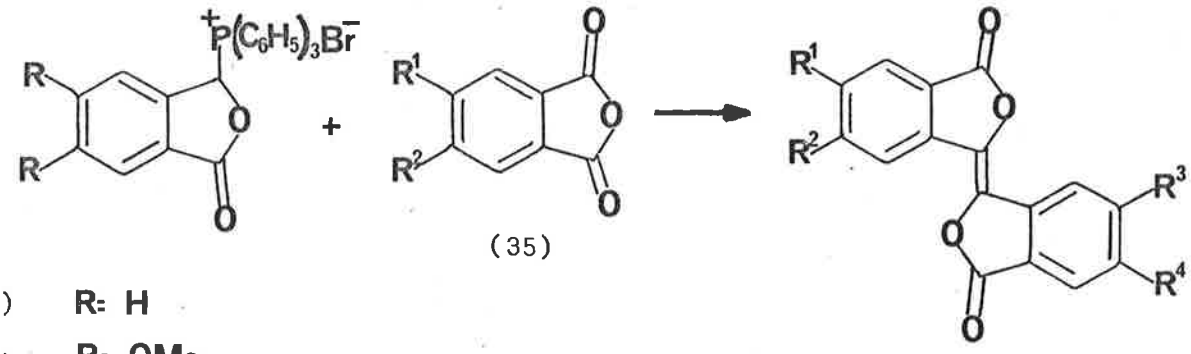
Scheme 2.08

The most successful approach to biphthalide is by the treatment of phthalic anhydride with triethyl phosphite.[62] The generality of these methods, however, has not been investigated.

Because the preparation of (30) is best achieved using the method of Ramirez[62] the synthesis of oxygenated biphthalides was first investigated using this procedure. When 4,5-dimethoxyphthalic anhydride (35b) was treated with triethyl phosphite either starting material or polymeric material was obtained depending on the conditions employed. This was in indirect agreement with the work of Ramirez[62] who postulated that electron withdrawing groups would assist in the biphthalide formation. Here, the dimethoxy groups, because of their electron donating ability, hindered the formation of the biphthalide. Because the other methods used in the preparation of biphthalides were not efficient, a new general synthetic method was investigated.

Since aromatic anhydrides are known to undergo Wittig reactions with stabilised ylids[67,68] a logical approach to substituted biphthalides involves the reaction of phthalic anhydrides (35) with phosphonium salts

of the form (36; Scheme 2.09). This methodology allows the synthesis of both symmetrical and unsymmetrical biphthalides.



(35)

(36) R= H

(37) R= OMe

	R^1	R^2
(35a)	H	H
(35b)	OMe	OMe
(35c)	NO_2	H
(35d)	Me	H

	R^1	R^2	R^3	R^4
(38)	H	H	OMe	OMe
(39)	H	H	H	NO_2
(40a)	H	H	H	Me
(40b)	H	H	Me	H
(41)	OMe	OMe	OMe	OMe

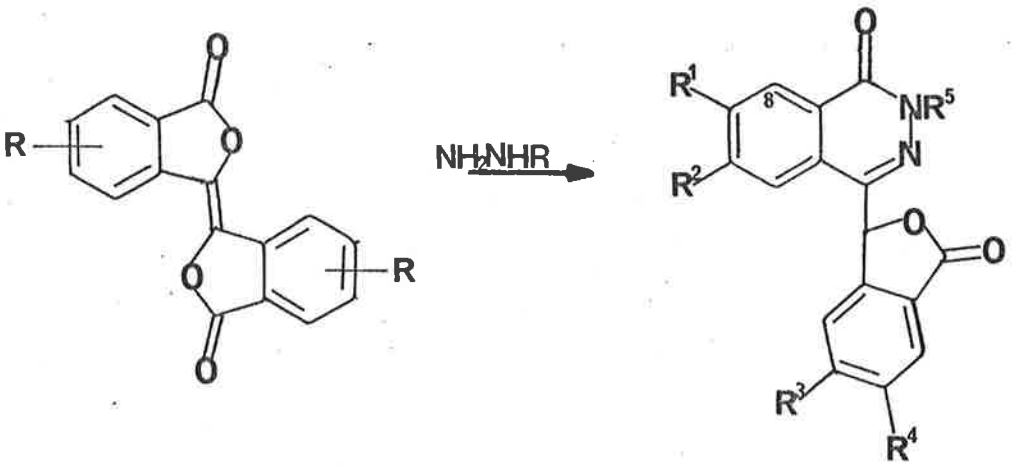
Scheme 2.09

The phosphonium salts (36)[69] and (37) are readily available by treatment of either the corresponding phthalaldehydic acid or 3-bromophthalide with triphenylphosphine. The phosphonium salt (36) is known to undergo Wittig reactions with aromatic aldehydes[69]. The reaction between the phosphorane and the anhydride proceeded smoothly to yield the required biphthalides (38)-(41).

The preparation of the biphthalides was found to be general: stirring a solution of molar equivalents of the anhydride, phosphonium bromide and triethylamine in dichloromethane at room temperature, under nitrogen, for between 12-48 hours afforded the corresponding biphthalide

(38)-(41) in yields between 70-90%. The formation of (41) in high yields required an additional 12 hours at reflux temperature. These products all had intense yellow colours and in most cases had only limited solubility in a variety of organic solvents. The melting points of the biphthalides were sharp, probably indicating exclusive formation of one isomer, that being the E isomer. While preparing benzylidenephthalides, using (36), Howe[69] found a 80-90% predominance of the E isomer. Further evidence that the conformation of the biphthalide was E in each case was obtained from the infrared spectrum. Becker[65] has confirmed that E-biphthalide (yellow) exhibits only one carbonyl absorption at 1780cm^{-1}, while the colourless biphthalide, with Z configuration, shows two carbonyl absorptions at 1720 and 1740cm^{-1}. The biphthalides (38)-(41) besides being an intense yellow colour, all had absorptions at 1780cm^{-1}. 4-Methylphthalic anhydride (35d) formed two isomers, as evidenced by the formation of four products when (40) was treated with hydrazine. The two isomers of (40) could not be separated by fractional crystallisation or chromatography and showed only one peak by HPLC and one spot by t.l.c. The reaction between 4-nitrophthalic anhydride (35c) and (36) yielded a single product (39). This is clearly expected as the carbonyl *para* to the nitro group is the most electrophilic. The product (39) was assigned the E configuration by infrared spectroscopy and was the opposite isomer to that obtained by Graebe and Guye[63].

The unsymmetrical biphthalides (38)-(41) could, in principle, form two products on treatment with hydrazine, but the substituents should control the position of nucleophilic attack because of their electron withdrawing and donating ability and only single products should result. Only (40) is likely to give a mixture of isomers, firstly because there are two non separable reacting isomers and secondly, the methyl group is unlikely to be sufficiently electron donating to render one of the carbonyl carbons substantially less electrophilic than the other; that is, there will be



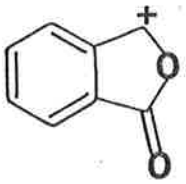
	R^1	R^2	R^3	R^4	R^5
(42)	OMe	OMe	OMe	OMe	H
(43)	OMe	OMe	OMe	OMe	Me
(63)	OMe	OMe	OMe	OMe	Et
(44)	H	H	OMe	OMe	H
(45)	H	H	OMe	OMe	Me
(46)[a]	———		Me	———	H
(47)[a]	———		Me	———	Me
(48)	NO_2	H	H	H	Me
(60)	H	H	H	H	Et

a: These were isolated as an inseparable mixture of four isomers with a methyl group at R^1 (46a), R^2 (46b), R^3 (46c) and R^4 (46d).

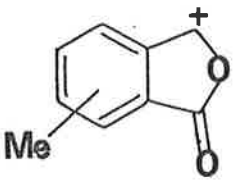
b: These were isolated as an inseparable mixture of four isomers with a methyl group at R^1, R^2, R^3, and R^4.

no preferential site of nucleophilic attack. In most cases, the reaction of the biphthalides with either hydrazine or methyl hydrazine afforded good yields of the desired phthalidylphthalazinones.

Due to the low solubility of (41), excess hydrazine was required to facilitate the formation of (42) and (43) in high yields. As expected, (38), on treatment with hydrazine and methyl hydrazine afforded (44) and (45) respectively. On treating (40) with hydrazine, four isomers were obtained as evidenced by the appearance of four aromatic methyl signals in the region of δ 2.6 in the p.m.r. spectrum. These isomers could not be separated, but if they could be separated, at least the isomers (46a) and (46b) could be distinguished from the other two isomers by examination of the mass spectra. The mass spectra of the bicuculline analogues which we have prepared, show a diagnostic base peak attributable to the phthalide portion of the molecule. Thus, the isomers (46a) and (46b) will exhibit a base peak at 133 corresponding to (49), whereas the isomers (46c) and (46d) will exhibit a base peak at 147, corresponding to (50). The p.m.r.



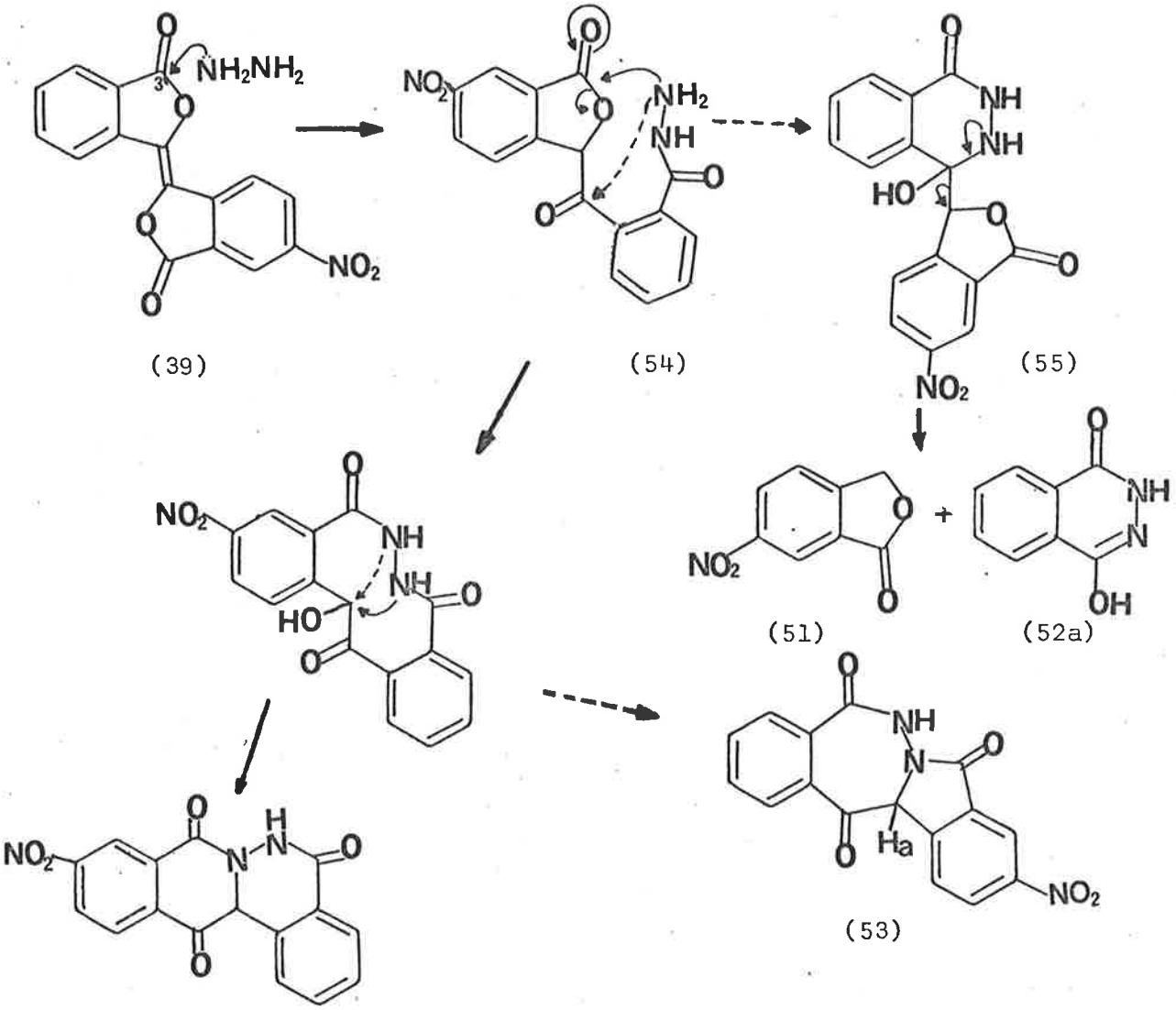
(49)



(50)

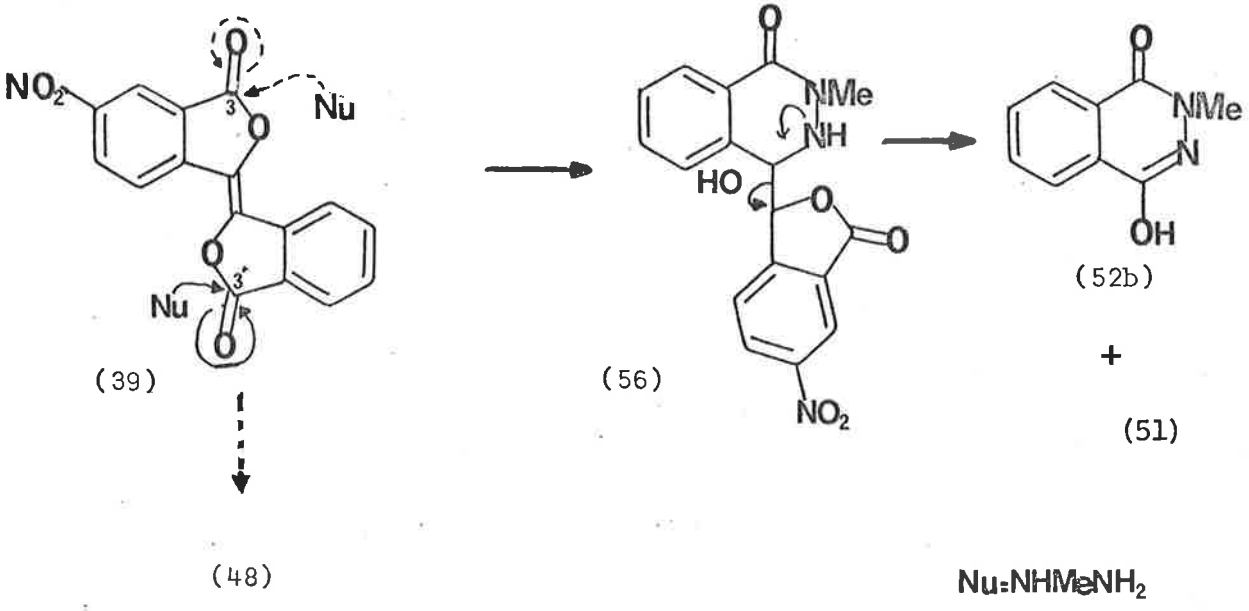
spectra may be used to further distinguish the isomers. Treatment of (40) with methyl hydrazine afforded four compounds as evidenced by the appearance of four N-methyl signals at about δ 3.8 in the p.m.r. spectrum. These isomers could not be separated by conventional methods such as chromatography or fractional crystallisation.

The reaction of hydrazine with (39) resulted in the formation of 6-nitrophthalide (51) and 1,4-Phthalazinedione (52a) and a product which is suggested to be the ketodiamide (53). A possible mechanism for the



(39) (54) (55) (51) (52a) (53)

Scheme 2.10



(39) (56) (52b) + (51)

(48)

Nu:NHMeNH2

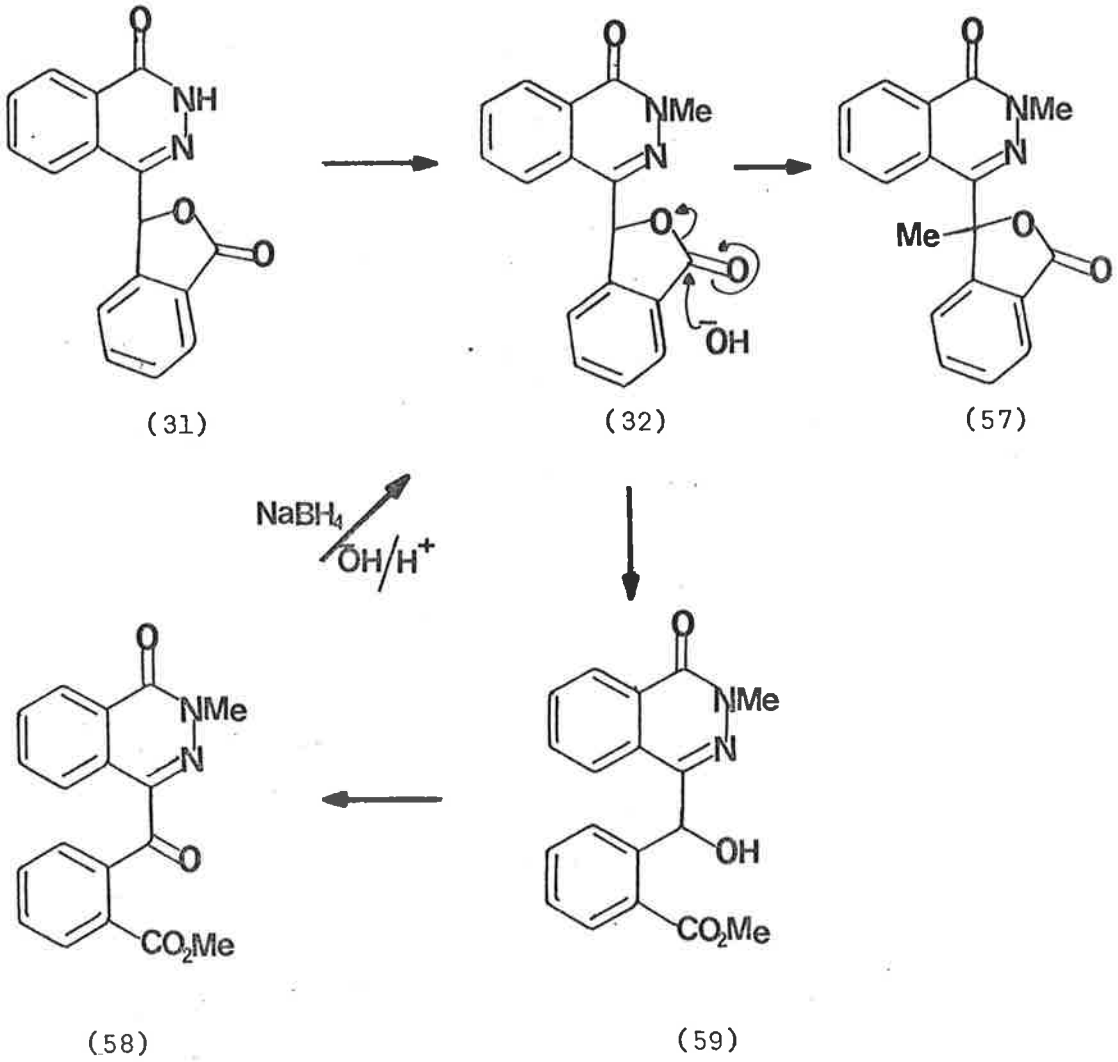
Scheme 2.11

formation of these compounds is shown in Scheme 2.10. If initial nucleophilic attack occurs at C3' to give (54), the free amino group then has two possible carbonyl carbons for reaction. Reaction at the ketone leads to the formation of the intermediate (55) which affords (52a) and 6-nitrophthalide. The latter is formed in preference to water due to the stability of the transient 6-nitrophthalide anion. Alternatively, the free amino group can react at the lactone carbonyl group. Subsequent ring closure affords the ketodiamide (53; Scheme 2.10). The product was assigned the structure (53) on the basis of the infrared spectrum which shows absorptions at 1720, 1690 and 1670cm^{-1}. This is consistent with the presence of five and seven membered lactams rather than two six membered lactams which would have no absorptions greater than 1700cm^{-1}.[70] The p.m.r. spectrum of (53) showed a one proton singlet at δ 4.8 and was ascribed to Ha. This is consistent with a calculated chemical shift of δ 5.3 using Schoolerys chemical shift data[71]. If attack had occurred at C3, the desired product would result, but there was no evidence for the formation of this product.

The reaction of methyl hydrazine with (39) afforded (48), (51) and 2-methyl-1,4-phthalazinedione (52b). A plausible explanation is outlined in Scheme 2.11. Nucleophilic attack at C3 leads to (48) whose p.m.r. spectrum exhibits a doublet, J = 1Hz, at δ 8.9, ascribed to H8. This structure is confirmed by the mass spectrum which shows a base peak m/e 133, corresponding to (49). Alternatively, attack at C3' leads to an intermediate (56) which cleaves to give (51) and (52b).

Phthalazinones can be readily N-methylated using base and methyl iodide[72-74], a procedure which provides an alternative method to prepare 2-methylated phthalidylphthalazinones. When (31) was treated with potassium carbonate and methyl iodide in acetone, without the exclusion of water and air, two products were isolated which were identified as (57) and (58), the latter arising via aerial oxidation of the hydroxy ester (59). Under

anhydrous anaerobic conditions, the only methylation products of (31) were (32) and (57), the former being capable of C-alkylation to give (57). Sodium borohydride reduction of (58) followed by hydrolysis and lactonisation yielded (32; Scheme 2.12). Methylation of (44) using



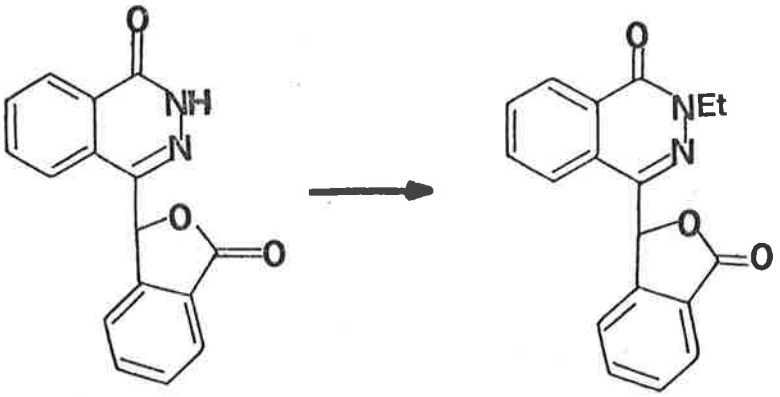
(31) (32) (57)

(58) (59)

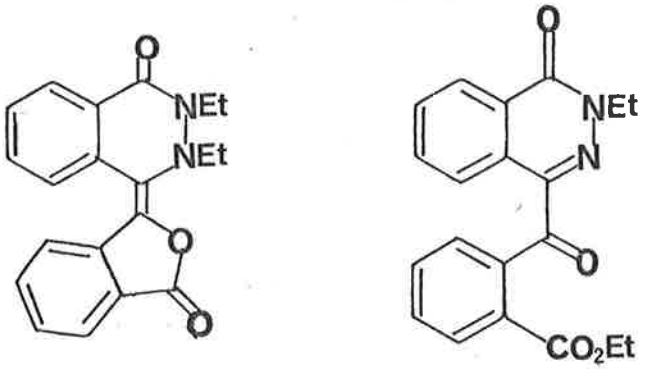
Scheme 2.12

potassium carbonate and methyl iodide in acetone afforded (45).

Alkylation of (31) at room temperature with ethyl iodide and potassium carbonate in acetone afforded 2-ethyl-4-phthalidylphthalazinone (60) but more vigorous conditions afforded a mixture of products which could not be separated using preparative t.l.c. Examination of the p.m.r.



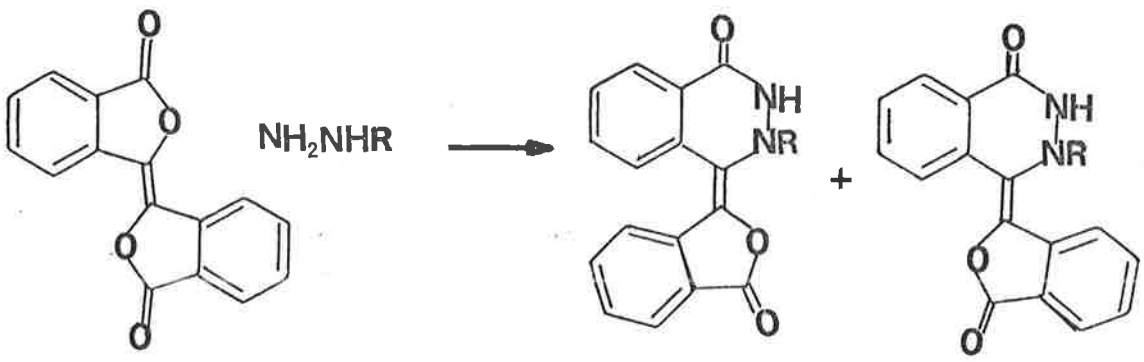
(60)



(61) (62)

spectrum of the reaction products showed no obvious Cl' alkylation products, presumably due to the bulkiness of the ethyl group, but compounds (60), (61) and (62) were apparently present. Alkylation of (42) with potassium carbonate and ethyl iodide at high temperatures afforded (63) in high yield without any serious contamination by other products.

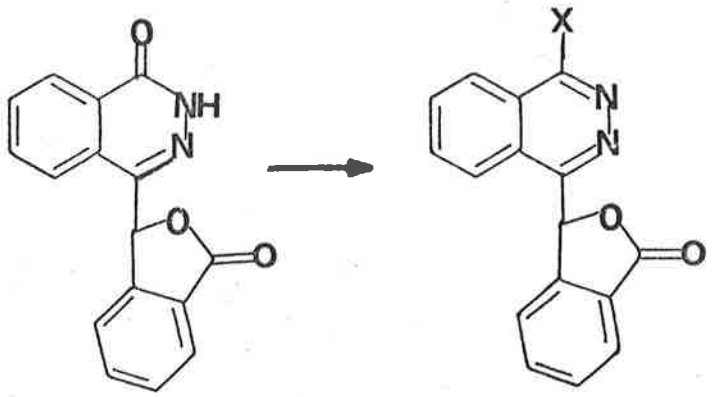
$R=C_6H_5$



(30) (64a) (64b)

Whereas alkylhydrazines react through the secondary nitrogen, arylhydrazines[75] react through the primary nitrogen so that phenylhydrazine on reaction with biphthalide afforded the isomers (64a) and (64b). No attempt was made to separate these isomers as their physiological activity was minimal. These products were consistent with the reaction proceeding at the primary nitrogen as they were a yellow colour, similar to the biphthalides.

For the purpose of biological screening and due to the low solubility of the phthalidylphthalazinones, the preparation of phthalidylphthalazines also warranted investigation. The most direct route to these compounds appeared to be via the 4-chlorophthalidylphthalazine (66) which was expected to be easily reduced to (67).



(31)

(65) X=OPOCl$_2$

(66) X=Cl

(67) X=H

(68) X=OMe

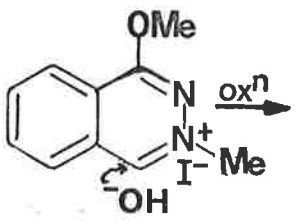
A variety of attempts to react (31) with phosphorus oxychloride resulted only in the recovery of starting material. The isolation of (68) in one experiment suggested (66) had been formed, although (68) may arise from the reaction of methanol with the intermediate (65). It was possible that (66) was too reactive to survive the work up conditions, so a reduction was attempted on the crude reaction product but only polymeric material was obtained. The inability to prepare (66) was surprising but Chimici[76] could not prepare high yields of the chloro intermediate of a hydroxypyridazine[76].

A logical alternative approach to (67) involved the nucleophilic substitution by the phthalidyl anion (8) on 1-chlorophthalazine as described in the introduction. The phthalidyl anion was generated with potassium t-butoxide, but the reaction with (13) proved unsuccessful and yielded only polymeric material. Because of the low concentration of the anion when generated with potassium t-butoxide, lithium isopropyl cyclohexylamide was used to provide a high concentration of the anion[33,34] but on reaction with (13), only polymeric material and some starting 1-chlorophthalazine were obtained. The phthalazines (69)-(71) failed to

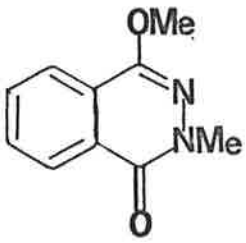
(69) R=H

(70) R=Me

(13)



(71)

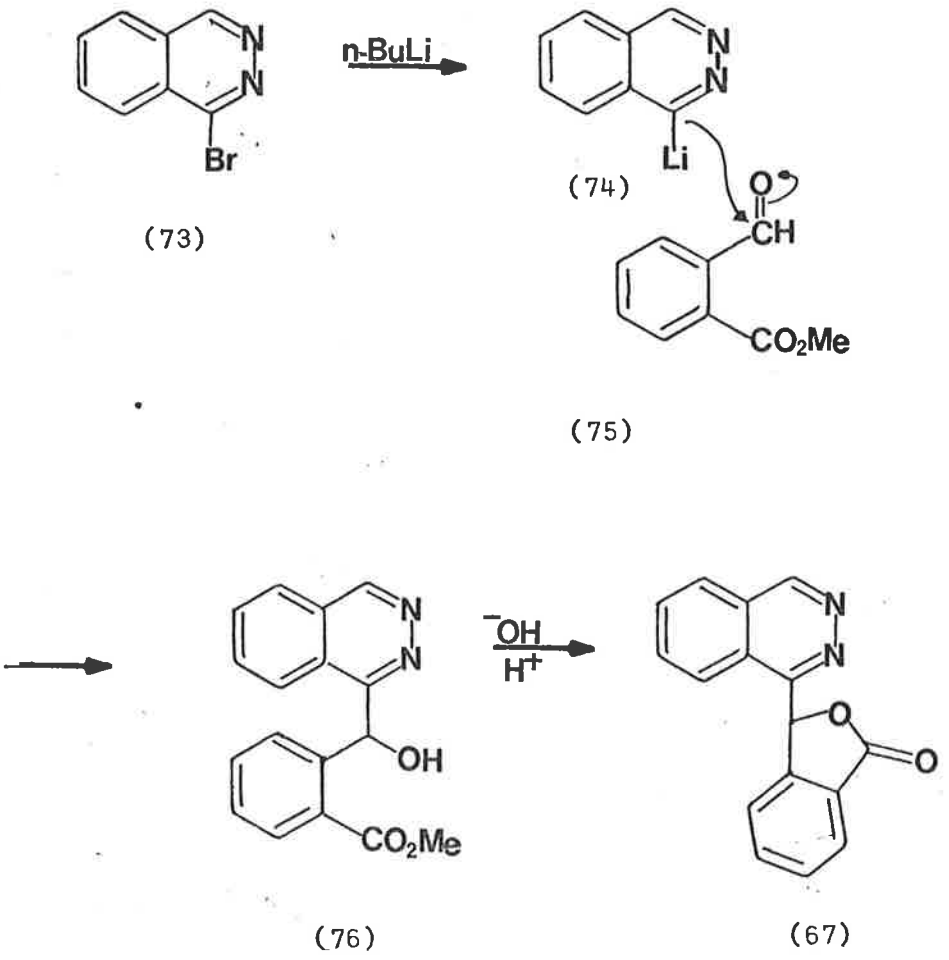


(72)

react with the phthalidyl anion, which was generated by the reaction of either, sodium methoxide, potassium t-butoxide, or lithium isopropyl-cyclohexylamide, with phthalide. In most experiments either starting material or polymeric material was obtained. In one experiment, one product which was identified as (72) probably arose due to the presence of potassium hydroxide in the sample of potassium t-butoxide. The band on preparative t.l.c. corresponding to the product (72) was found to darken on standing in the air, suggesting that the oxidation took place on the plate.

At this stage the use of the phthalidyl anion as a nucleophilic species appeared to be very limited in its application and further use was abandoned.

Since phthalide could not be used successfully as a nucleophile, it was thus apparent that a nucleophilic phthalazine species was required to form the key Cl-Cl' bond. One possibility appeared to be the metal-halogen exchange of bromophthalazine (73), in the expectation that the resultant aryl lithium (74) on reaction with (75) would yield (76). Hydrolysis and lactonisation would then afford the required phthalidyl-phthalazine (67; Scheme 2.13). Unfortunately, the reaction of freshly



(73) (74) (75) (76) (67)

Scheme 2.13

prepared 1-bromophthalazine[†77] with butyl lithium then (75) afforded polymeric material. The p.m.r. spectrum of the crude product showed the presence of a butyl group, suggesting butyl lithium had apparently participated in nucleophilic addition.

Although there do not appear to be very many examples of trans-metallations of aryl chlorides, an attempt to lithiate (13) was made, primarily because it was more stable than (73). Also, it was hoped that polymerisation may be reduced. The red colour resulting from the reaction of butyl lithium with (13) disappeared immediately on addition of (75). The p.m.r. spectrum of the isolated product exhibited a signal, attributable to a butyl group, in the region δ 1.4 which suggested that the butyl anion had added to the aromatic ring. The infrared spectrum of this product showed an absorption at 1780cm^{-1}. Therefore, the two most likely products were either (78) or (79) and a plausible mechanism for their formation is shown in Scheme 2.14. Dehydrochlorination of (79) should proceed smoothly to yield (80), however, treatment of the product with a variety of bases did not yield (80) but a mixture of compounds. Therefore, these results suggest that the product was not

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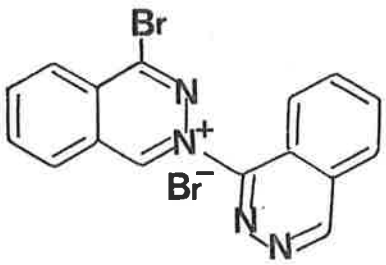
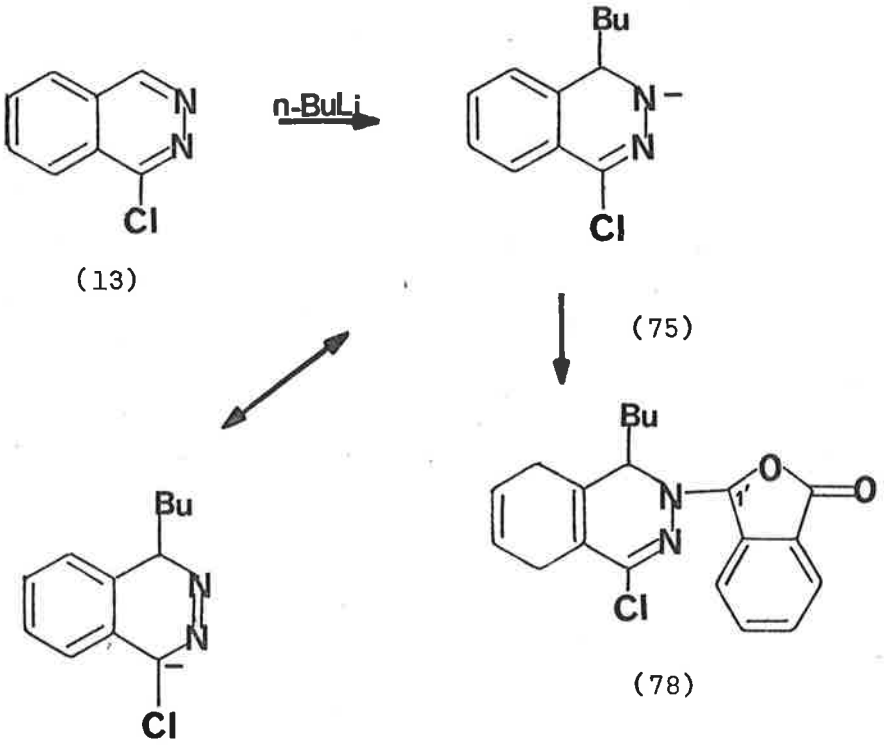
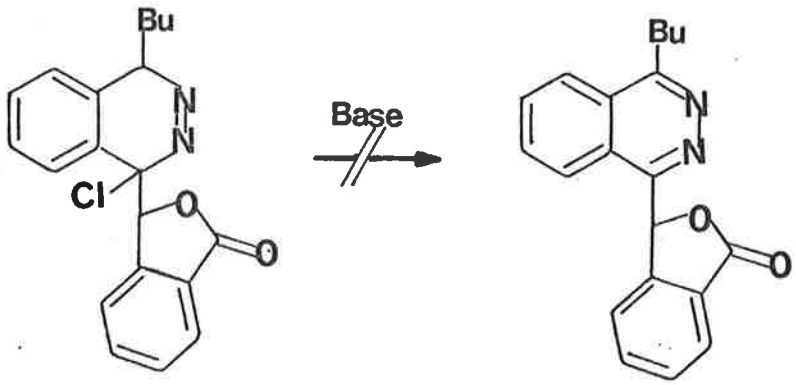
† Freshly prepared (73) darkened on exposure to light and after thirty minutes a new compound had been formed which was assigned the structure



(77)

(77) by a mechanistic consideration. It has been reported that 4-chlorophthalazine undergoes a similar dimerization process[78].

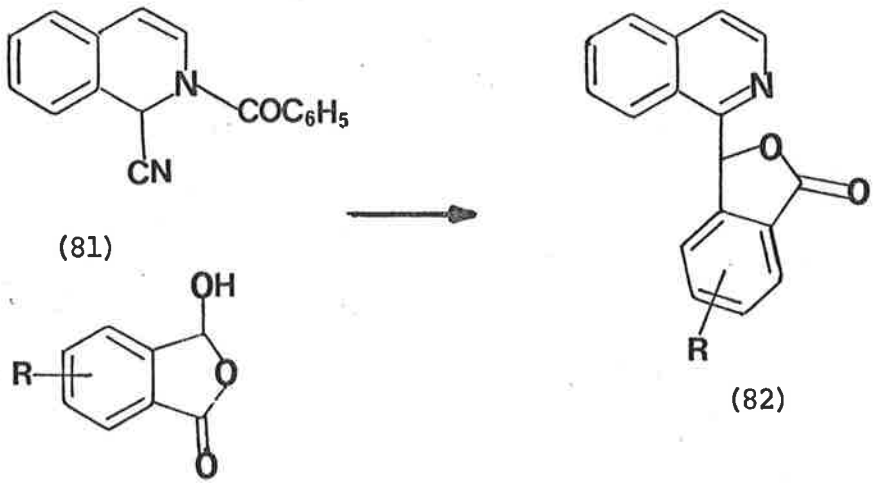




Scheme 2.14

(79), but rather (78). Examination of the ^{13}C n.m.r. spectrum of the product confirmed the structure as (78) due to the presence of six sp^3 carbon signals. Furthermore, the signal at 94 ppm, which is ascribed to Cl', is consistent with this carbon being attached to nitrogen, as the ^{13}C n.m.r. spectrum of the phthalidylcinnolinones (Part II. 2.2) exhibits Cl' in the region 87-90 ppm. If the product was (79) this carbon would be observed in the region 84 ppm[79].

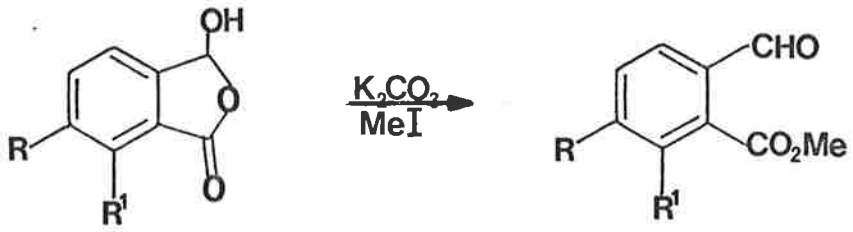
An alternative source of a nucleophilic phthalazine synthon was clearly necessary. A significant amount of work has been associated with isoquinoline Reissert compounds and one report in particular had significant bearing on the preparation of phthalidylphthalazines[80]. The isoquinoline Reissert compound (81) has been used to prepare a variety of phthalideisoquinolines[80] (82; Scheme 2.15). The phthalazine Reissert



Scheme 2.15

compound (83) has also been prepared by the reaction of phthalazine with potassium cyanide and benzoyl chloride[81,82]. The Reissert compound (83) has been successfully methylated[81] and more importantly, it condenses readily with benzaldehyde[83].

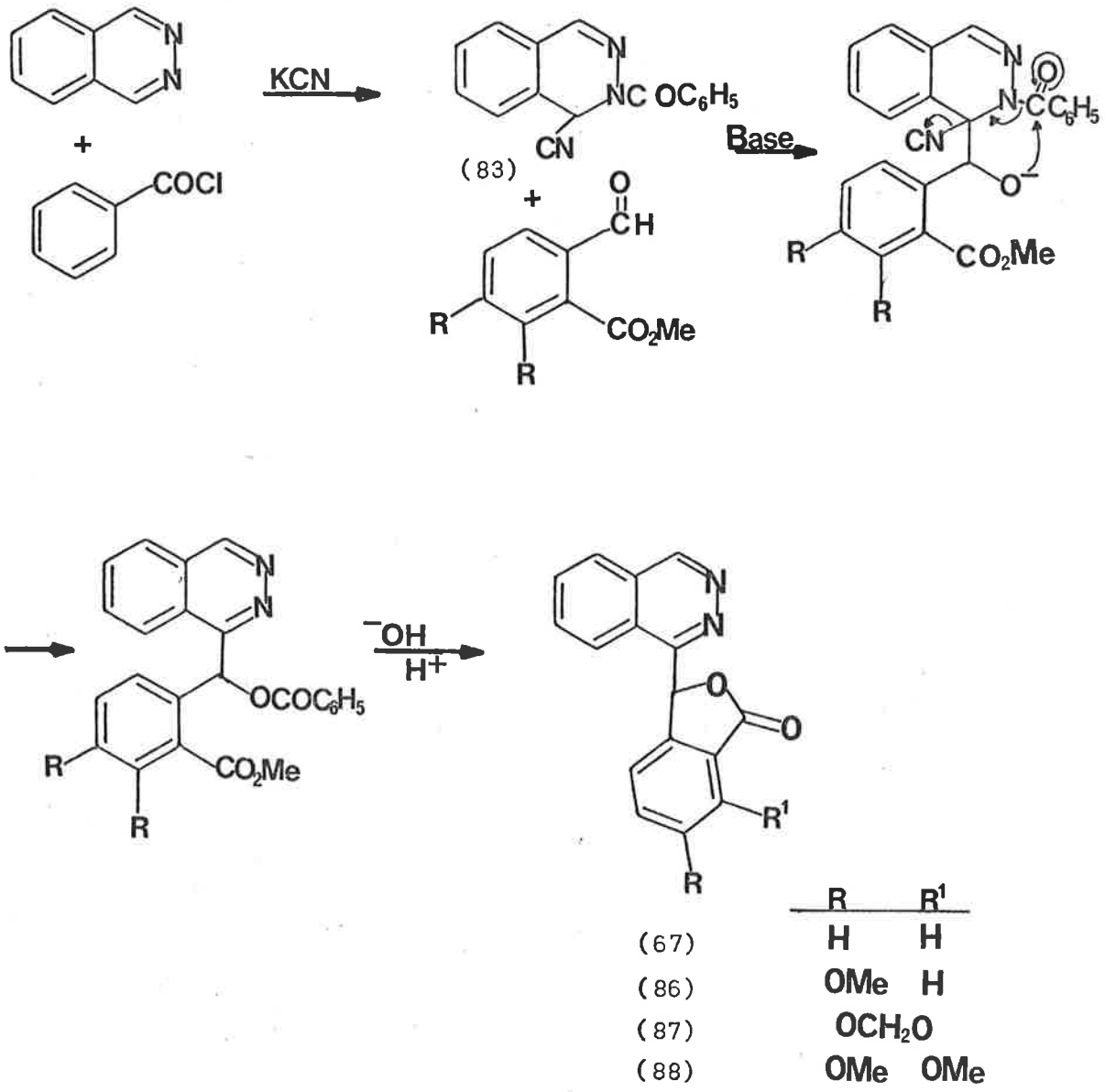
Thus, a logical approach to the phthalidylphthalazines involves the reaction of (83) with suitably substituted electrophilic phthalide synthons. Previous work[80] had shown that a higher yield of the phthalide-isoquinoline was obtained when (81) was treated with the benzoate (75). Thus the formylbenzoates (75), (84) and (85), were prepared from the corresponding phthalaldehydic acid using potassium carbonate and methyl iodide.



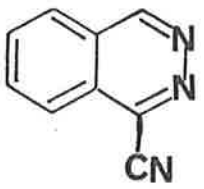
	R	R^1
(75)	H	H
(84)	OMe	H
(85)	OCH_2O	

Using a two phase system of saturated sodium hydroxide and dichloromethane with the phase transfer catalyst, benzyltriethylammonium chloride, (83) on reaction with the benzoate afforded the phthalidylphthalazines (67), (86) and (87), presumably by the pahtway shown in Scheme 2.16. The preparation of (88) was achieved under identical conditions, but opianic acid was used instead of the corresponding benzoate.

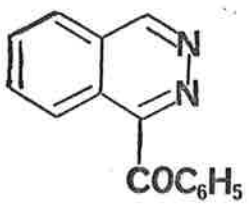
The yield of these products was only low. This is due, in part, to the alternative pathways that the Reissert anion can take. Examination of the p.m.r. spectrum of the crude reaction mixture suggests the presence of phthalazine and possibly 1-cyanophthalazine (89) and 1-benzoylphthalazine (90). These byproducts are not unexpected as isoquinoline Reissert compounds are known to form either isoquinoline[84], 1-cyanoisoquinoline[85] or 1-benzoylisoquinoline[86] on treatment with base.



Scheme 2.16

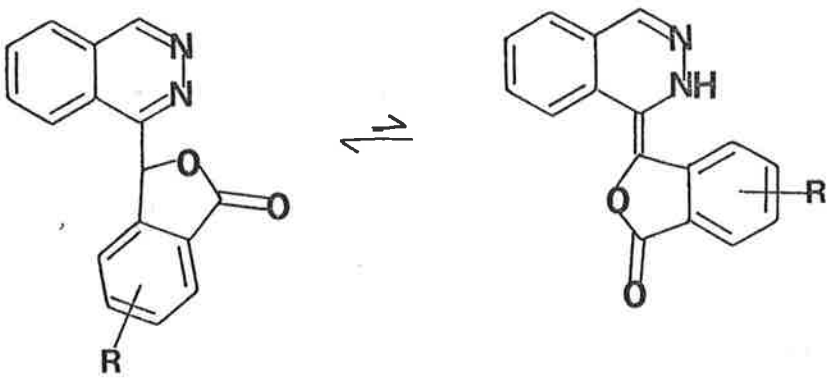


(89)



(90)

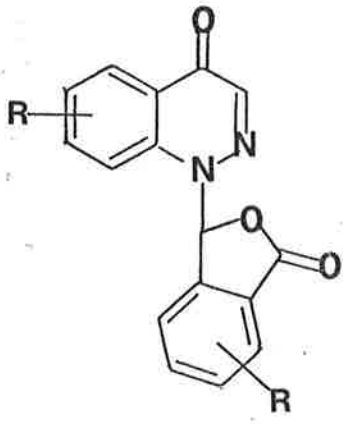
The phthalidylphthalazines were isolated as white powders but on recrystallisation afforded an apricot coloured powder, a change which is probably due to the presence of a small percentage of the tautomeric form (91a), which may be expected to be slightly coloured due to the extended π conjugation. This conjugation is very similar to that in the biphthalides and (64) prepared earlier, which were a yellow colour.



(91) (91a)

2.2 SYNTHESIS OF PHTHALIDYLCINNOLINONES

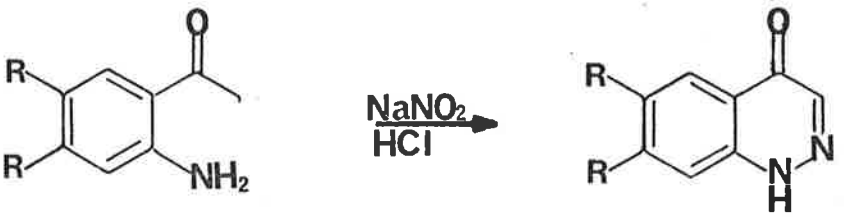
The phthalidylcinnolinones (4) provide an interesting contrast to the phthalidylphthalazinones because the phthalide ring is now bonded to a nitrogen and no compounds of this type have previously been prepared.



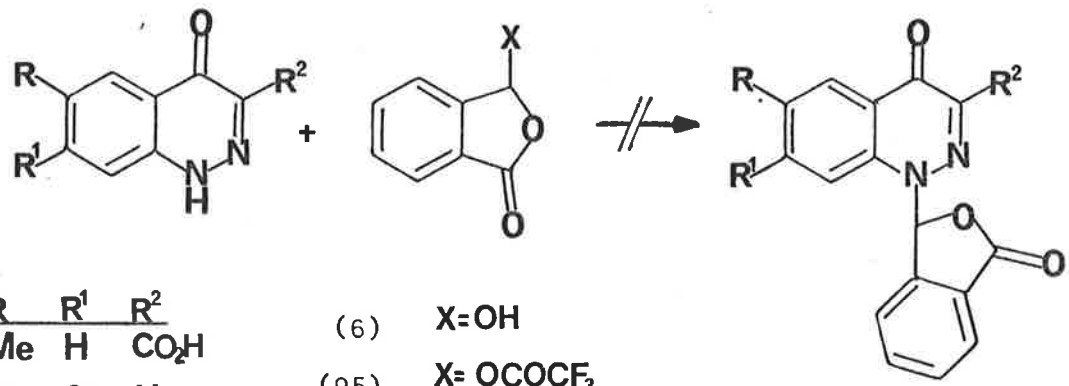
(4)

The synthetic strategy to be employed in the preparation of (4) requires oxygenated 4-hydroxycinnolines for which there are several methods of preparation. These include the Richter synthesis[87], and the Friedel-Crafts cyclisation of mesoxalyl chloride phenylhydrazones[88], but the Borsche synthesis[89] is the most widely employed method and the one with greatest versatility and is used to prepare the majority of the 4-hydroxycinnolines appearing in the literature. This synthesis involves the diazotisation of o-aminoacetophenones in concentrated hydrochloric acid followed by thermal cyclisation, affording the 4-hydroxycinnoline in high yields.

The initial approach to compounds of type (4) involves a direct condensation reaction between a 4-hydroxycinnoline and phthalaldehydic acid (6), in a similar manner to the reaction of (92) and acetic anhydride[58]. Because of the substituent at C3, 6-methyl-4-hydroxycinnoline-3-carboxylic acid (94) should be alkylated at N1, and although (6) is a powerful electrophile, it failed to react with (94). A similar lack of reactivity was observed in the reaction between (92) and (6). By using



	R	R
(19)	H	H
(92)	OMe	OMe
(93)	OCH_2O	



	R	R^1	R^2
(94)	Me	H	CO_2H
(92)	OMe	OMe	H

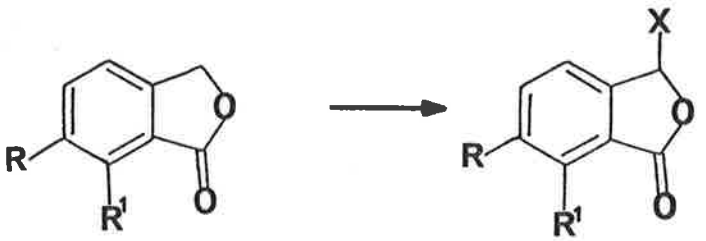
(6) X=OH

(95) X= $OCOCF_3$

the electrophilic species (95), it was hoped that we would overcome the previous lack of success, however, no reaction took place between (92) and (95).

Thus the alternative electrophile, 3-bromophthalide, was investigated. This phthalide[90] and its methoxy derivatives are obtained in high yields from the corresponding phthalide by benzylic bromination using N-bromosuccinimide. Treatment of the readily available 6,7-methylenedioxyphthalaldehydic acid[30] (98) with thionyl chloride affords the phthalide

(99) quantitatively.

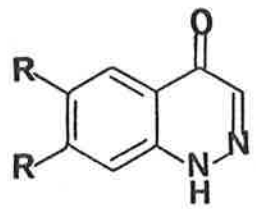


	R	R^1	X
(7)	H	H	Br
(96)	OMe	H	Br
(97)	OMe	OMe	Br
(98)	OCH_2O		OH
(99)	OCH_2O		Cl

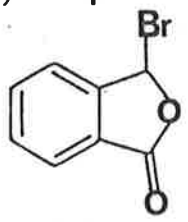
Because the 4-hydroxycinnoline exists predominantly in the amide form (20a)[51], treatment with a strong base such as sodium hydride would form the anion irreversibly, thus allowing for N1-alkylated products in preference to N2- and O-alkylated products.

Treatment of 6,7-dimethoxy-4-hydroxycinnoline with sodium hydride, followed by addition of (7) yielded after chromatography, a solid of molecular weight 338 as required by (102). Unfortunately, there is no obvious feature which distinguishes the three possible products (100), (101) and (102). This product showed a sharp singlet in the p.m.r. spectrum at δ 8.48 and infrared absorptions at 1780, 1625 and 1615cm^{-1}.

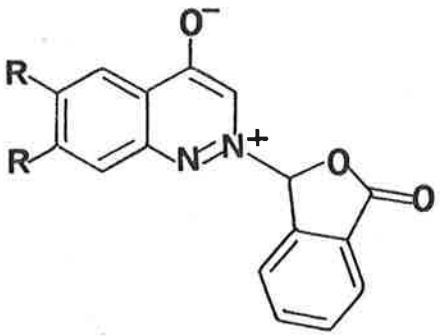
It was therefore necessary to examine structurally related compounds so that unambiguous product identification could be made. Those compounds most likely to lend valuable assistance in the structural elucidation were the simple methylated and acetylated cinnolines (21), (22), (103)-(108), as their p.m.r. and i.r. spectra are all well documented[58,91]. Only the p.m.r. spectra of the methoxy substituted cinnolines were compared to the p.m.r. spectrum of the product. For analysis, the cinnoline protons at C3, C5, and C8, are diagnostic as these undergo large variations in chemical shifts, depending upon the position of the substituent.



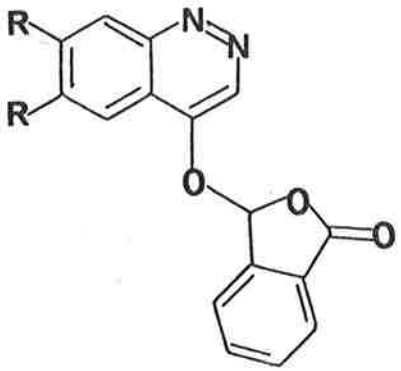
(92) +



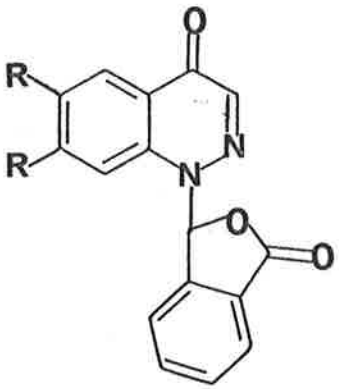
(7)



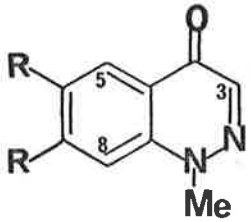
(101) R=OMe



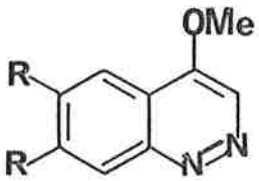
(100)



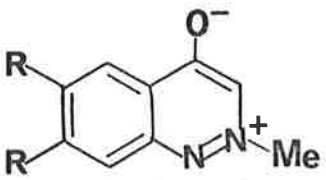
(102)



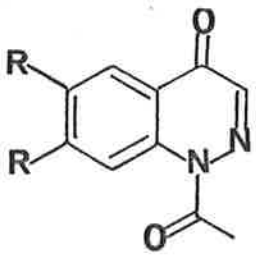
(22) R=H
(103) R=OMe



(104) R=H
(105) R=OMe



(21) R=H
(106) R=OMe



(107) R=H
(108) R=OMe

TABLE I. P.m.r. Chemical Shifts of Cinnolines

Compound	H3 (ppm)	H5 (ppm)	H8 (ppm)
(22)	7.77	8.30	7.40
(103)	7.77	7.61	6.70
(105)	8.85	7.68	7.29
(21)	8.01	8.39	7.52
(106)	7.84	7.61	7.07
(107)	7.84	8.16	8.91
(108)	7.89	8.16	8.51

When examination is made of the p.m.r. spectrum of (103), (105) and (106), some significant features become apparent (Table I.) In all three compounds, the high field aromatic proton is H8[91] and is above δ 7.29, while the low field proton H3 resonates at a surprisingly low field, in (105) at δ 8.85. The important feature of the acetylated cinnolines (107) and (108) is the chemical shift of H8 at δ 8.91 and 8.51 respectively, and this is in fact the lowest field proton[58]. This has been attributed to the deshielding by the acetyl carbonyl and similarly the spectrum of 1-acetyl-3-phenyloxindole shows a quartet at much lower field than the remaining aromatic resonances and this is due to deshielding of H8 by the acetyl substituent[58]. Some 1-acetylnaphthalenes show a deshielding effect of similar magnitude for H8[58].

If the reaction between (92) and (7) had occurred at the oxygen to give (100) it is reasonable to expect the cinnoline protons of (100) to have similar chemical shifts to those of (105), unless the phthalide ring significantly shields or deshields the cinnoline ring protons. The product had a one proton low field singlet at δ 8.48 and there were no signals above δ 7.6. This discounts the O-alkylated product (100) as H8 would be

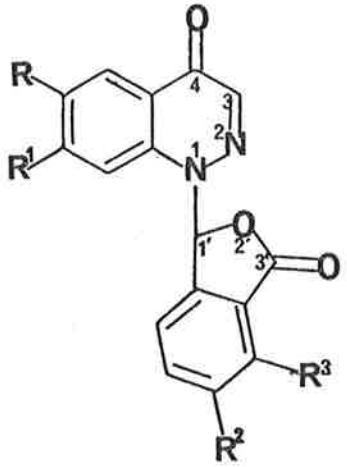
expected at approximately 7.29, compared with (105), unless it was deshielded by the phthalide ring. Examination of a model indicates H8 is not deshielded, and therefore it seems reasonable to assume the product is not the O-alkylated compound (100).

The anhydro base product (101) was unlikely as there is no apparent reason why there should be a low field proton at δ 8.48, as the lowest signal for (106) appears at δ 7.84. More importantly it would be expected that H8 of (101) possesses a similar chemical shift to H8 of (106) as it is not influenced by the substituent. The p.m.r. spectrum of (106) exhibits a high field signal at δ 7.07, ascribed to H8, but the highest field signal for the product occurs at δ 7.6 and thus the isolated product was not (101).

Examination of a model of the required product (102) shows the proton at the 8 position to be influenced by the γ-lactone ring, causing an apparent deshielding effect. The deshielding of H8 is observed in the 1-acetyl cinnolines (107) and (108)[58]. Clearly, the product isolated was the required one so we proceeded to prepare the remainder of these phthalidylcinnolinones by the method described below†.

The remaining phthalidylcinnolinones (109)-(117) were obtained by treating the appropriate 4-hydroxycinnoline (either (20), (92) or (93)) with sodium hydride for 15 hours, followed by the addition of the 3-bromophthalide and the reaction mixture stirred at ambient temperature for 24 hours, then at reflux temperature for 24 hours. The most successful, albeit tedious, method to obtain a pure product was achieved by absorbing the reaction mixture directly onto silica and then separating the products by column chromatography on silica, but yields were never greater than 65%. Yields were always higher when freshly prepared 3-bromophthalides were used. Besides a small quantity of starting 4-hydroxycinnoline being

† This method must be followed, otherwise the required compound is not obtained, and the O-alkylated product is apparently isolated. This is discussed later.

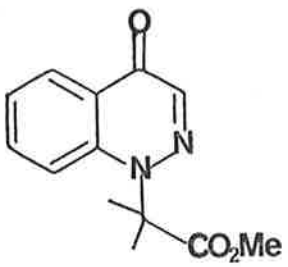


	R	R^1	R^2	R^3
(109)	H	H	H	H
(110)	H	H	OMe	H
(111)	H	H	OMe	OMe
(102)	OMe	OMe	H	H
(112)	OMe	OMe	OMe	H
(113)	OMe	OMe	OMe	OMe
(114)	OCH_2O		H	H
(115)	OCH_2O		OMe	H
(117)	OCH_2O		OMe	OMe
(116)	OCH_2O		OCH_2O	

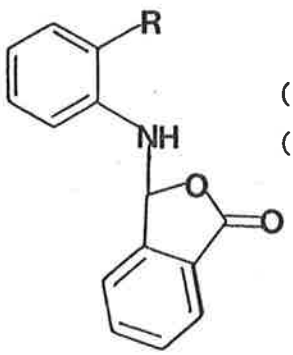
recovered, there was between 25-35% of material unaccounted for and this is suggested to be the corresponding anhydro base product, which is said to predominate in the methylation of 4-hydroxycinnoline, and because of its polarity cannot be recovered from the column.

The compounds (109)-(117) all had similar p.m.r. spectra to (102), although in the majority of cases these spectra were quite complicated. There were slight variations of the position of the low field proton, but this was probably due to substituent effects, both electronic and steric, which results in a variation in the degree of deshielding. All the p.m.r. spectra were consistent with the isolated product being the required one.

The infrared spectrum of each product lent further spectroscopic evidence for the structure of the alkylated products (Table II). Each of the products, (102), (109)-(117) show an absorption in the region 1760-1785cm^{-1}, ascribed to the lactone carbonyl. The cinnolinones (22) and (118)[92] show absorptions, due to the cinnolinone ring, at 1625, 1608, 1594cm^{-1}



(118)



(119) R=H

(120) R=COCH$_3$

and 1632, 1606cm^{-1} respectively[92]. These absorptions are seen in the phthalidylcinnolinones in the region 1640-1620 and 1615-1595cm^{-1}.

TABLE II. Infrared C=O and C=N Stretching Frequencies of Cinnolinones.

Compound	Absorption Maxima cm^{-1}
(109)	1780 , 1625 , 1610
(110)	1780 , 1645 , 1610
(111)	1760 , 1620 , 1600
(102)	1780 , 1625 , 1615
(112)	1785 , 1640 , 1615
(113)	1780 , 1625 , 1600
(114)	1780 , 1630 , 1600
(115)	1785 , 1625 , 1600
(116)	1780 , 1630 , 1595
(117)	1780 , 1630 , 1605
(22)	1625 , 1608 , 1594
(103)	1620 , 1585
(118)	1738 , 1632 , 1606

The ^{13}C n.m.r. spectra of products (102), (109)-(116)* were diagnostic and unambiguously confirmed their structure as the N1-alkylated products. The compounds (102), (109)-(116) should possess two carbonyl carbons in the ^{13}C n.m.r. spectrum whereas the other two possible isomeric products should not. The ^{13}C n.m.r. spectra of phthalide,6,7-dimethoxyphthalide, and 6,7-methylenedioxyphthalide, have been reported[79] so that signals due to

* Due to solubility difficulties, a satisfactory ^{13}C n.m.r. spectrum of (117) could not be obtained. The method of preparation of (117) is identical to the other products so that is is reasonable to assume that it is the required compound. Furthermore the p.m.r. and i.r. spectra are consistent with it being the desired compound.

these substituents could be assigned, thus allowing for a comparison to be made between the remaining signals of the products, and the reference compounds (22), (103), (104), (119) and (120).

Phthalide, oxygenated phthalides[79], (119)[31] and (120) all show a carbonyl signal in the ^{13}C n.m.r. spectrum at approximately 170 ppm as do the cinnolinones (22) and (103). The phthalidylcinnolinones, (102), (109)-(116), showed two signals in the region 170 ppm, one due to the phthalide carbonyl and one due to the cinnolinone carbonyl. The phthalidylcinnolinones all showed at least one signal at approximately 140 ppm which is ascribed to C3 of the cinnolinone ring. The reference cinnolinones (22) and (103) also showed a signal in this region. The products (102), (109), and (114) had a signal in the region 144 ppm: this is ascribed to C7a of the phthalide ring. This carbon was observed at about δ 140 ppm for the remaining products. By comparison of the signals of (104) with those of the products (102), (109)-(116), the possibility of O-alkylation is eliminated because these compounds would not exhibit signals, due to the cinnoline ring, in the region 153-131 ppm, except for carbons bearing alkoxy substituents. If the signals, due to the phthalide substituent are assigned, a comparison between the remaining signals and the signals of either (22) or (103) discounts any possibility that the products are N2- or O- alkylated structures. For example, if (109) is examined, and those signals due to phthalide assigned by use of the literature values[79], the remaining signals are indeed very similar to those signals corresponding to (22) as would be expected (Figure 1). Slight variations may occur due to conformational changes of (109). A close degree of resemblance between the chemical shifts of the cinnolinone carbons of (102) and (103) is also observed, as indicated below (Figure 2). As can be seen, the introduction of alkoxy groups onto the cinnolinone ring results in two low field signals, one in the region of 155 ppm and the other at 148 ppm. The presence of a methoxyl group in the phthalide

TABLE III. ^{13}C N.m.r. Chemical Shift Data of Phthalidylcinnolinones and Reference Compounds.

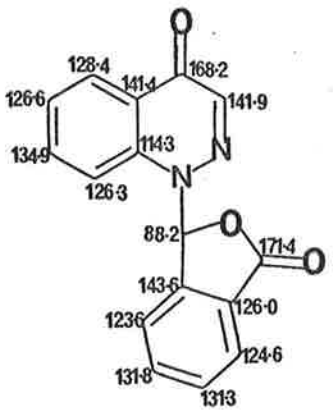
	Compound														
	(109)	(110)	(111)	(102)	(112)	(113)	(114)	(115)	(116)	(22)	(103)	(104)	(119)	(120)	(9)
a	171.4	170.9	176.0	168.5	168.5	169.6	168.8	169.1	170.9	171.4[a]	170.1[a]	153.3	169.3	201.9	170.4
b	168.2	167.8	171.4	168.4	168.1	169.5	168.8	169.0	168.8	141.3	155.6	130.9	145.5	169.3	146.3
	143.6	161.1	165.4	155.5	161.1	165.4	154.1	161.9	153.8	140.4[c]	148.9	130.5	143.9	147.8	133.6
	141.9	140.9	154.4	148.7	155.3	155.4	148.0	154.3	149.9	134.2	139.7[c]	130.0	134.5	145.6	128.5
c	141.4	140.9	141.2	144.9	148.7	153.8	144.0	147.3	146.7	126.1	138.4	130.0	134.5	135.4	125.2
	134.9	134.5	141.1	140.0	139.0	148.8	139.9	140.0	144.0	125.2	120.2	129.1	130.9	134.8	124.9
	131.8	128.4	135.8	138.8	138.2	140.1	139.8	140.0	139.7	124.8	104.8	121.0	129.7	132.6	122.0
	131.3	126.2	134.9	135.2	137.2	140.1	135.2	136.8	136.3	115.0	95.9	118.9	128.4	130.9	69.5
	128.4	125.6	134.7	131.0	127.7	136.8	131.0	128.0	119.8	43.6	56.8	56.4	125.8	127.9	
	126.6	125.3	126.4	126.7	125.7	135.5	125.2	126.2	117.2		56.8		123.5	125.9	
	126.3	125.1	126.1	125.2	123.1	119.5	124.9	123.6	115.9		44.1		121.3	123.3	
	126.0	123.3	125.7	124.7	118.3	119.2	120.1	120.4	114.2				115.5	120.1	
	124.6	123.2	119.6	117.7	107.6	118.9	103.2	108.0	103.8				87.8[c]	118.8	
	123.6	114.1	118.8	103.5	103.4	104.4	103.1	103.4	102.8					114.2	
	114.3	108.0	114.3	96.9	96.8	95.6	100.8	99.3	102.7					85.6[c]	
d	88.2	87.9	87.7	87.6	87.4	88.0	94.7	94.1	100.7					28.2	
		55.9	62.6	56.7	56.6	62.3	87.8	87.9	94.3						
			56.9	55.9	55.9	56.7		56.3	87.6						
					55.9	56.5									
						56.2									

a : Signal ascribed to C4

b : Signal ascribed to C3'

c : Signal ascribed to C3

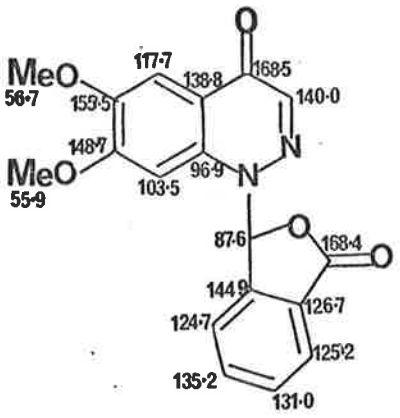
d : Signal ascribed to C1'



(109)

Signals due to the cinnolinone ring	Signals of (22)
168.2	171.4
141.9	141.3
141.4	140.4
134.9	134.2
128.4	126.1
126.6	125.2
126.3	124.8
114.3	115.0

Figure 1.



(102)

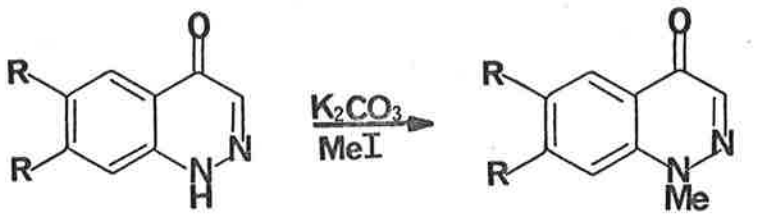
Signals due to the cinnolinone ring	Signals of (103)
168.5	170.1
155.5	155.6
148.7	148.9
140.0	139.7
138.8	138.4
117.7	120.2
103.5	104.8
96.9	95.9
56.7	56.8
55.9	56.8

Figure 2.

ring results in a characteristic signal at 165 ppm. The most significant and diagnostic signal which unequivocally confirmed the assignment as N1-alkylated products and eliminated the other two possible N2- and O-alkylated structures, was the signal between 87.4-88.2 ppm, ascribed to C1'. This is almost identical to the chemical shift of C3 of (119) and (120) at 87.8 ppm and 85.6 ppm respectively. The anhydro base structures would be expected to exhibit C1' 5-11 ppm further downfield[93], as quaternized aliphatic amines show a downfield shift, for the carbon bonded to nitrogen, of 11 ppm compared with the corresponding tertiary amine[93]. Similarly, the O-alkylated structures would result in C1' being further downfield as a N-methyl and a O-methyl group show a difference of at least 10 ppm for the methyl signal[79]. Because of the similarity of the chemical shift of C3 of (119) and (120), and the chemical shift of C1' of the products (102) and (109)-(116), as well as the existence of two carbonyl signals for each of the products (102), (106)-(116), they are assigned the structure of the desired N1-alkylated products.

Ultraviolet spectroscopy was not employed for structural elucidations as absorptions due to the phthalide ring tended to mask the relevant absorptions of the cinnoline ring and made structural assignment by this technique equivocal.

The cinnolinones (22) and (103) were prepared by stirring the appropriate 4-hydroxycinnoline with potassium carbonate and methyl iodide in acetone at room temperature. The yields of the N1-methylated products were higher than those reported by Ames[52]. There was a small amount of the N2-methylated product formed, as evidenced by the p.m.r. spectrum of the crude reaction product, but it was not isolated.

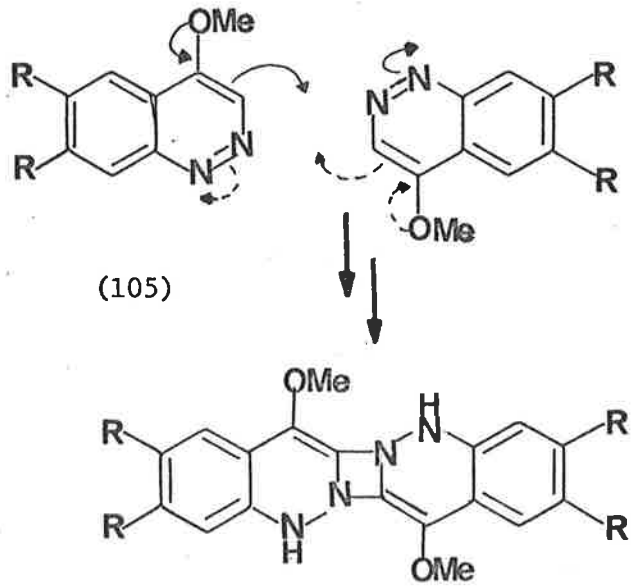


R= H or OMe

(22) R=H

(103) R=Me

When 4,6,7-trimethoxycinnoline (105) was initially prepared for examination of its ^{13}C spectrum, the p.m.r. spectrum (δ 8.85, 7.68, 7.29, each a singlet corresponding to one proton and δ 4.10, 4.06 corresponding to nine protons) was identical to that reported in the literature[58]. After storing, the solid material showed the following signals, δ 9.20, broad and exchangeable, 7.81, s ; 7.40, s, each corresponding to one proton and three, three proton singlets at δ 4.20, 4.15, 4.10. It is suggested that this compound is a dimer and the assigned structure (121) is based



(105)

R=OMe

(121)

Scheme 2.17

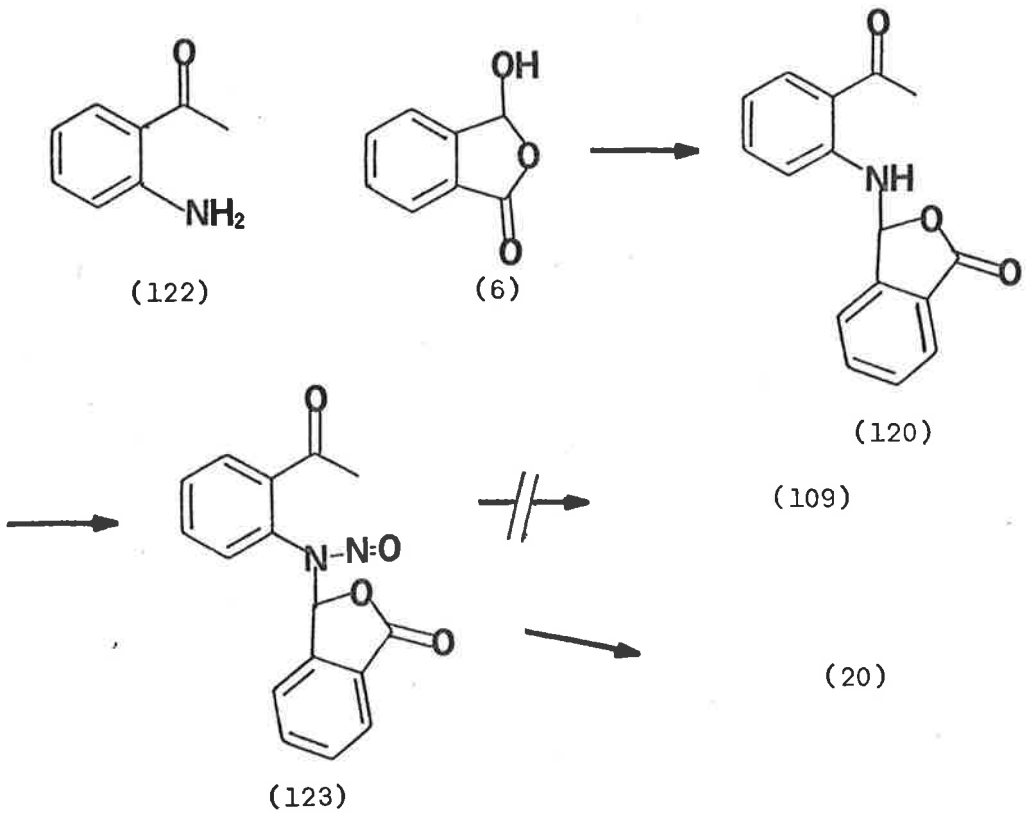
on a mechanistic consideration (Scheme 2.17). In order to determine whether this type of dimerization was a general reaction, the stability of (104) was investigated. On exposure of (104) to sunlight, examination of the p.m.r. spectrum of the product suggested demethylation had occurred. It therefore seems that 4-methoxycinnolines are susceptible to various dimerization and photochemical reactions.

Before ^{13}C n.m.r. spectroscopy was used to confirm the structure of the phthalidylcinnolinones, an independent synthesis of two of the possible products was attempted (Schemes 2.18 and 2.19).

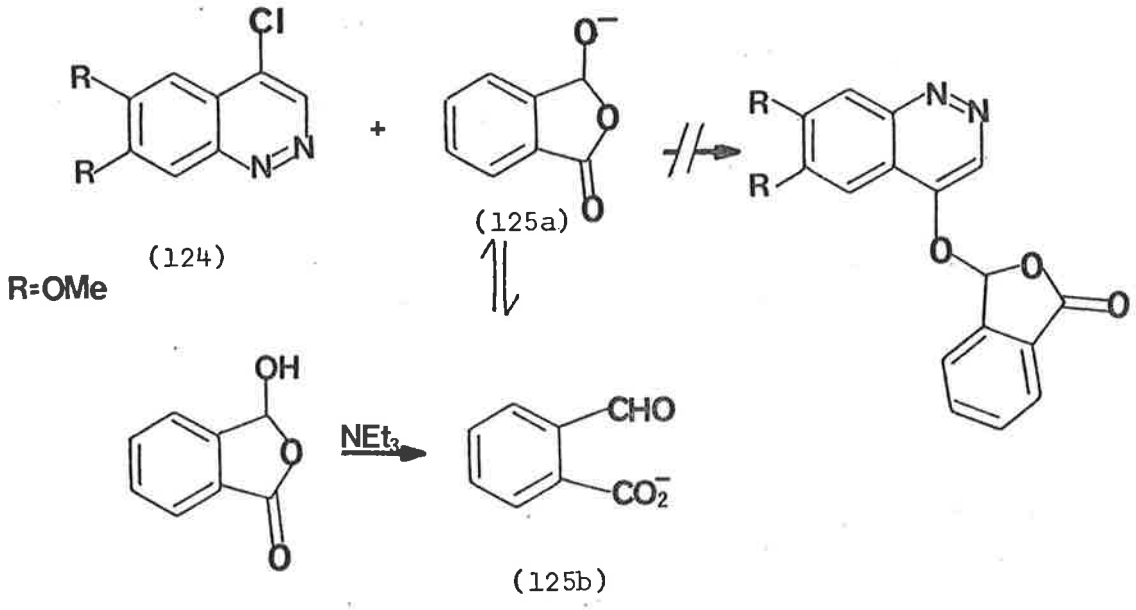
Despite the ease of condensation of o-aminoacetophenone (122) with (6) to give (120), attempts to produce (123) failed and the only product obtained was a small quantity of 4-hydroxycinnoline (20) which presumably arises by hydrolysis of (120) followed by diazotization and cyclization under the reaction conditions. The 4-chlorocinnolinone (124) is readily substituted by alkoxides at the 4-position[51], and it was anticipated that in the presence of triethylamine there may be a sufficient concentration of the ring closed anionic form (125a) to effect nucleophilic substitution, but this attempt also proved unsuccessful. Because ^{13}C n.m.r. spectroscopy confirmed the products structure, no further work was undertaken towards an independent synthesis.

In a preliminary experiment, aimed at the preparation of (115), the reaction mixture was heated at reflux for only 8 hours, and afforded a white solid which exhibited different spectral properties to those of the N1-alkylated product discussed above. The p.m.r. spectrum included one proton singlets at δ 8.45, 7.72, 7.10 and the infrared spectrum showed absorptions at 1820, 1610 and 1590cm^{-1}. Compound (115) possessed corresponding signals at δ 8.25, 7.87 and 7.60, and infrared absorptions at 1780, 1640 and 1610cm^{-1}. It is suggested that this product is the O-alkylated compound (126)†. It has been suggested that O-alkylated

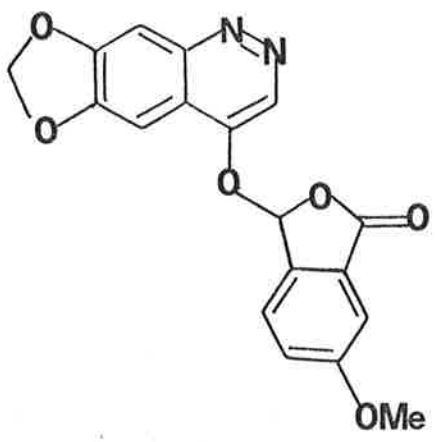
† There was insufficient material to obtain a ^{13}C n.m.r. spectrum.



Scheme 2.18



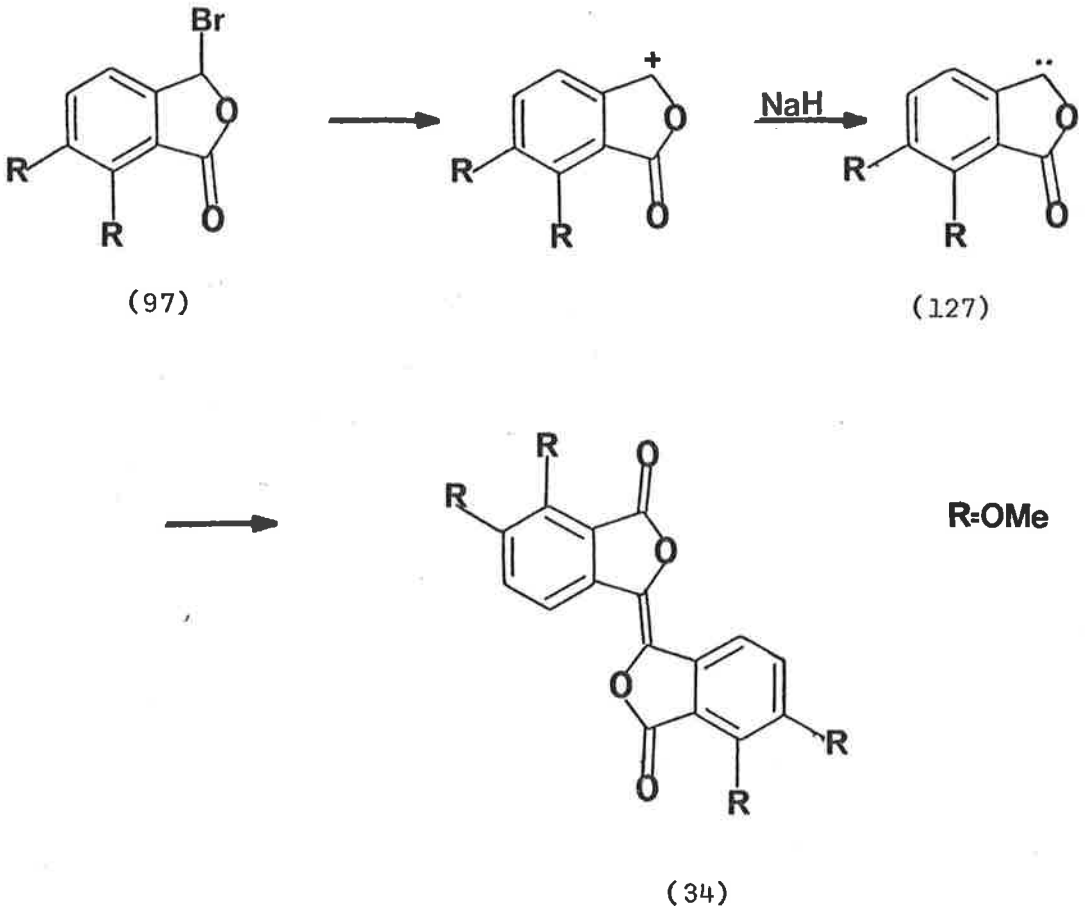
Scheme 2.19



(126)

cinnolines can be converted to the N1-alkylated cinnolines[51] on heating, and prolonged heating at reflux temperatures in later experiments converted any O-alkylated products to the N1-alkylated product. Some evidence for this was seen when a sample of (126) was heated in tetrahydrofuran and the infrared spectrum of the mixture was seen to change.

In the preparation of (111) an excess of sodium hydride and 3-bromo-6,7-dimethoxyphthalide was used in an attempt to increase the yield. No significant increase in yield resulted, but a bright yellow solid was isolated and identified as the biphthalide (34). This arose, presumably by the formation of the carbene intermediate (127), which then coupled with another carbene intermediate to give (34; Scheme 2.20). Carbene intermediates have been postulated in the preparation of biphthalide from phthalic anhydride and triethyl phosphite[62].



(97)

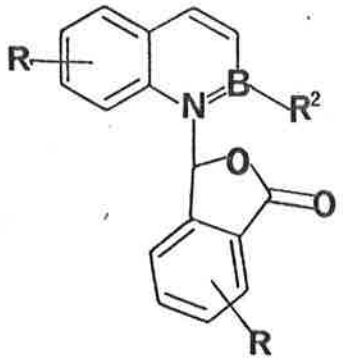
(127)

(34)

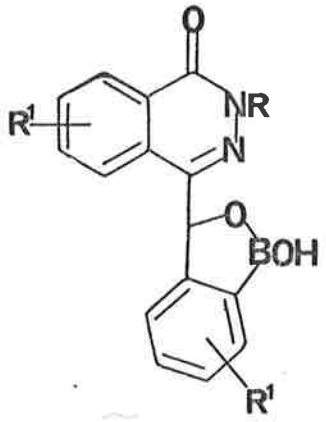
Scheme 2.20

2.3 ATTEMPTED SYNTHESIS OF PHTHALIDYLBORAZANAPHTHALENES.

The synthesis of bicuculline analogues containing boron in either the isoquinoline ring (5) or γ-lactone ring (23) aroused interest, firstly as a synthetic challenge, and also to investigate their physiological activity.



(4)



(23)

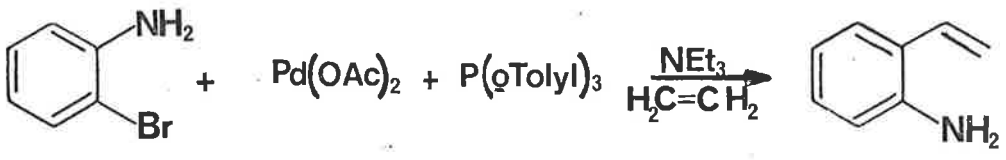
As mentioned previously, the 2,1-borazanaphthalenes (24) and (128) provided ideal starting substrates as the N-Cl' bond could, in principle, be formed between the nitrogen and an electrophilic phthalide moiety. The 2,1-borazanaphthalenes (24) and (128) are readily prepared by the action of a Grignard reagent on the borazanaphthalene (129, Scheme 2.21), which is derived from o-aminostyrene (130) and boron trichloride[94]. The reaction of o-aminostyrene and phenylboron dichloride yields (128) directly[94]. Unfortunately, there is no report of the preparation of alkoxy-substituted 2,1-borazanaphthalenes of the type (131).

The success of this project thus depended on the development of a synthesis of aminostyrenes applicable to alkoxy derivatives. The more

	R	R	R^1
(24)	H	H	Me
(128)	H	H	C_6H_5
(129)	H	H	Cl
(131a)	OMe	OMe	Me
(131b)	OCH_2O		Me
(132)	OMe	OMe	C_6H_5

Scheme 2.21

commonly employed methods used to prepare o-aminostyrene were investigated and found to be either very low yielding or totally unsatisfactory*. A recent report[95] using palladium catalysed ethylenation of o-bromoaniline (133) affords (130) in reasonable yield, but when palladium chloride was used instead of the acetate only starting material was recovered. This pathway was not pursued further because of the uncertainty of whether alkoxy substituted bromoanilines would afford the required

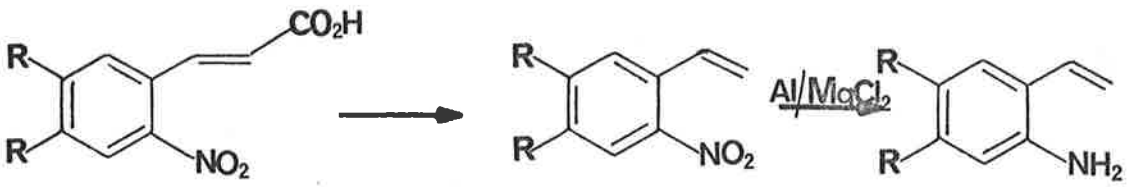


(133) (130)

styrenes. Furthermore, because the synthetic pathway detailed below proved successful, the other approaches were discontinued.

The decarboxylation of o-nitrocinnamic acid (134) affords (135)[96], which can be reduced to (130; Scheme 2.22) using aluminium amalgam[97].

* These results are detailed in the experimental section.



(134)	R=H	(135)	R=H	(130)	R=H
(136)	R=OMe	(138)	R=OMe	(140)	R=OMe
(137)	R+R=OCH_2O	(139)	R+R=OCH_2O	(141)	R+R=OCH_2O

Scheme 2.22

The recommended procedure for decarboxylation uses quinoline and copper[96], but it was found that a very efficient and simple decarboxylation involves merely heating (134) with copper bronze powder to give (135), in yields comparable to the literature values. This method was then applied to the cinnamic acids (136) and (137) which decarboxylated readily to give (138) and (139). The nitrostyrenes (138) and (139) were reduced to the corresponding aminostyrenes using aluminium amalgam. This procedure for the synthesis of alkoxy-aminostyrenes is most useful, not only in the present context, but because of the importance of styrenes as polymer precursors and also as synthetic intermediates; for example, 2-acetaminostyrenes have been used in the synthesis of indoles and quinolines[98].

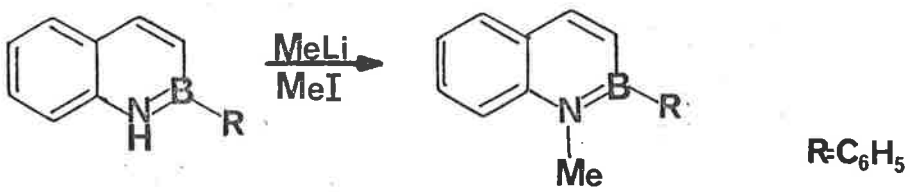
A preliminary investigation of the preparation of (132) was made using phenylboron dichloride in a similar manner to that in which (128) was prepared. This approach suffers from the possibility that boron trichloride may demethylate the aryl methyl ethers[99]. Nevertheless, treatment of (140) with phenylboron dichloride afforded (132), albeit in low yield†. It does seem likely, however, that (140) and other alkoxy-borazanaphthalenes may be prepared successfully, as it has recently been

† Due to the unsuccessful attempts to alkylate (24), as described later, no further work was undertaken in this area.

reported that treatment of methoxyanilines with boron trichloride and alkyl isocyanates yielded *ortho* formylated secondary anilines[100].

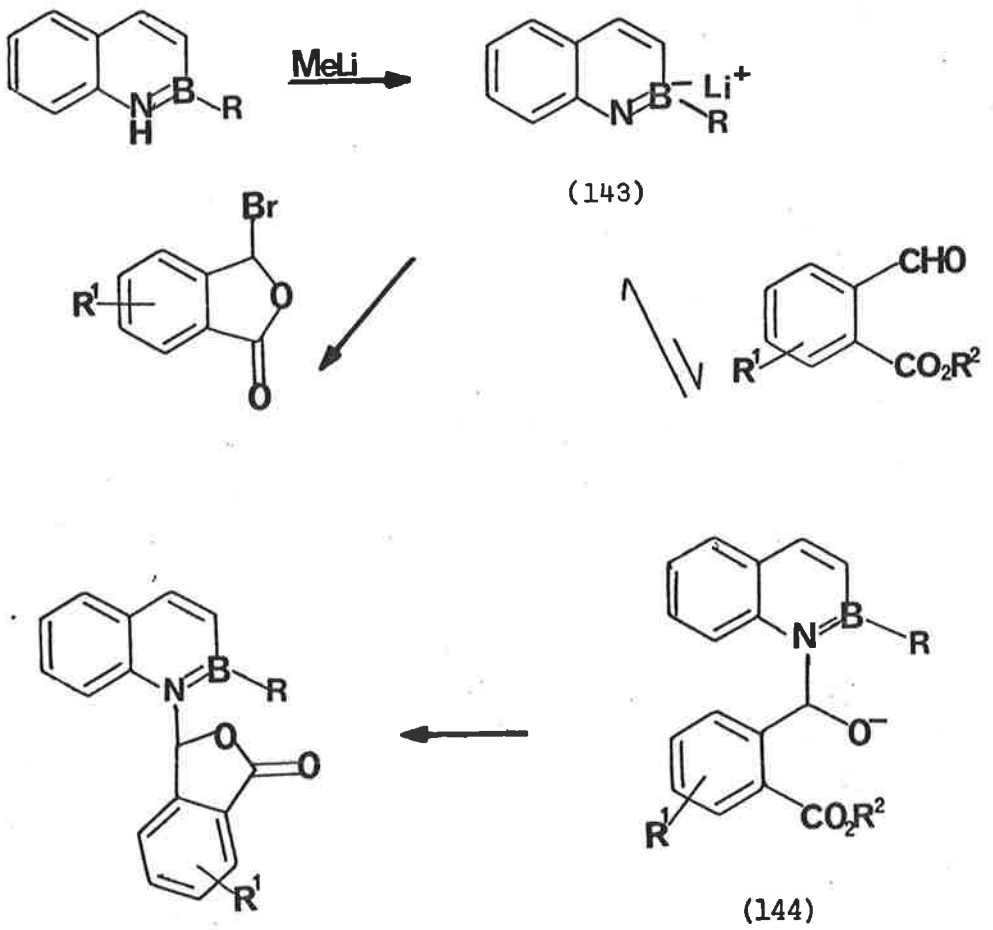
With the availability of (24) and (128) we proceeded to investigate the alkylation of the borazanaphthalenes.

The key step leading to the formation of (5) involves the alkylation of the N-lithio derivative (143) with a 3-bromophthalide. Although we were able to methylate (128) to give (142), numerous attempts to effect the condensation between (128) and the 3-bromophthalides, using various reaction conditions, proved unsuccessful. Alternatively, it was hoped that (128) would condense with methyl-2-formylbenzoates, to yield (144) which should then lactonise (Scheme 2.23), but unfortunately this too proved unsuccessful. The failure of (128) to be alkylated was initially believed to be due to the bulk of the phenyl ring, which prevents the formation of the N-Cl' bond. Steric interactions are not the problem as the B-methyl analogue (24) also fails to react with 3-bromophthalides or methyl-2-formylbenzoates*. There was some suggestion that the initial intermediate (144) was formed as evidenced by the p.m.r. spectrum of the crude reaction product which showed the complete disappearance of the aldehydic proton of the formylbenzoate, but no products were isolated. A possible explanation for the failure to achieve the desired alkylation was that the intermediate (144), which is similar



(128) (142)

* These results are detailed in Table V in the experimental section.



(143)

(144)

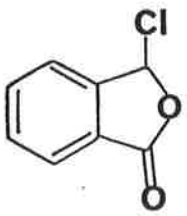
(5) R= Alkyl or Aryl

(26) R= Me

R= Me or C_6H_5

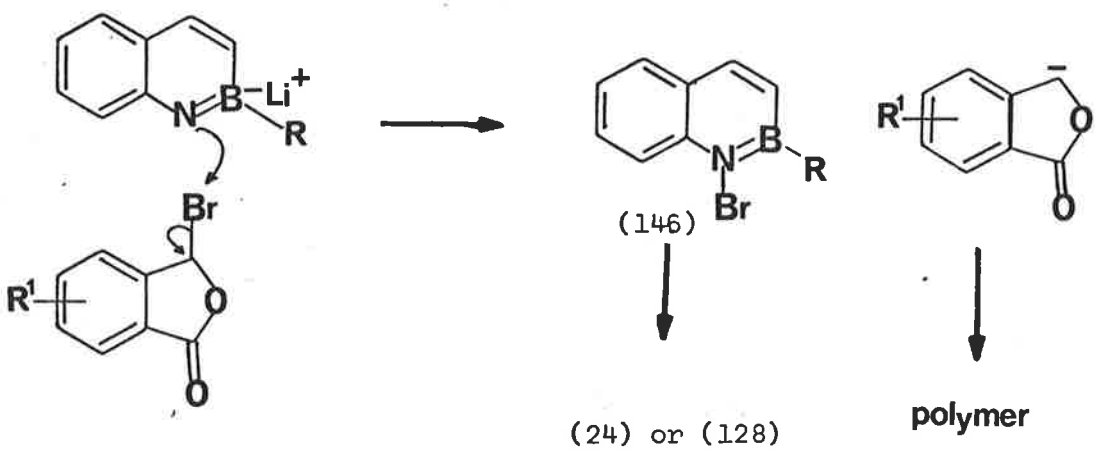
R^2= Me

Scheme 2.23



(145)

to an acetal, was thermodynamically less stable than the reactants, particularly on work up. The course of the reaction of (143) with 3-bromophthalides is believed to proceed as depicted in Scheme 2.24, where



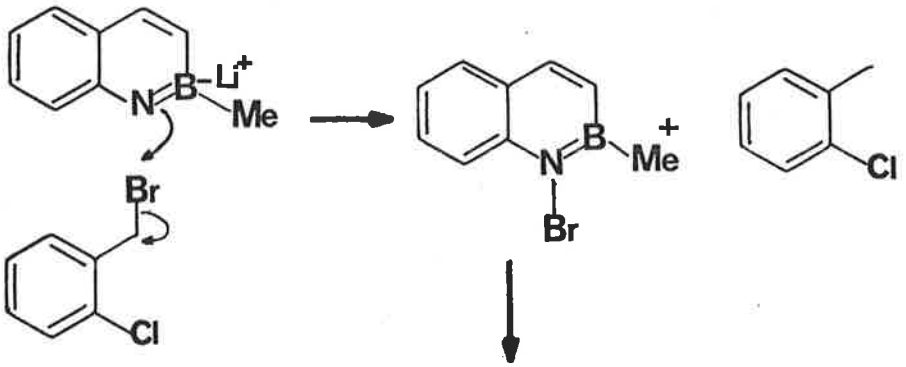
Scheme 2.24

the lithiated intermediate reacts at the bromine to give (146) and a phthalide anion. Further reactions lead to starting 2,1-borazanaphthalenes and polymeric material (Scheme 2.24).*

The results obtained later and discussed below suggested that a reaction between (143) and 3-chlorophthalide (145) may have warranted investigation but due to an insufficient quantity of (24) this reaction could not be attempted.

Due to the previous lack of success, an alternative approach was investigated. A possible approach is detailed in Scheme 2.26. If the nitrogen-carbon bond was formed, the lactone ring could then be constructed by benzylic bromination and internal displacement by carboxylate, thus yielding the desired compounds of type (5). An exploratory reaction between (24) and o-chlorobenzyl bromide proceeded via an unexpected pathway

* This suggested pathway is based on the results obtained when an attempt was made to alkylate (143) with o-chlorobenzyl bromide (147) described below.



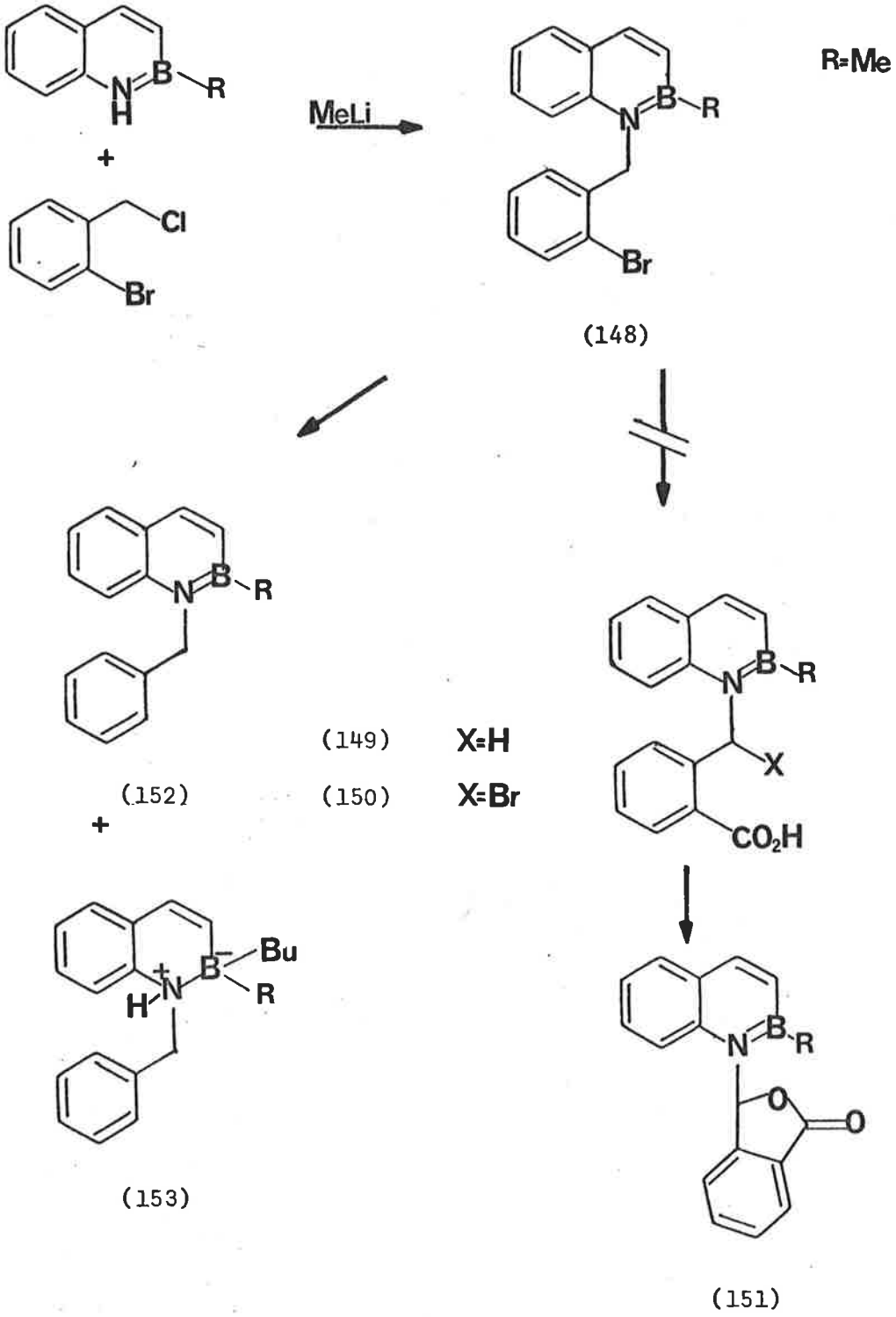
(24)

Scheme 2.25

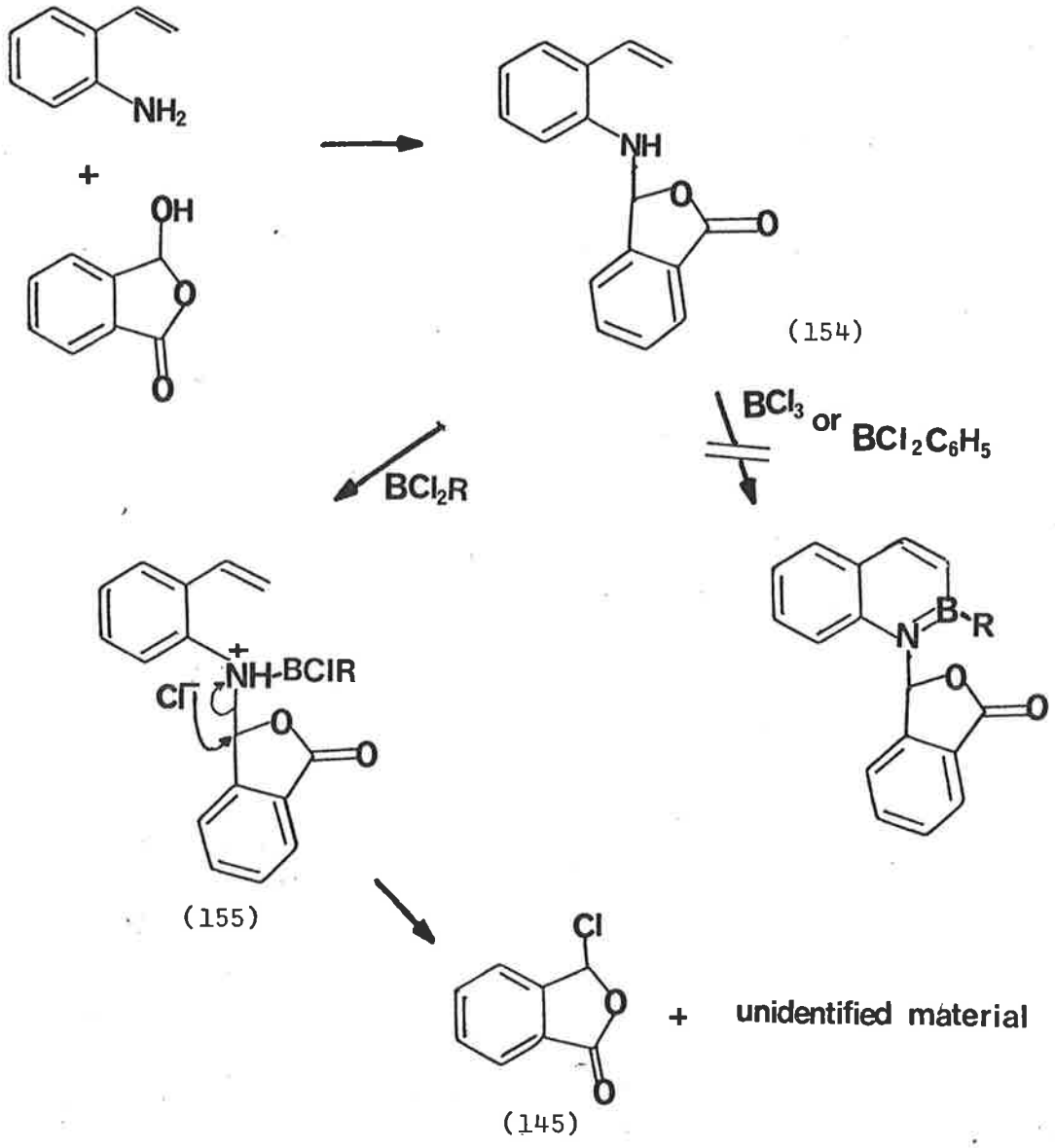
which led to the formation of o-chlorotoluene and (24; Scheme 2.25). The desired reaction was achieved, however, when (24) was alkylated with o-bromobenzyl chloride (147) to give (148). It was anticipated that lithiation of (148) with butyl lithium and then carboxylation would afford (149). Benzylic bromination with N-bromosuccinimide (150), followed by lactonisation would then yield (151; Scheme 2.26). Surprisingly, the lithiation of (148) with butyl lithium and carboxylation with carbon dioxide gave two products, (153) and (152), neither of which was the expected product (149).

The remaining synthetic pathway leading to compounds of the type (5), involved the introduction of boron in the final step (Scheme 2.27).

Although o-aminostyrene condensed smoothly with phthalaldehydic acid to give (154), the addition of either phenylboron dichloride or boron trichloride to the double bond occurred more slowly than cleavage of the benzylic carbon-nitrogen bond. Presumably the intermediate (155) is involved (Scheme 2.27). Because of the difficulties associated with the cleavage of the carbon-nitrogen bond, no further work in this area was undertaken.

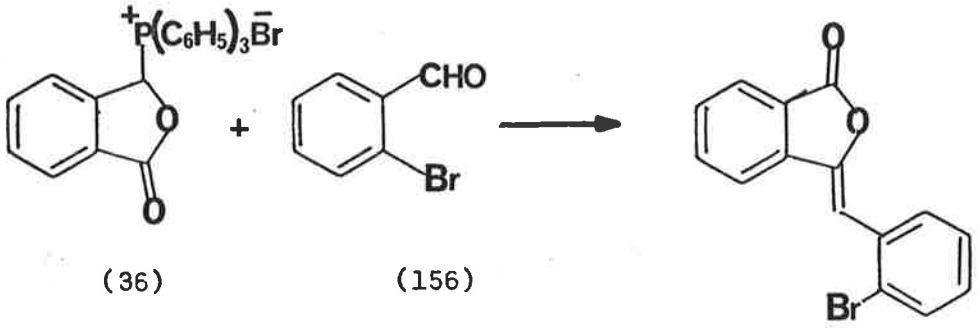


Scheme 2.26

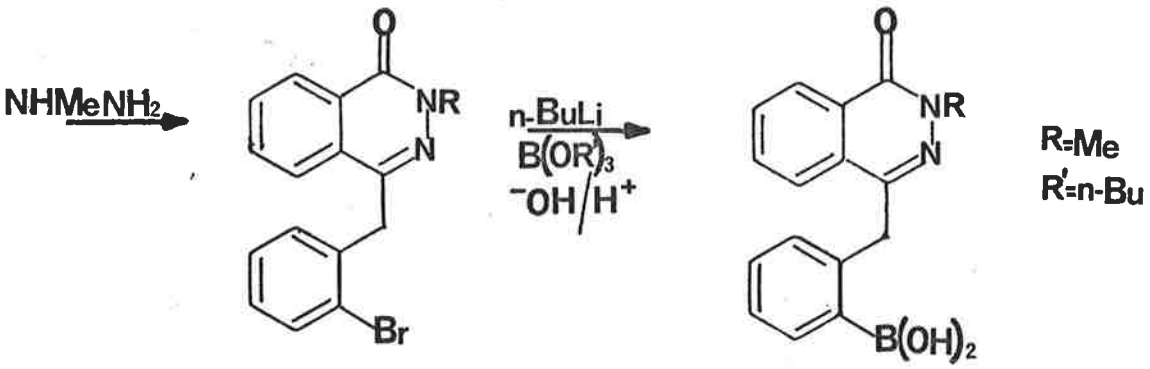


Scheme 2.27

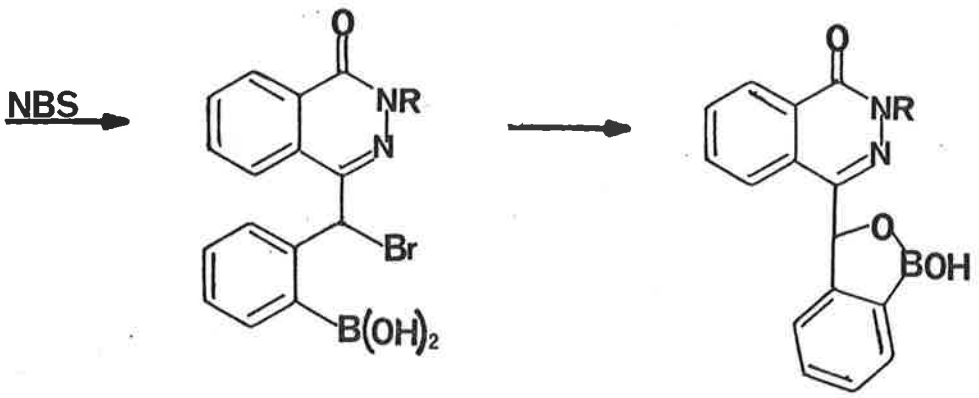
Two possible approaches were investigated as methods for the synthesis of compounds of type (25) (Schemes 2.28 and 2.30). It was anticipated that treatment of (158) with butyl lithium and then tributyl-borate (or similar species) would yield (159). This could then be brominated to give (160) and then cyclised to give (161).



(36) (156) (157)



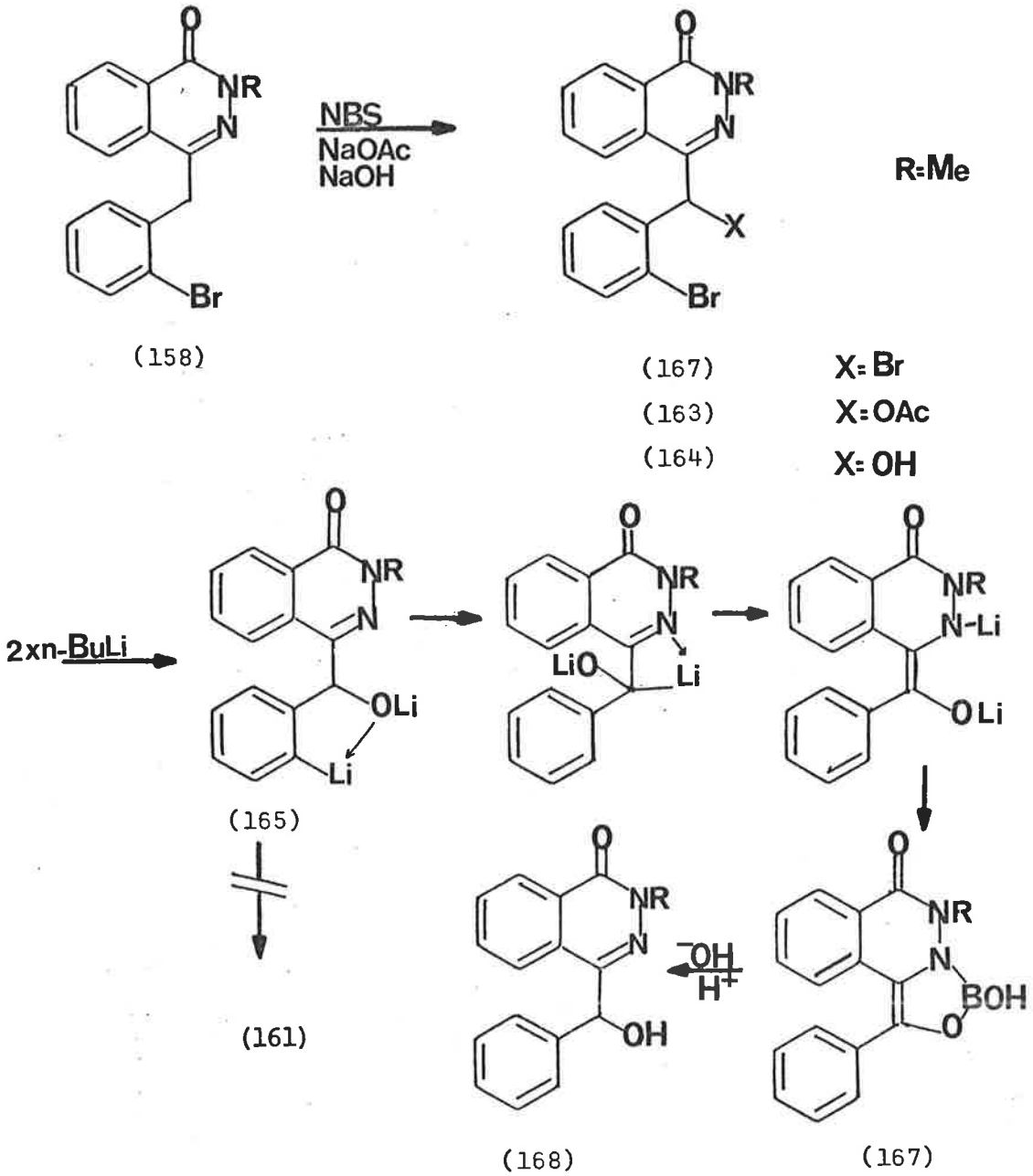
(158) (159)



(160) (161)

Scheme 2.28

o-Bromobenzaldehyde (156) and (36) reacted smoothly to give (157) which was converted directly to (158) with methylhydrazine. Unfortunately, treatment of (158) with butyl lithium and then tributylborate gave a mixture of products. It appears that although the transmetallation occurred, the aryl lithium underwent an alternative reaction pathway involving the amide carbonyl. By introducing another functional group at the benzylic position, for example, a hydroxyl group, it was hoped that an increase in the stability of the aryl lithium would result. The stabilizing effect of



(158) (167) (163) (164) (165) (161) (168) (167)

Scheme 2.29

the additional oxygen on the aryl lithium (165)†, should thus reduce the possibility of any side reactions. Although (158) underwent benzylic bromination cleanly with N-bromosuccinimide, attempted hydrolysis afforded a complex mixture. Thus, (162) was converted to (163) with sodium acetate in dimethylformamide and then hydrolysed readily to (164; Scheme 2.29). Treatment of (164) with two equivalents of butyl lithium and then tributyl borate did not give the expected product, but gave various unidentified compounds. A similar experiment was attempted with 2'-bromopapaverine (described in Part III) but only papaverine was recovered. Results obtained from the experiments associated with the lithiation of 2'-bromopapaverine suggest that the transmetallation of (158) and (164) occurs readily, but because the benzylic proton is quite acidic, due to stabilisation of the resultant anion, and because tributyl borate is a relatively weak electrophile, the reaction occurs at nitrogen to give (167)*. Hydrolysis then affords (168; Scheme 2.29) and several unidentified products.

The second approach (Scheme 2.30) to compounds of type (25) applied a similar strategy to that used successfully in the synthesis of the phthalidylphthalazinones. It was hoped that a Wittig reaction between (172) and phthalic anhydride (35a) would yield the intermediate (173) which on treatment with methylhydrazine and then acid would give (159). The bora lactone ring could then be constructed as described previously to give (161).

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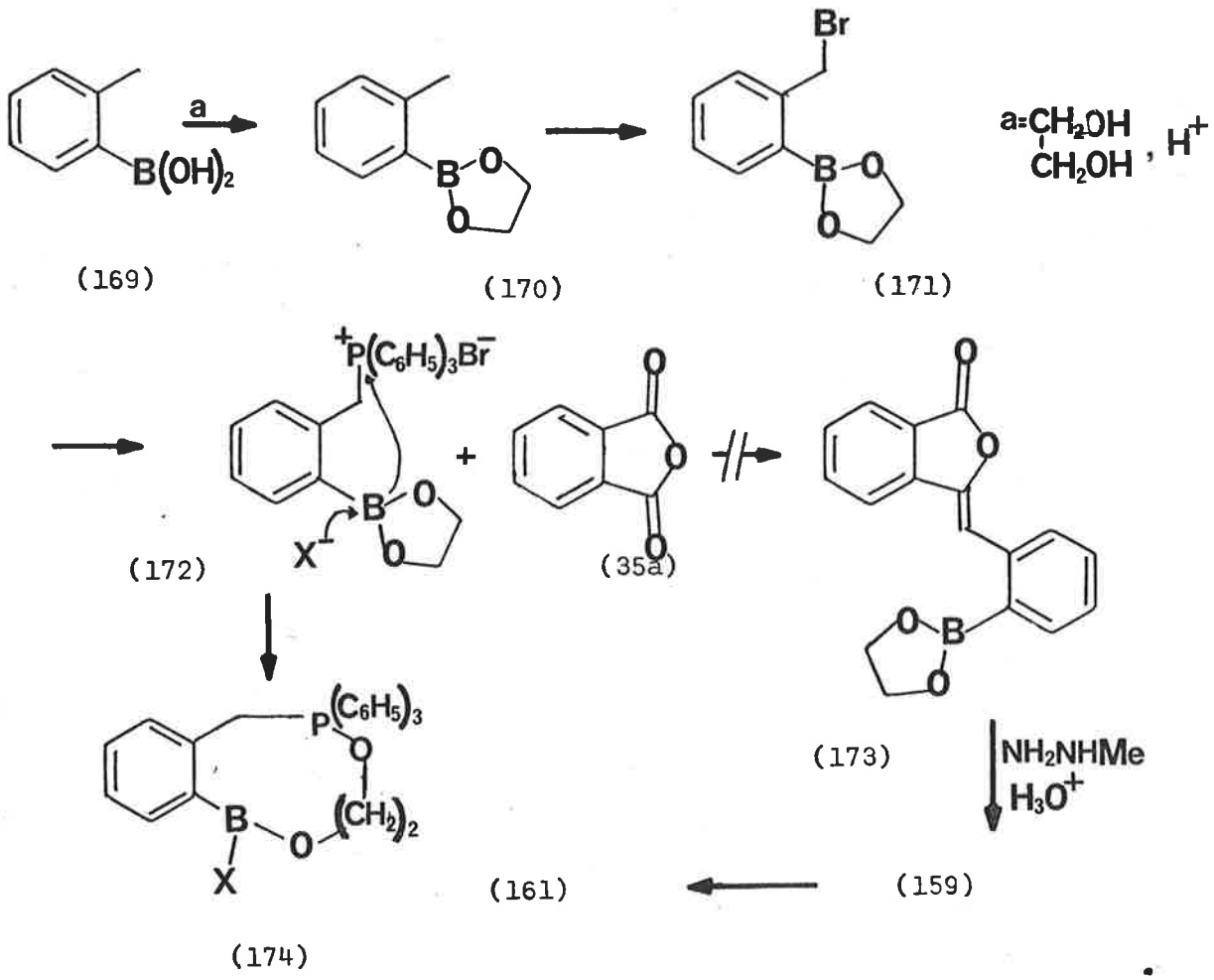
† This type of stabilisation has been utilised in the synthesis of alkoxy-phthalides, as described in Part III of this thesis.

* Similar results have been observed in attempts to prepare phthalide-isoquinolines using transmetallation reactions[80].



Scheme 2.30

o-Tolylboronic acid (169) was converted to the boradioxalane (170) which then afforded (171) on treatment with N-bromosuccinimide and benzoyl peroxide. Although (171) and triphenylphosphine reacted smoothly to give (172), the required Wittig reaction did not proceed as expected. A number of bases were used in attempts to generate the phosphorane but without success, and it appears that a reaction between the base and boron predominates over the formation of the phosphorane. The nature of the reaction is uncertain, but the extraordinary lability of the boradioxalane group even under neutral conditions suggests that the formation of a phosphorane of type (174) is facilitated by nucleophilic attack at boron. An additional complication of the approach using the phosphonium salt, was the ease with which the acetal group was hydrolysed. Because of these experimental difficulties the synthesis was not further investigated.

PART III

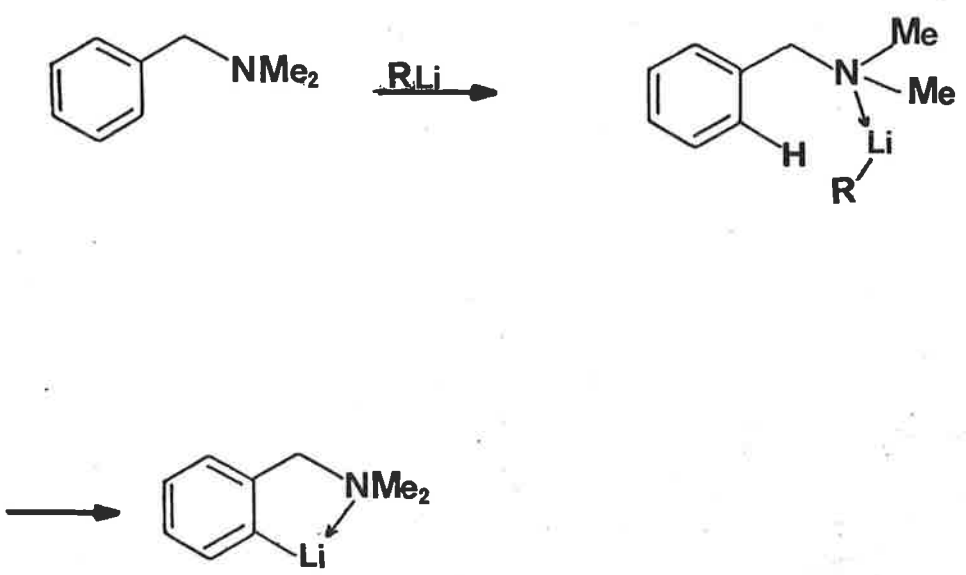
AROMATIC LITHIATIONS

CHAPTER I : INTRODUCTION

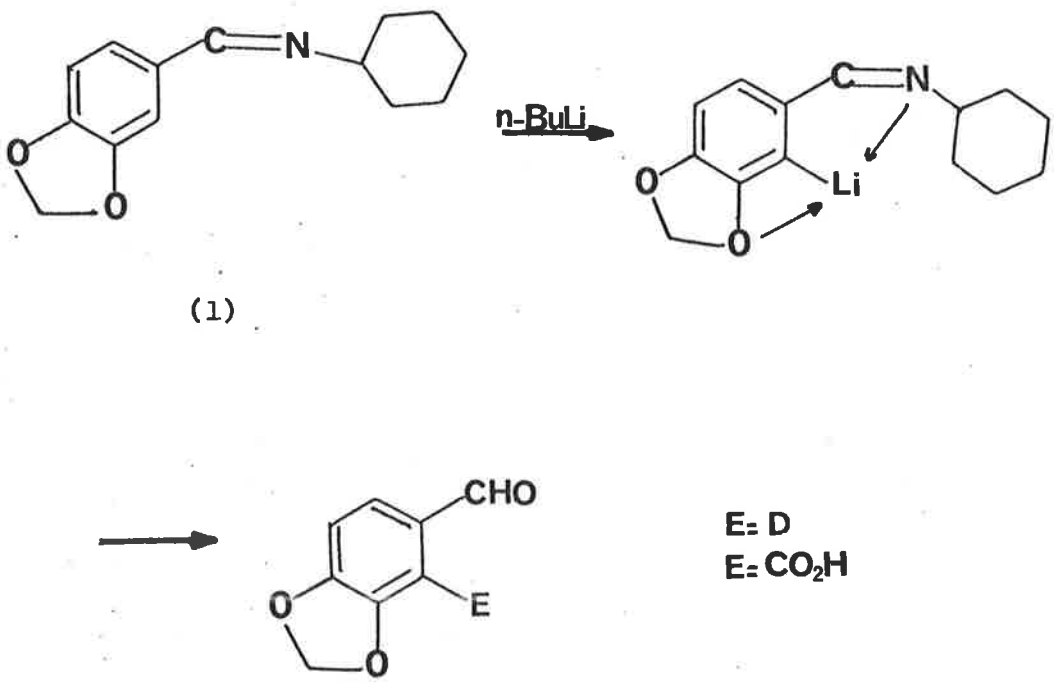
The replacement of a hydrogen atom by a metal in general is termed metallation and in particular, by lithium, is termed lithiation[1]. Heteroatom facilitated lithiation has become an important synthetic tool in carbocyclic, aromatic, heteroaromatic as well as aliphatic systems[1]. This is a result of the commercial availability of organolithium reagents which has allowed the discovery of various functional groups that promote metallation and the elaboration of a variety of metallatable species.

The lithiation of aromatic systems either by direct lithiation or lithium-halogen exchange has been used extensively in organic chemistry to afford substituted aromatic compounds that are otherwise difficult to prepare[1-4]. *Ortho* disubstituted aromatic compounds can be prepared virtually uncontaminated by *meta* or *para* isomers due to the ability of certain substituents to direct lithiation *ortho* to the substituent[2]. The substituents capable of directing lithiation to the *ortho* position upon metallation with n-butyllithium include NMe_2[5], CH_2NMe_2[6], $CH_2CH_2NMe_2$[7], OMe[8], CONHR[9,10], SO_2NHR[11] and SO_2NR_2[12]. Intramolecular competition reactions have shown that tertiary amide functions are superior to sulfonamides, oxazoline, methoxyl, (dimethylamino)methyl, chloro, carboxyl and methyl groups in their ability to direct lithiation to an adjacent position[10]. These lithiations are presumably facilitated by the initial coordination of the lithium atom with the heteroatom which is followed by attack at the proton *ortho* to the substituent, leading to an internally chelated organolithium species (e.g. Scheme 3.01)[13,14].

Only a limited number of reports have used modified aromatic aldehydes as a means of ortho direction for aromatic substitution. The cyclohexylimine of piperonal (1) was lithiated and quenched with various electrophiles to give the 2-substituted aldehydes (2) in moderate yields (Scheme 3.02)[3]. Because of the greater bulk of the freely rotating methyl groups in the cyclohexylimines of veratraldehyde and m-anisaldehyde,



Scheme 3.01

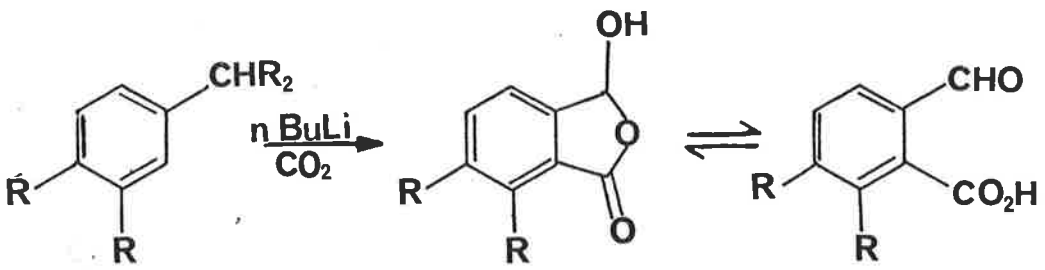


(1)

(2)

Scheme 3.02

analagous experiments failed[15]. Recently however, Rodrigo[15] *et al.* have successfully lithiated regiospecifically, the 2 position of the dimethyl acetal of benzaldehyde and some 3-, 3,4-, and 3,4,5-oxygenated derivatives. This method is important as it leads to a cheaper and more efficient preparation of opianic acid (3; Scheme 3.03).



(3)

Scheme 3.03

Such substances are important in the synthesis of various naturally occurring isoquinoline alkaloids[16].

The aromatic bromine-lithium exchange is two to eight times faster than the corresponding aromatic deprotonation reaction[17]. Thus the halogen-metal exchange, due to its greater velocity, allows lithiation at a less acidic position and so gives an organo lithium compound that cannot be obtained by direct metallation[17]. This selectivity of transmetallation against direct metallation is exemplified in the results of Wittig *et al.*[18] who reported that treatment of 2,4-dimethoxybromobenzene (4) with n-butyl lithium forms an aryl lithium at the 4-position (5), while resorcinol dimethyl ether (6) deprotonates at the position mutually *ortho* to the two methoxyl groups (7). The redox reaction of nitro aromatic compounds is very fast even at -100° in tetrahydrofuran, but 2-nitrobromobenzene

(4) (5)

(6) (7)

undergoes even faster bromine-lithium exchange at -100° [17]. Gilman *et al.*[19,20] and others[21] have shown that treatment of bromobenzyl alcohols (8), or bromoanilines, with at least two equivalents of butyl lithium, followed by the reaction with a particular electrophile resulted in the substitution of the aromatic bromine. (Scheme 3.04).

(8)

Scheme 3.04

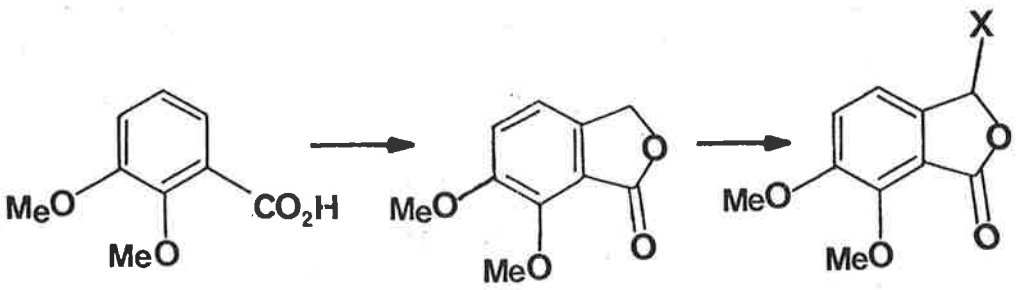
Aromatic lithiation is now an important method in synthetic chemistry and our interest was stimulated to apply this chemistry to obtain a simple and efficient procedure for preparing oxygenated phthalides and derivatives, which are important synthons in the synthesis of isoquinoline alkaloids.

CHAPTER 2

RESULTS AND DISCUSSION

2.1 SYNTHESIS OF ALKOKY- AND CARBOXYPHTHALIDES

Substituted phthalides or their derivatives have been used extensively in the synthesis of various compounds including anthraquinones[22], naphthols[23], phthalideisoquinolines[24] and other naturally occurring alkaloids[16]. An important precursor in some of these syntheses is 6,7-dimethoxyphthalide, commonly called meconine (9). It has been used successfully by Tippett[22] as a nucleophilic species in the preparation of cordrastine, while (±)-α-narcotine was first prepared using meconine[25]. Benzylic bromination of (9) with N-bromosuccinimide affords an electrophilic species (10) which was used in the synthesis of phthalidylcinnolinones (Part II). Hydrolysis of (10) affords opianic acid, which has been



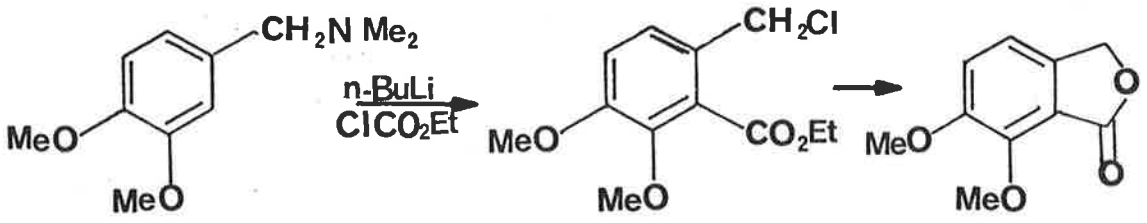
(11) (9)

(3) X:OH
(10) X:Br

used in the preparation of phthalideisoquinolines[16,26] and related compounds.[27] The usual method for the preparation of meconine involves formylation of the expensive 2,3-dimethoxybenzoic acid (11) and yields are low and the method involves prolonged separation procedures[28]. The method of Rodrigo[15] affords (3) in high yields, and this acid on reduction gives rise to meconine, but such procedures are not always

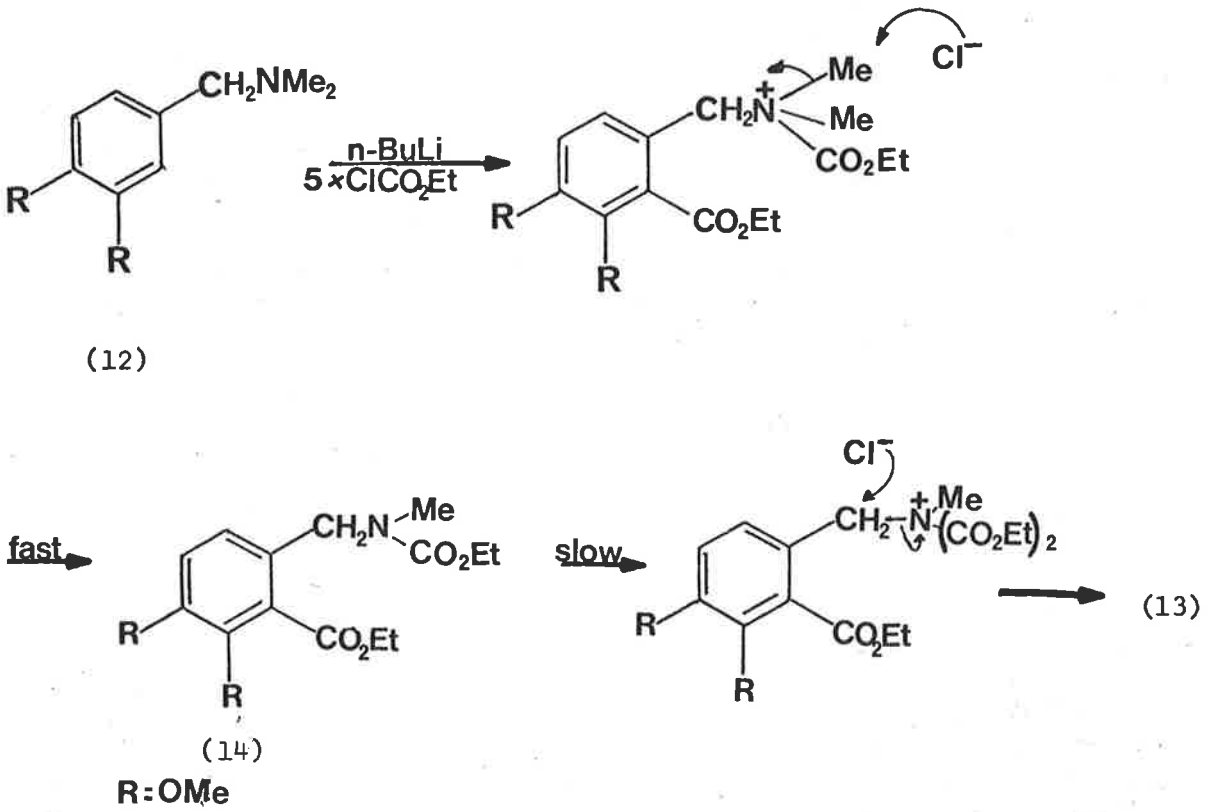
efficient[29]. Sniekus[4] has reported the preparation of meconine by a four step sequence starting with (11). A simple and efficient preparation of meconine would clearly be desirable and we considered that a suitable approach would be based on the metallation of a 1,3,4-trisubstituted aromatic species.

Hauser[6] has successfully performed *ortho* metallation of benzyldimethylamines with butyl lithium and Slocum and Jennings[2] report that metallation of 3-methoxybenzyldimethylamine occurs exclusively at the position mutually *ortho* to both the methoxyl group and the aminomethyl side chain. Rapoport and Dean[30] extended these results in their synthesis of berbines whereby they treated (3,4-dimethoxyphenylmethyl)-N,N-dimethylamine (12) with butyl lithium and ethyl chloroformate to produce (13), which potentially, could lactonize to yield (9)[31]. Surprisingly, no comment had been made on the mechanism of the deamination process which led



(12) (13) (9)

to the formation of (13). When the metallation of (12) was attempted and the reaction followed by p.m.r. spectroscopy, the stepwise nature of the reaction pathway became obvious. (Scheme 3.05).



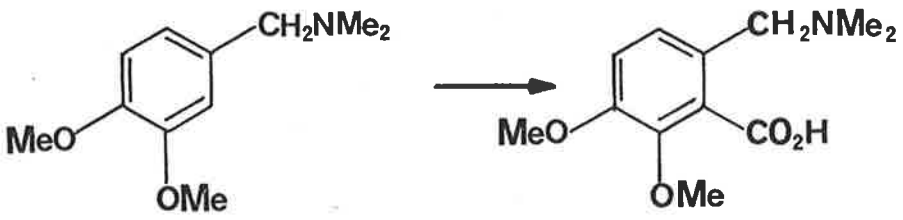
Scheme 3.05

One N-methyl group was seen to cleave rapidly and, as expected, the intermediate carbamate (14) was acylated only slowly. This dealkylation pathway was also seen to occur when (12) was stirred with excess ethyl chloroformate.

Although ethyl chloroformate has recently been used for the demethylation of amines by Krauss and Nador[34], phenyl chloroformate has more frequently been used for the demethylation of amines[35]. During the dealkylation of amines using phenyl chloroformate, benzylic cleavage is known to predominate over N-methyl cleavage[36,37], so it was somewhat surprising that in the reactions shown in Scheme 3.05, the first methyl group was removed so rapidly.

When the reaction of Rapoport's[30] was repeated, a high yield of (13) was obtained, but on substituting carbon dioxide for ethyl chloroformate, a very low yield of the amino acid (15) was obtained, probably in part, due to its high water solubility. The synthesis of (9) by the

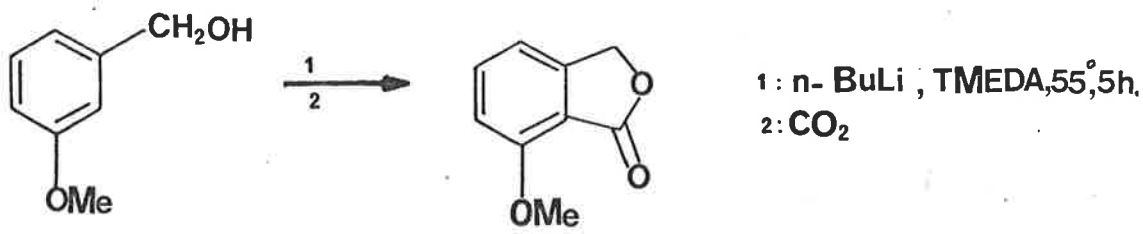
lactonisation of (13) or (15) is limited in its usefulness because the methods for preparing (12) are plagued by low yields or expensive and inconvenient starting material[32,33]. Despite the above procedures a simple and more efficient preparation of meconine was still required.



(12) (15)

Uemura and *co-workers*[38] have reported the successful synthesis of methoxyphthalide derivatives by carboxylation of the lithiated aromatic compounds derived from m-alkoxybenzyl alcohols.

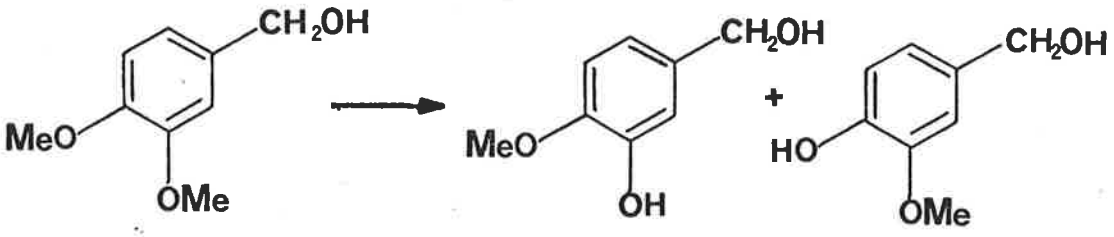
For example, 3-methoxybenzylalcohol (16) was converted to 7-methoxyphthalide (17) on treatment with two equivalents of butyl lithium followed by carbon dioxide. They report, however, that 3,4-dimethoxybenzyl



(16) (17)

alcohol (18) fails to lithiate, but instead undergoes demethylation to give

(19) and (20). Despite the reported failure of (18) to metallate, and with the knowledge that (12) metallates under very mild conditions, it was



(18) (19) (20)

believed that the preparation of meconine via the lithiation of (18) warranted further investigation. The choice of solvent is critical: it is known that as the alkyl lithium aggregate size diminishes, the alkyl lithium becomes kinetically more basic[1]. Thus a variation in choice of solvent may result in the formation of the desired aryl lithium. It was anticipated that the reaction of (18) with two equivalents of butyl lithium would readily produce the intermediate (21) which appears to be ideally substituted for stabilisation, especially as (12) is reported to metallate so readily[30]. Additionally, the intermediate (21) is stabilised inductively by the methoxyl group *meta* to the carbon-lithium bond.

Treatment of (18) with two equivalents of butyl lithium in tetrahydrofuran at 20° for 2 hours resulted in the formation of a white suspension into which dry carbon dioxide was bubbled. Lactonisation under the acidic work up conditions afforded 6,7-dimethoxyphthalide (9) in 65% yield. 3,4-Methylenedioxybenzyl alcohol (22) was similarly converted to 6,7-methylenedioxyphthalide (24)†.

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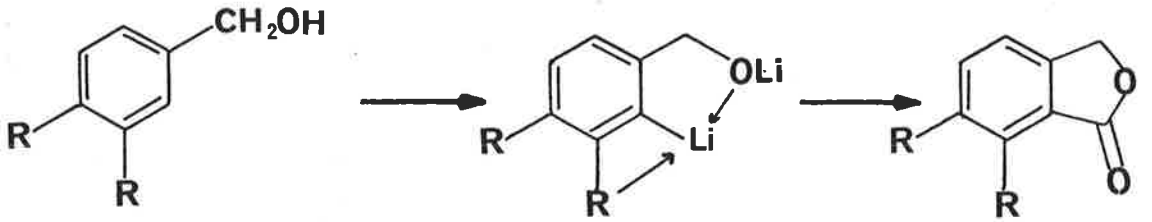
† While this Thesis was being prepared Trost[54] reported the synthesis of 5-methoxy and 5,7-dimethoxyphthalides by the metallation of the appropriate benzyl alcohol.



(18) R=OMe

(22) R+R=OCH_2O

(21) R=OMe

(23) R+R=OCH_2O

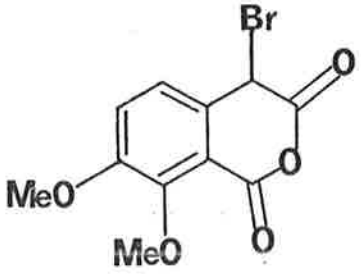
(9) R=OMe

(24) R+R=OCH_2O

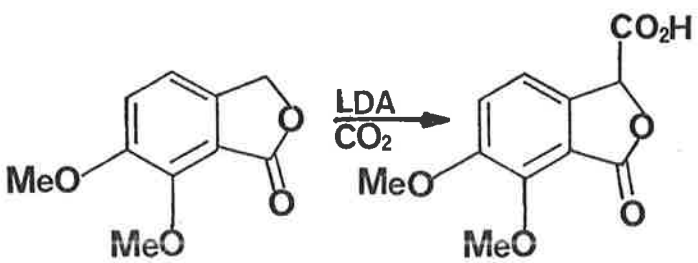
The above conditions were found to be optimum, as extended metallation time, use of hexamethylphosphoric triamide as a co-solvent, or ether as a solvent, resulted in only starting material being recovered. These results raised some interesting mechanistic aspects which will be dealt with later.

Since alkoxy benzyl alcohols are readily available, the lithiation and carboxylation of these alcohols provides a quick and efficient synthesis of phthalides, in particular, meconine and (24).

While the investigation into an improved synthesis of meconine was in progress, Snieckus[39] reported the preparation of the bromohomophthalic anhydride (25) via a four step sequence in an overall yield of about 40%.



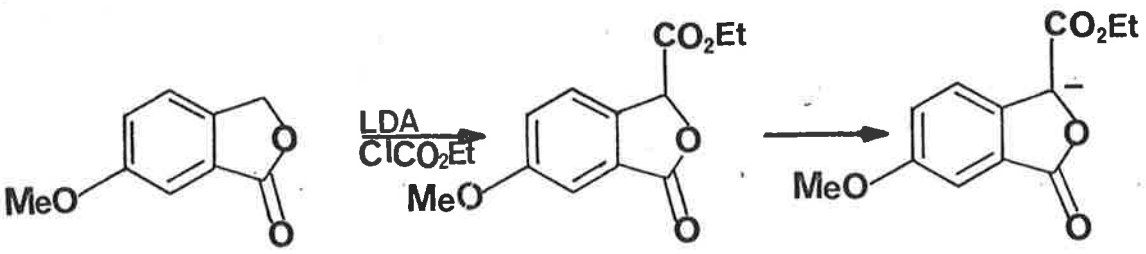
(25)



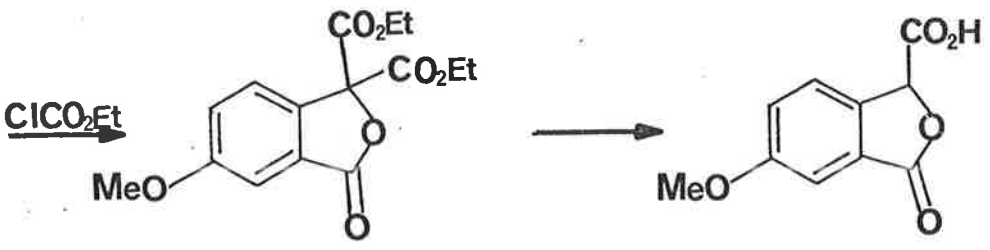
(26)

Both (25) and the carboxylic acid (26) have been used in the synthesis of phthalideisoquinolines[16,39-41]. The use of (26) and similar acids in synthesis has been limited, since they were not readily available. The results of two groups of workers[22,23] who successfully generated and reacted the anion of various phthalides, prompted us to investigate the preparation of (25) by the carboxylation of the anion of meconine.

Treatment of meconine with lithium diisopropylamide at -78° for 2 minutes and then carbon dioxide afforded (26) quantitatively. Thus (26) can be prepared in two steps in an overall yield of 65% from a cheap starting material (18). This compares favourably with the method of Snieckus[4,39] which required the more expensive 2,3-dimethoxybenzoic acid. A complication arises when ethyl chloroformate is substituted for carbon dioxide in the above procedure. Thus, the product from 6-methoxyphthalide (27) and lithium diisopropylamide reacts with excess ethyl chloroformate, to give a complicated product mixture. The initially formed ester (28) was rapidly deprotonated by diisoproplyamine and then carboxylated (Scheme 3.06).



(27) (28)

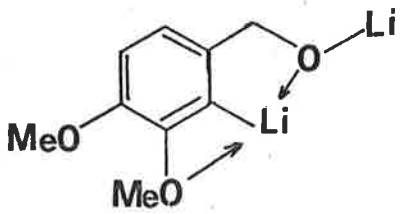


(29)

Scheme 3.06

The mixture of esters was successfully hydrolysed and decarboxylated to the desired acid (29). Thus, alkoxyphthalides of the type (9) and carboxyphthalides of the type (26) are now readily available.

A puzzling mechanistic detail remains. As previously mentioned, lithiation of (18) under various conditions led only to the recovery of starting material. It was interesting to note that metallation of (18) afforded a white precipitate at room temperature, compared with the metallation of (22) which resulted in a pale yellow solution at 0°. This difference in solubility of the dilithiated species (21) and (23) is presumably due to the better co-ordinating ability of the methylenedioxy



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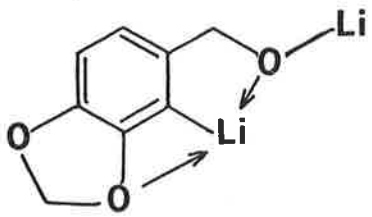
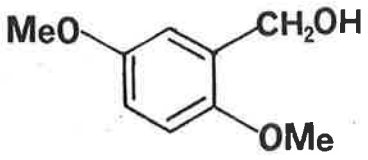


(23)



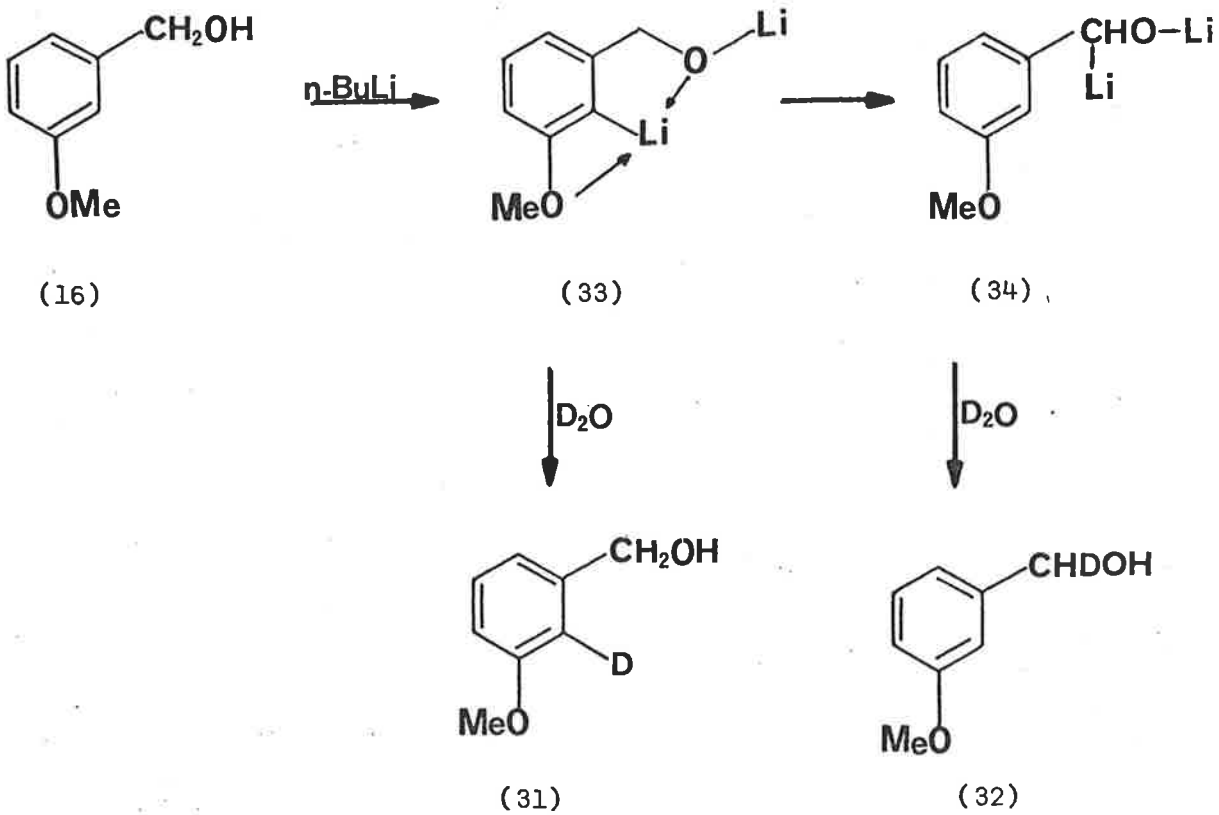
(30)

group[15], thus decreasing the ionic character of the dilithiated species (23) with a subsequent increase in solubility. This white precipitate (21) was unexpected, as treatment of 2,5-dimethoxybenzyl alcohol (30) with two equivalents of butyl lithium affords only a red solution[42].

The failure to observe carboxylation of (21) under the extended reaction times or more polar solvent suggests that the aryl lithium reacts with tetrahydrofuran. It is known that alkyl and aryl lithium reagents abstract protons from etheral solvents[43-45,48]. It appears that the optimum yields are related to the stability of the aryl lithium (21). Thus in the presence of hexamethylphosphoric triamide, a solubilizing co-solvent, the reactive dilithiated species, because it is in solution and

not suspension, reacts very readily with the solvent, thus yielding starting material. On extended metallating times, the dilithiated species (21) reacts slowly with tetrahydrofuran to again yield starting material. When ether was used as a solvent, the dilithiated species failed to form because the initially formed alkoxide (white precipitate) was too insoluble to allow the formation of the aryl lithium.

Another interesting result was observed when 3-methoxybenzyl alcohol (16) was treated with butyl lithium and then quenched with deterium oxide. After 3 hours, deuterium incorporation occurred exclusively on the aromatic ring to the extent of 60%. A shorter metallation time of 1.5 hours yielded only 10% aromatic deuterated product (31) but on allowing the metallation to proceed for 16 hours, the isolated product showed a mixture of benzylic deuterated alcohol (32) and aryl deuterated alcohol (31).



(16) (33) (34)

(31) (32)

This suggests that the kinetic product may be the aryl lithium (33), as it is known that in tetrahedronfuran the kinetic product predominates[1], but

that (33) converts to the more stable benzylic anion intermediate (34). The formation of (32) was surprising in view of the results of Ronald and *co-workers*[42]. They failed to observe any evidence for deprotonation at the benzylic position of (30). More recently, however, kinetic and thermodynamic products have been observed in the lithiation of some benzyl alcohols[53].

It is interesting to note, that the metallation of (16) is slower than the metallation of (18). Clearly, the additional electron withdrawing *meta* methoxyl group increases the rate of metallation.

2.2 THE TRANSMETALLATION OF 2'-BROMOPAPAVERINE

The introduction of boron into the phthalideisoquinoline ring system to produce bicuculline analogues containing boron (Part II, 2.3) had unfortunately proved unsuccessful. Our approach to the synthesis of these bora lactones depended primarily on transmetallation reactions. It was hoped that greater success might be achieved in similar transmetallation reactions with 1-benzylisoquinolines as the amide function of the phthalazinone appeared to interfere with the transmetallation. Also, the higher basicity of the isoquinoline nitrogen may assist in the delivery of the butyl lithium to the aryl bromide.

A most convenient and easily accessible model substrate was 2'-bromopapaverine (36) which is readily obtained by the bromination of papaverine (35)[46]. This compound had the advantage of having only a limited number of aromatic protons which made the analysis of the products by p.m.r. spectroscopy, less complicated.

(35) (36)

Because halogen-metal exchange reactions occur so readily[17], it was envisaged that treatment of (36) with butyl lithium would afford an aryl lithium which would act as a precursor for boron containing analogues of

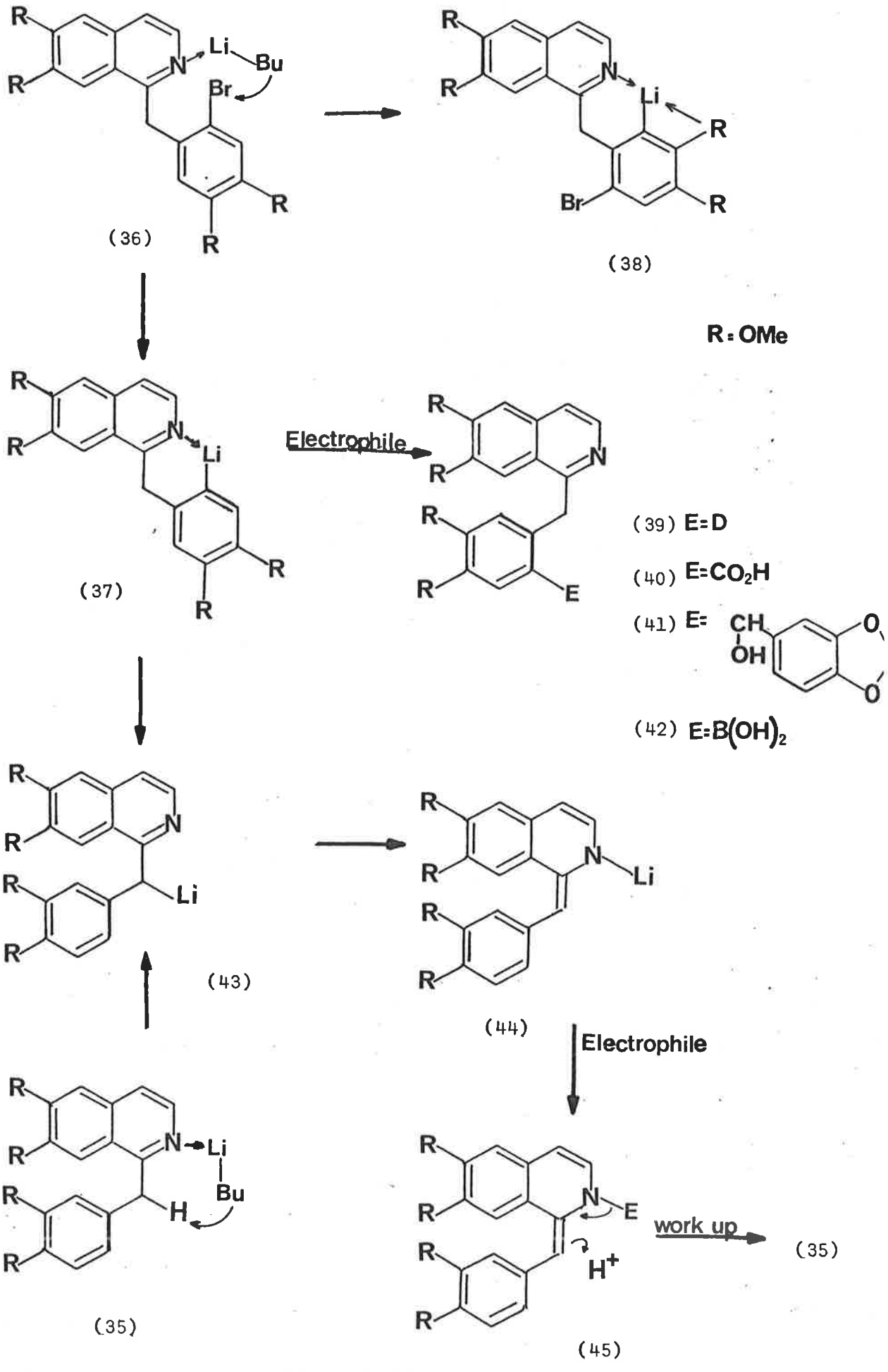
bicuculline. The system (36) has the advantage that due to the chelating effect of nitrogen with lithium, the butyl lithium will be delivered readily to the bromine increasing the rate of halogen-lithium exchange, which should thus compete successfully with direct deprotonation, which would lead to (38), similarly stabilized.

Treatment of (36) with butyl lithium at -78°C afforded immediately a deep red coloured solution, which was quenched after 6 minutes with the appropriate electrophilic species. The compounds (39)-(41) were obtained in yields between 35-95%, but the reaction failed in the case of the boron compound (42). If the transmetallation was allowed to proceed for longer periods, yields of the required product were markedly reduced and the product was frequently only papaverine. When the electrophile was added, a yellow coloured solution resulted immediately and became colourless on workup.

The rapid protonation of 2'-lithiopapaverine (37) was a little difficult to comprehend and initially it was believed that the proton source was slightly moist solvent or perhaps the tetrahydrofuran, but further experimental results suggested this was not the case.

When tributylborate or boron trifluoruide etherate was used as the electrophile, the product was only papaverine. At -78° the red colour persisted, but after some time at -78° (about 2 hours), or on allowing the reaction mixture to warm to room temperature, a pale yellow coloured solution resulted. Apparently, the electrophilic boron species is too unreactive to react with the aryl lithium at these low temperatures. This lack of reactivity is seen in the preparation of o-tolylboronic acid[47] where the reaction between o-tolylmagnesium bromide and tributylborate requires 8 hours reaction time at 20°.

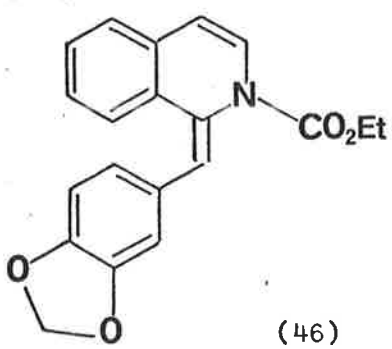
When papaverine was treated at -78° with butyl lithium, a blood red solution resulted instantly and afforded a yellow solution when dry carbon dioxide was introduced into the mixture. After acidification, the result-


(36)
(38)
R = OMe
(37)
Electrophile
(39) E=D
(40) E=CO2H
(41) E=
(42) E=B(OH)2
(43)
(44)
Electrophile
work up
(35)
(35)
(45)

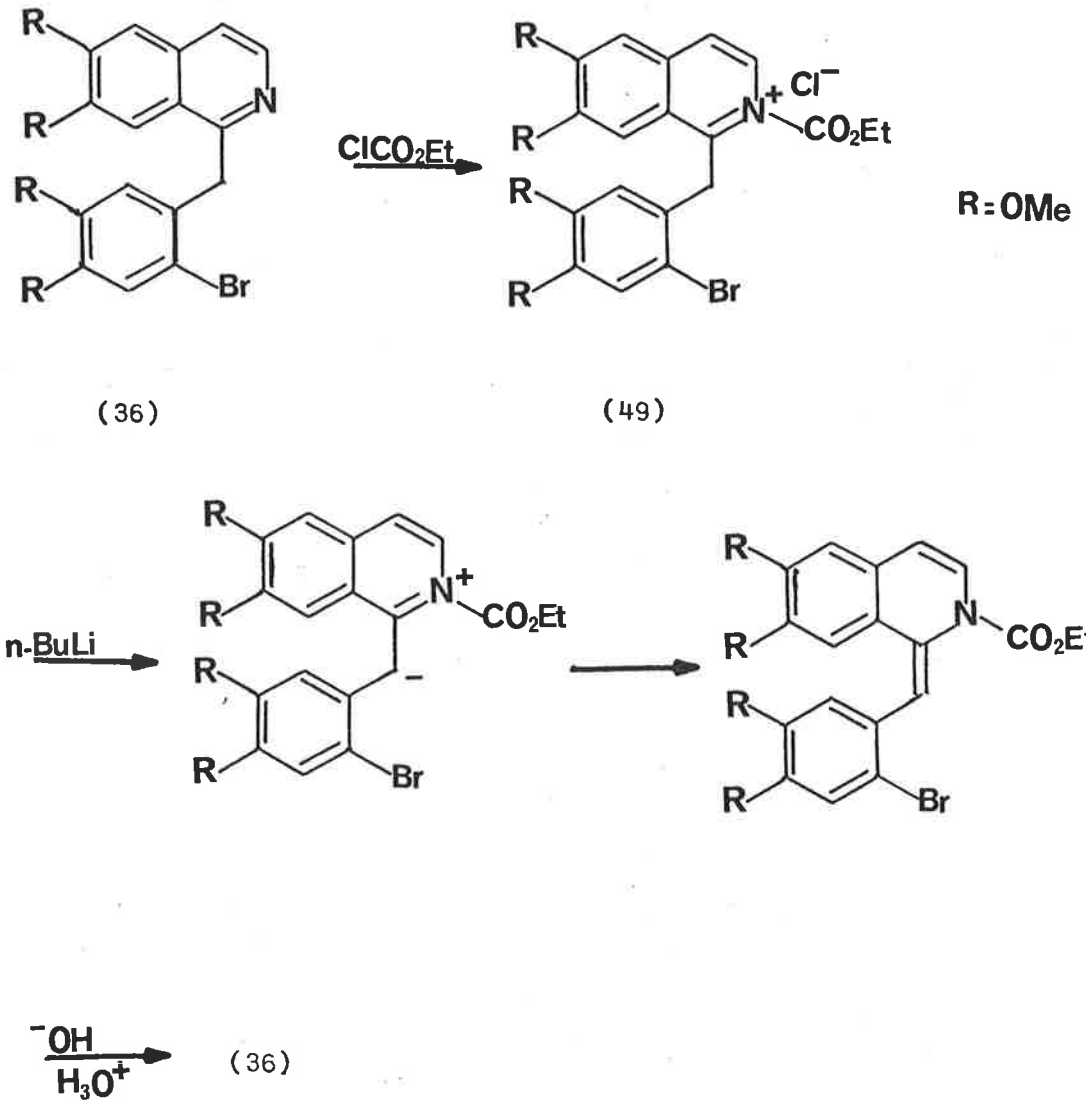
Scheme 3.07

ant colourless solution gave unchanged papaverine. Clearly, this red colour, apparently identical to that obtained during the transmetallation of (36), is due to the formation of the intermediate (43). This intermediate is formed preferentially because of the initial coordination of butyl lithium with the nitrogen of (35) which renders the benzylic proton more acidic than the aryl proton.

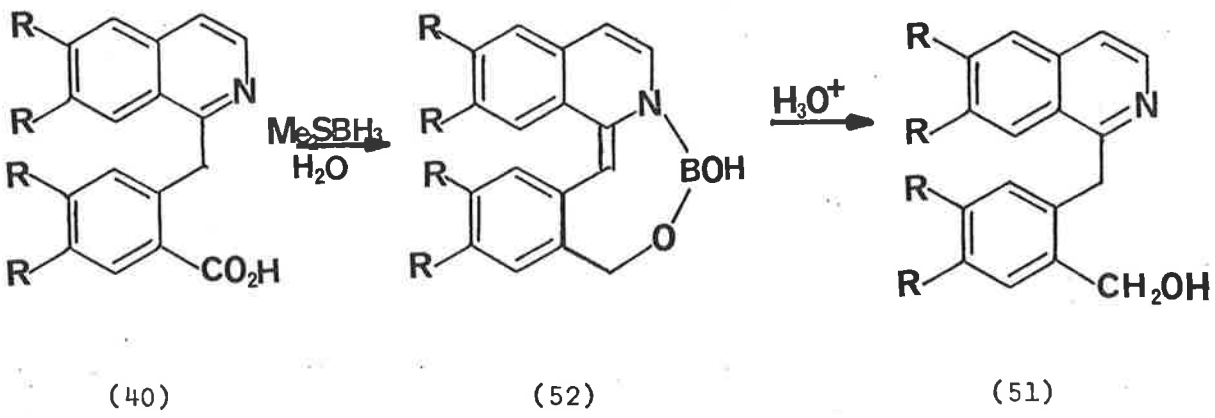
It now appears that the rapid protonation of (37) is not due to the nature of the solvent, but is associated with the acidity of the benzylic proton. The halogen-metal exchange reaction occurs very quickly but then two alternative reaction pathways are available for the 2'-lithiopapaverine (37). Reaction of (37) with an electrophile will give the products (39)-(41). However, the additional chelating effect between nitrogen and lithium renders the benzylic proton in (37) very acidic so that deprotonation of the benzylic carbon occurs very rapidly, with the result that considerable negative charge now resides on the nitrogen. Furthermore, this anion is extensively delocalised over three aromatic rings which lends further stability to this lithiated species. This intermediate (44) is the same as the one obtained on treating papaverine with butyl lithium. On quenching, the electrophile reacts at nitrogen to give the product (45) which, although not isolated, is yellow (similar to (46) which has been reported as being yellow[26]) and readily aromatises on work up to give papaverine. Because tributylborate or borontrifluoride etherate did not react sufficiently rapidly with (37), the reaction then proceeded at nitrogen to yield the product (45) which readily affords (35) on work up.



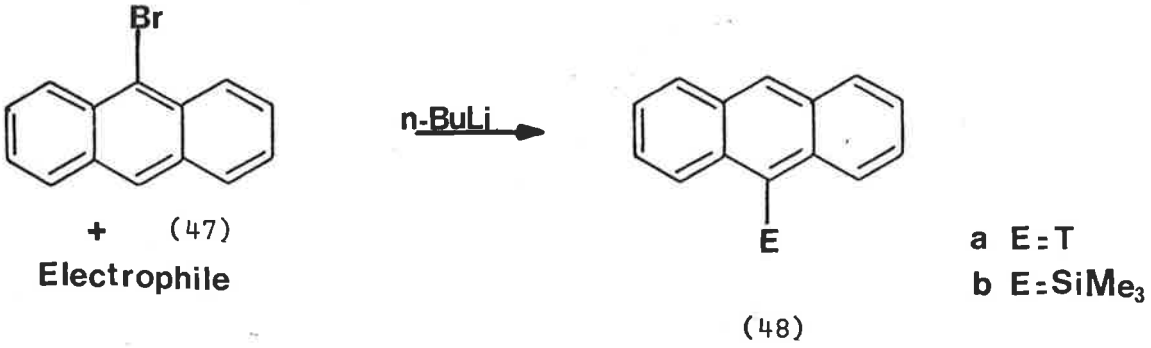
(46)


R
N
Br
ClCO2Et
Cl−
N+
CO2Et
R=OMe
(36)
(49)
n-BuLi
CO2Et
−OH
H3O+
(36)

Scheme 3.08


R
N
CO2H
Me2SBH3
H2O
BOH
O
H3O+
CH2OH
(40)
(52)
(51)
R:OMe

These observations and results suggest that transmetallation reactions occur extremely rapidly and in fact they are so rapid that Taylor[48] has treated 9-bromoanthracene (47) in the presence of tritium oxide or trimethyl-



(48)

silyl chloride, to give the corresponding 9-substituted anthracene (48).

This result prompted an attempted modification in the method of introducing a carboxyl group at C2' of (35). In an endeavour to increase the amount of carboxylation at C2' of (37), the reaction between (36) and butyl lithium was performed in the presence of ethyl chloroformate and, although the red anion was formed transiently, work up led only to the recovery of (36). This can be rationalised by postulating the formation of the carbamate (49) which thus renders the benzylic proton sufficiently acidic so that deprotonation occurs unexpectedly faster than the transmetallation. Alkaline work up resulted in the recovery of 2'-bromopapaverine (Scheme 3.08). It was hoped that the problem could be overcome by the use of two equivalents of both ethyl chloroformate and butyl lithium, the resultant dianion reacting with ethyl chloroformate to yield (50; Scheme 3.08). Once again, (36) was recovered.

Confirmation of the site of carboxylation of (37) was obtained by reduction of the acid (40) with dimethylsulfide-borane to the known 2'-hydroxymethylpapaverine[49] (51), a process that occurred by way of the relatively stable borate complex (52).

PART IV

BIOLOGICAL ACTIVITY.

The caprolactams, phthalidylphthalazinones, phthalidylphthalazines, and phthalidylcinnolinones have been subjected to preliminary screening for CNS activity by intraperitoneal injection into mice. The results are detailed in Tables I, II, and III, which show that all compounds caused at least mild activity.

The allyl ethers were the most active of the caprolactams prepared. They induced considerable muscular depression or paralysis. The caprolactam (62d) was significantly more active than the other lactams (62) and is consistent with previous reports that long alkyl groups at the 6 position tend to be more active[†].

The phthalidylphthalazinones and phthalidylcinnolinones were generally not as active as the caprolactams. This in fact may be due, in part, to the low solubility of these compounds in propolene glycol which reduces the amount of compound reaching the CNS. The more closely the phthalidylcinnolinone resembled bicuculline, the higher the activity. It was rewarding to find that, in fact, the phthalidylcinnolinones (112) and (115) compete with GABA at the binding site. The Phthalidylphthalazinones (31) and (58) were only 50% as effective as (112) and (115)[*].

ED is the minimum level at which the designated effect was observed.

[†] See reference 22, in Part I.

[*] We are grateful for these results which were provided by Prof G.A.R. Johnston.

TABLE I. Biological Activity of the Caprolactams.

Approximate ED doses to cause convulsion (C) or loss of muscle control (L)

Compound	ED mg/kg	Fatal dose mg/kg	Type of Activity
(14)	40	90	L
(20)	45	80	L
(21)	90		L
(22)	20		L
(23)	45	110	L
(24)	40	100	C
(26)	65	110	L
(15)	50	95	C
(28)	65		L
(29)	25		L
(30)	100		L
(32)	65	125	L
(52)	12	50	C
(53)	50	100	L
(33)	110		L
(31)	50		L
(36)	80		L
(40)	70		L
(54)	40		C
(57)	55		L
(55)	110		L
(56)	60		L
(46)	60	83	L
(45)	70		L
(39)	60	100	L

continued

TABLE I. continued...

Compound	ED mg/kg	Fatal dose mg/kg	Type of Activity
(62_a)	>90		C
(62b)	80		L
(62c)	80		L
(62d)	50		L
(65)	50		C
(62g)	70		L
(62h)	60		L

TABLE II. Biological Activity of the Phthalidylphthalazinones and Phthalidylphthalazines.

Approximate ED doses to cause convulsion (C) or loss of muscle control (L).

Compound	ED mg/Kg	Type of Activity
(31)	30	C
(32)	60	L
(60)	>100	L
(42)	90	L
(43)	100	L
(63)	>100	L
(44)	85	L
(45)	85	L
(46)	80; 117[a]	L
(47)	45	C
(48)	100	L
(58)	80; 119[a]	L
(64)	70	L
(67)	110	L
(78)	90	L
(86)	75	L
(87)	75	L
(88)	70	L
(158)	55	L
(164)	50	L

a: This is the fatal dose.

TABLE III. Biological Activity of the Phthalidylcinnolinones.

Approximate ED doses to cause convulsion (C) or loss of muscle control (L).

Compound	ED mg/Kg	Type of Activity
(109)	90	L
(110)	200	L
(111)	100	L
(102)	90	L
(112)	40	L[b]
(113)	100[a]; 80	L
(114)	40	L[b]
(115)	40	L
(116)	45	L
(117)	35	L

a: This is the fatal dose.

b: A short convulsion was initially observed.

EXPERIMENTAL

GENERAL

Melting points were determined using a Kofler hot-stage melting point apparatus under a Reichert microscope and are uncorrected.

Microanalyses were performed by the Australian Microanalytical Service, Melbourne.

Infrared spectra (i.r.) were recorded on a Unicam SP.200 or a Jasco IRA-1 spectrophotometer.

Proton magnetic resonance (p.m.r.) spectra were recorded on a Varian T-60 or a Jeol PMX-60 spectrometer, operating at 60 MHz. Deuterochloroform was used as a solvent unless otherwise stated and tetramethylsilane as an internal standard. Data are given in the following order: chemical shift (δ) in ppm, multiplicity described with the aid of the following abbreviations, s, singlet; d, doublet; t, triplet; m, multiplet; br, broad, first order coupling constant expressed in Hz, relative intensity as number of protons, assignment. ^{13}C nuclear magnetic resonance spectra were recorded on a Bruker - WP80DS spectrometer. Either deuterochloroform or deuterodimethylsulfoxide was used as solvent and peak positions were measured relative to the tetramethylsilane signal at 0 ppm.

Mass spectra were recorded with a Hitachi Perkin-Elmer TMV - 7D double focussing mass spectrometer operating at 70eV. Accurate masses were determined on a AEI-MS3074 mass spectrometer with a WF-028 peak matching unit.

Column chromatography was carried out on Spence alumina or Sorbsil silical gel. Preparative thin layer chromatography (t.l.c.) plates were prepared from a 50% mixture of Merck Kieselgel G and HF254 (35 g) applied to glass plates (20 cm x 20 cm) as a suspension in water (91 ml). The plates were dried in the air for two days and then at 100^{o}

for three hours.

All photolysis were carried out using light of wavelength 254 nm.

All organic extracts were dried over anhydrous magnesium sulfate unless otherwise stated. Redistilled solvents were used for extractions and chromatography. In this text, light petroleum refers to the hydrocarbon fraction of b.p. 60-70° and petroleum ether refers to the hydrocarbon fraction of b.p. 30-40°. Dry ether and tetrahydrofuran (THF) were obtained by redistillation from sodium wire and benzophenone immediately prior to use. All other solvents used were dried and purified according to standard laboratory procedures.

n-Butyl lithium was prepared by the method of Bryce-Smith*. n-Butyl lithium was used for all metallation reactions.

Sodium hydride was used as a 50% dispersion in oil.

Biological Testing of compounds

Mice weighing 20-30 gms were injected intraperitoneally with a solution of the relevant compound in propylene glycol. The concentration of each injection was lowered until no effect was observed. ED is the minimum level at which the designated effect was observed. Signs of central nervous system activity were monitored over a period of 18 hours.

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* Ref. 124, Part II.

WORK DESCRIBED IN PART I

2.1

4-Chloro-6,6-dimethyl-2,5,6,7-tetrahydro-1H-azepin-2-one (18) and 6-chloro-4,4-dimethyl-2,3,4,5-tetrahydro-1H-azepin-2-one (19).

These compounds were prepared by a literature method[24] from 3-chloro-5,5-dimethylcyclohex-2-en-1-one[72]. The crude product (20 g) was chromatographed on silica (600 g). Elution with light petroleum/ethyl acetate (7:3) yielded the 6-chloro isomer (5.1 g, 25%), m.p. 93-94° (lit.[72] 95-96°). Elution with ethyl acetate gave (18) as pale yellow needles after recrystallisation from light petroleum (11.5 g, 56%) m.p. 85-86° (lit.[23] 84.5-85.5°).

Preparation of the allyl ethers (14), (20)-(24).

These compounds were prepared by one of two general methods.

(a) 4-Chloro-6,6-dimethyl-2,5,6,7-tetrahydro-1H-azepin-2-one (2.0 g, 11.5 mmol) was added to a solution of sodium (0.24 g) in the required alcohol (10 ml) and the mixture was stirred under nitrogen at room temperature for 48h. The alcohol was removed under reduced pressure, chloroform was added and the sodium chloride removed by filtration. Concentration of the filtrate *in vacuo* afforded the crude product.

(b) Sodium hydride (0.33 g, 6.9 mmol) and the required alcohol (1.0 ml) in dry ether (50 ml) were stirred under nitrogen until hydrogen evolution had ceased. The 4-chloro compound (5) (1.0 g, 6 mmol) was added and stirring was continued for a further 10h at room temperature. The reaction mixture was poured into brine (15 ml), the organic layer was separated and the aqueous phase was extracted with dichloromethane. The combined organic extracts were dried and evaporated to afford the crude product.

(i) 4-Allyloxy-6,6-dimethyl-2,5,6,7-tetrahydro-1H-azepin-2-one (14) was prepared by method (a) and purified by chromatography on silica. Elution with dichloromethane/ethanol (19:1) gave the ether (72%), m.p. 83-84.5° after recrystallisation from light petroleum (Found: C, 67.6; H, 8.7; N, 7.2. $C_{11}H_{17}NO_2$ requires C, 67.7; H, 8.8; N, 7.2%). ν_{max} 3200, 1650, 1610cm^{-1}. P.m.r.: δ 6.85, br, NH; 6.3-5.1, m, $\underline{CH}=\underline{CH_2}$; 5.05, s, OC=CH; 4.33, d, J 6Hz, OCH_2; 2.92, d, J 5Hz, CH_2N; 2.25, s, $CH_2C=C$; 1.02, s, $C(CH_3)_2$.

(ii) 4-(But-2'-enyloxy)-6,6-dimethyl-2,5,6,7-tetrahydro-1H-azepin-2-one (2a) was prepared (65%) by method (b) and recrystallised from light petroleum/ethyl acetate, m.p. 128-130° (Found: C, 68.9; H, 9.2; N, 6.8. $C_{12}H_{19}NO_2$ requires C, 68.9; H, 9.2; N, 6.7%). ν_{max} 3200, 1650, 1610cm^{-1}. P.m.r : 7.3, br, NH; 5.60, m, $-\underline{CH}=\underline{CH}-$; 4.92, s, OC=CH-; 4.24, d, J 6Hz, OCH_2; 2.87, d. J 6Hz, CH_2N; 2.17, s, $CH_2C=C$; 1.73, br, s, $C=CH\underline{CH_3}$; 0.98, s, $C(\underline{CH_3})_2$.

(iii) 4-(2'-Methylprop-2'-enyloxy)-6,6-dimethyl-2,5,6,7-tetrahydro-1H-azepin-2-one (21) was prepared (65%) by method (b) and recrystallised from light petroleum, m.p. 78-84° (Found: C, 68.9; H, 9.2; N, 6.8. $C_{12}H_{19}NO_2$ requires C, 68.9; H, 9.2; N, 6.7%). ν_{max} 3170, 1650, 1610cm^{-1}. P.m.r : δ 7.9, br, NH; 4.98, m, C=CH, $C=CH_2$; 4.15, s, OCH_2; 2.82, d, J 5Hz, CH_2N; 2.15, s, $CH_2C=C$; 1.70, s, $CH_3C=C$; 0.95, s, $C(CH_3)_2$.

(iv) 4-(3'-Methylbut-2'-enloxy)-6,6-dimethyl-2,5,6,7-tetrahydro-1H-azepin-2-one (22) was prepared using method (a) and the crude product was chromatographed on silica. Elution with ethyl acetate gave (4d) (70%), m.p. 88-91°, after recrystallisation from light petroleum (Found: C, 70.3; H, 9.7; N, 6.1. $C_{13}H_{21}NO_2$ requires C, 69.9; H, 9.5; N, 6.3%). ν_{max} 3160, 1640, 1600cm^{-1}. P.m.r : δ 6.75, br, NH; 5.33, t, J 5Hz,

$-CH_2\underline{CH}=C$; 4.97, s, OC=CH; 4.24, d, J 7Hz, OCH_2; 2.85, d, J 6Hz, CH_2N; 2.16, s, $CH_2C=C$; 1.75, 1.67, both s, $C=C(CH_3)_2$; 0.95, s, $C(CH_3)_2$.

(v) 4-(3'-Phenylprop-2'-enyloxy)-6,6-dimethyl-2,5,6,7-tetrahydro-1H-azepin-2-one (23) was prepared by method (a) and the crude produce was chromatographed on silica. Elution with ethyl acetate/ethanol (9:1) gave (23) (40%), m.p. 163-165°, after recrystallisation from ethyl acetate (Found: C, 75.4; H, 8.0; N, 5.3. $C_{17}H_{21}NO_2$ requires C, 75.3; H, 7.8; N, 5.2%). ν_{max} 3200, 1650, 1600cm^{-1}. P.m.r: δ 7.40, s, ArH; 6.9-6.2, m, NH, $\underline{CH}=\underline{CH}$; 5.14, s, OC=CH; 4.52, d, J 6Hz, OCH_2; 2.94, d, J 6Hz, CH_2N; 2.28, s, $CH_2C=C$; 1.05, s, $C(CH_3)_2$.

Reaction of cinnamyl alcohol, butyl lithium and (18).

Butyl lithium (5.7 mmol) in hexane (0.5 ml) was added to a solution of cinnamyl alcohol (0.77 g, 5.7 mmol) in dry tetrahydrofuran (40 ml) at 5° under nitrogen, yielding a deep purple solution. After stirring for twenty min. (5) (1.0 g, 5.7 mmol) was added and the colour was discharged to yellow. The stirring was continued at room temperature overnight after which time t.l.c. indicated no starting material remained. Brine (50 ml) was added carefully and the mixture was extracted with dichloromethane (3 x 25 ml). The organic extracts were dried and evaporated to yield a crude product which was chromatographed on silica. Elution with light petroleum/dichloromethane (1:3) gave 2-benzylhexan-1-ol (25) (0.6 g) which was identified by i.r. and p.m.r. spectroscopy, b.p. 140-143°/15mm (lit.[75] 170-171°/27mm). Elution with dichloromethane/ethanol (19:1) gave a mixture (0.4 g) of four compounds (t.l.c.) of which two could be purified by preparative t.l.c. (ethyl acetate/dichloromethane 1:1). The first was cinnamyl alcohol(0.1 g) and the other (0.08 g), which could not be obtained crystalline, was assigned structure (26), ν_{max} (film) 3200, 1640, 1600cm^{-1}. P.m.r: δ 7.30, m, ArH; 6.4, br, NH; 4.96, s, C=CH; 3.65, d, J 6Hz, OCH_2;

2.88, d, J 6Hz, CH_2N; 2.64, s, $CH_2C{=}C$; 2.22, d, J 4Hz, $ArCH_2$; 2.0-0.9, m, CHC_4H_9; 1.03, s, $C(CH_3)_2$. Mass spectrum m/e 329. $C_{21}H_{31}NO_2$ requires 329. Elution with ethanol afforded a yellow solid (0.07 g) m.p. 205-210° (dec) which could not be further purified and which was assigned structure (27), ν_{max} 3400, 1650cm^{-1}. Mass spectrum m/e 463. $C_{30}H_{41}NO_3$ requires 463. The p.m.r. spectrum was consistent with structure (8), but was poorly resolved due to the presence of several diastereoisomers.

4-(Prop-2'-ynyloxy)-6,6-dimethyl-2,5,6,7-tetrahydro-1H-azepin-2-one (24)

This compound was prepared using method (b) and the crude product was recrystallised from light petroleum/ethyl acetate to give the *ether* (24) (85%), m.p. 133.5-134° (Found: C, 68.5; H, 7.9; N, 7.1. $C_{11}H_{15}NO_2$ requires C, 68.4; H, 7.8; N, 7.3%). ν_{max} 3200, 2120, 1650, 1610cm^{-1}. P.m.r: δ 7.0, br, NH; 5.15, s, OC=CH; 4.54, d, J 3Hz, $CH_2C{\equiv}C$; 2.90, d, J 6Hz, CH_2N; 2.55, t, J 2Hz, C≡CH; 2.24, s, $CH_2C{=}C$; 1.05, s, $C(CH_3)_2$. Mass spectrum m/e 193 (M).

Claisen rearrangement of the allyl vinyl ethers (14), (20)-(24).

(i) In a typical experiment the allyl vinyl ether (20) (0.1 g, 0.6 mmol) was heated in a sealed ampoule at 210° for thirty min. The resulting black oil was purified by preparative t.l.c. using dichloromethane/ethyl acetate (1:1), to yield 3-(2'-but-3'-enyl)-6,6-dimethylhexahydroazepine-2,4-dione (28) (0.08 g, 80%), m.p. 118-120°, after recrystallisation from light petroleum (Found: C, 69.0; H, 9.0; N, 6.5. $C_{12}H_{19}NO_2$ requires C, 68.9; H, 9.2; N, 6.7%). ν_{max} 3240, 3100, 1715, 1670cm^{-1}. P.m.r: δ 6.9, br, NH; 6.1-4.9, m, $CH{=}CH_2$; 3.6-2.9, m, CH, CH_2N, $CHCH_3$; 2.40, s, CH_2CO; 1.15, d, J 7Hz, $CHCH_3$; 1.05, 1.00, s, $C(CH_3)_2$.

(ii) Using the above procedure 3-allyl-6,6-dimethyl-hexahydroazepine-2,4-dione (15) (70%) was obtained after recrystallisation from light petroleum, m.p. 98-100° (Found: C, 67.6; H, 9.0; N, 7.0. $C_{11}H_{17}NO_2$ requires C, 67.7; H, 8.8; N, 7.2%). ν_{max} 3220, 3100, 1720, 1680, 1640cm^{-1}. P.m.r: δ 7.0, br, NH; 6.20-4.85, m, CH=CH$_2$; 3.78, t, J 5Hz, CHCH$_2$; 3.55, dd, J 6Hz J 15Hz, 1H, CH$_2$N; 2.98, dd, J 6Hz, J 15Hz, 1H, CH$_2$N; 2.65, t, CH$_2$C=C; 2.45, br s, CH$_2$CO; 1.08, 1.01, s, C(CH$_3$)$_2$.

(iii) Using the above procedure 3-(2'-methylprop-2'-enyl)-6,6-dimethyl-hexahydroazepine-2,4-dione (29) (75%) was obtained after recrystallisation from light petroleum, m.p. 115-120° (Found: C,68.8; H, 9.4; N, 6.7. $C_{12}H_{19}NO_2$ requires C, 68.9; H, 9.2; N, 6.7%). ν_{max} 3320, 3200, 1700, 1665, 1645cm^{-1}. P.m.r: δ 7.2, br, NH; 4.54, br, C=CH$_2$; 4.1-2.2, m, CH$_2$-CH$_2$N, CH, CH$_2$C=C; 1.70, s, C=CCH$_3$; 1.06, 0.93, s, C(CH$_3$)$_2$.

(iv) A test-tube containing (22) (0.3 g, 1.35 mmol) was heated in an oil bath at 190° for exactly two min. The cooled mixture was extracted with dichloromethane to yield a solid which was recrystallised from light petroleum to give 3-[2'-(2'-methylbut-3'-enyl)] -6,6-dimethylhexahydroazepine-2,4-dione (30) (40%) m.p. 130-132°, after recrystallisation from light petroleum. (Found: C, 70.1; H, 9.5; N, 6.0. $C_{13}H_{21}NO_2$ requires C, 69.9; H, 9.5; N, 6.3%). ν_{max} 3200, 3100, 1710, 1670cm^{-1}. P.m.r: δ 6.7, br, NH; 6.3-4.8, m, CH=CH$_2$; 3.53, s, CH; 3.25, dd, J 6Hz, J 15Hz, 1H, CH$_2$N; 3.13, dd, J 6Hz, J 15Hz, 1H, CH$_2$N; 2.46, d, J 11Hz, 1H, CH$_2$CO; 2.22, d, J 11Hz, 1H, CH$_2$CO; 1.27, s, C(CH$_3$)$_2$C=C; 1.03, 0.97, s, C(CH$_3$)$_2$.

When the reaction time was extended to fifteen min. the crude product was purified by preparative t.l.c. (dichloromethane/ethyl acetate, 2:3) to yield 3-[2'-(3'-methylbut-3'-enyl)] -6,6-dimethylhexahydroazepine-2,4-dione (31) (78%), m.p. 153-155° after recrystallisation from light petroleum (Found: C, 69.8; H, 9.5; N, 6.0. $C_{13}H_{31}NO_2$ requires C, 69.9;

H, 9.5; N, 6.3%). ν_{max} 3200, 3080, 1710, 1670cm^{-1}. P.m.r: δ 6.8, br, NH; 4.65, br, C=CH_2; 4.0-2.3, m, CH_2, C$\underline{H}_2$N, C$\underline{H}$, C$\underline{H}$CH_3; 1.78, d, J 3Hz, C=CCH_3; 1.23, d, J 8Hz, CHC$\underline{H}_3$; 1.03, 0.97, s, C$(CH_3)_2$.

Rearrangement of (22) under other conditions gave the products listed in Table I.

TABLE I. Relative ratio of products from the thermal rearrangement of (22).

Temp °C	Time min.	Product (22)	:	Composition[a] (30)	:	(31)
196	15	0		0		100
190	1	65		35		0
196	2	50		50		0
194	3.2	0		50		50
190	5	0		20		80
215	1.5	60		40		0
190	3.5	0		43		57

[a] The products (30) and (31) could not be separated by chromatography or fractional crystallisation. The ratios were obtained from the p.m.r. spectra of the total product.

(v) Using the above general procedure the crude reaction product from (23) was separated by preparative t.l.c. (alumina, light petroleum/dichloromethane, 1:3) into two components. The low R_f material was crystallised from light petroleum to give 3-(1'-phenylprop-2'-enyl)-6,6-dimethylhexahydroazepine-2,4-dione (32) (31%) m.p. 155-165°

(Found: C, 75.4; H, 7.9; N, 5.2. $C_{17}H_{21}NO_2$ requires C, 75.3; H, 7.8; N, 5.2%). ν_{max} 3170, 1710, 1670cm^{-1}. P.m.r: δ 7.25, s, ArH; 6.9, br, NH; 6.3-4.8, m, -CH=CH$_2$; 4.35, m, CH, CHAr; 3.8-2.1, m, CH_2N, CH_2CO; 1.05, 1.00, s, $C(CH_3)_2$. The high R_f product was crystallised from light petroleum to give 3-phenyl-2,7,7-trimethyl-3,4,5,6,7,8-hexahydro-2H-furo-[3,2-c]azepin-4-one (33) (36%), m.p. 173-178° (Found: C, 75.6; H, 7.9; N, 5.2. $C_{17}H_{21}NO_2$ requires C, 75.3; H, 7.8; N, 5.2%). ν_{max} 3250, 1695, 1655cm^{-1}. P.m.r: δ 7.25, s, ArH; 6.3, br, NH; 3.4-1.8, m, CH_2, CH_2N, $CHCH_3$, CHAr; 1.30, d, J 6Hz, $CHCH_3$; 1.03, 1.00, s, $C(CH_3)_2$.

Attempted rearrangement of (24)

The propargyl ether (24) was heated neat, in diglyme and in o-dichlorobenzene in the temperature range 100-210° for 1.5 min. to 5h but in no case could any products be identified. When the ether was heated, under a variety of conditions, in acetic anhydride/acetic acid mixtures only acetylated starting material, 1-acetyl-4-(prop-2-ynyloxy)-6,6-dimethyl-2,5,6,7-tetrahydro-1H-azepin-2-one (39), was obtained as an oil (Found: M, 235.1206. $C_{13}H_{17}NO_3$ requires M, 235.1208). ν_{max} 3280, 2160, 1740, 1700, 1620cm^{-1}. P.m.r: δ 5.32, s, C=CH; 4.57, d, J 3Hz, OCH_2; 3.65, s, CH_2N; 2.62, t, J 3Hz, C≡CH; 2.51, s, $COCH_3$; 2.25, s, $CH_2C{=}C$; 1.03, s, $C(CH_3)_2$.

When the ether (24) was flash pyrolysed at 330° a glassy, orange solid was obtained whose p.m.r. spectrum was consistent with structure (36). P.m.r: δ 7.7-7.0, n, NH, CH=C; 6.6-5.7, m, CH=C, OCH_2; 3.00, d, J 6Hz, CH_2N; 2.50, br s, CH_2CO; 1.05, s, $C(CH_3)_2$. Mass spectrum m/e 193 (M).

Bromination of (15)

Bromine (0.082 g, 0.5 mmol) in carbon tetrachloride (3 ml) was added to a stirred, ice cold solution of (15) (0.1 g, 0.5 mmol) in carbon tetrachloride (15 ml) and the reaction mixture was allowed to warm to room temperature over a period of 1h. The resulting precipitate (0.17 g, 93%) was identified as the hydrobromide salt of 3-bromo-7,7-dimethyl-2,3,4,4a,-5,6,7,8-octahydropyrano[2,3-b]azepin-5-one (40), m.p. 188-194° (dec.) (Found: C, 37.3; H, 5.0, Br; 44.9; N, 3.8. $C_{11}H_{16}BrNO_2$. HBr requires C, 37.2; H, 4.8; Br, 45.0; N, 4.0%). ν_{max} 3100-2500, 1680, 1630cm^{-1}.

This salt was dissolved in sodium hydroxide (10%, 10 ml) and methanol (10 ml) and stirred at room temperature for five min. The solution was extracted with dichloromethane (5 x 10 ml), the organic extracts were washed with brine (2 x 10 ml), dried and evaporated to dryness. The crude product was purified by preparative t.l.c. (ethyl acetate) to yield 3-bromo-7,7-dimethyl-2,3,4,5,6,7,8,9-octahydropyrano [2,3-b]azepin-5-one (41a) (0.053 g, 43%) as an unstable white solid. Attempted recrystallisation resulted in decomposition of the product. ν_{max} 3200, 1700, 1645, 1600cm^{-1}. P.m.r: δ 6.5, br, NH; 4.85, m, CHBr; 3.50, d, J 6Hz, OCH_2; 3.2-2.8, m, CH_2N, $CH_2C{=}C$; 2.30, br s, CH_2CO; 1.09, s, $C(CH_3)_2$. Mass spectrum m/e 275, 273 (M).

The hydrobromide salt (40) (0.16 g) was stirred in methanol (15 ml) and water (10 ml) for 60h. The methanol was removed *in vacuo*, the aqueous solution was extracted with dichloromethane (2 x 15 ml) and the extracts were dried and evaporated to yield a solid (0.13 g) which was purified by preparative t.l.c. (ethyl acetate). A high R_f fraction (0.025 g) was identified as 3-bromo-7,7-dimethyl-2,3,4,4a,5,6,7,8-octahydropyrano [2,3-b] azepin-5-one (41b). Attempted recrystallisation resulted in decomposition of this material. ν_{max} 3200, 1700, 1645, 1600cm^{-1}. P.m.r: δ 4.7, m, CHBr: 3.6-2.4, m, CHCO, CH_2CHBr, CH_2O; 3.30, s, CH_2N; 2.45, br s, CH_2CO; 1.20, s, $C(CH_3)_2$.

Bromination of (14)

Bromine (0.082 g, 0.5 mmol) in carbon tetrachloride (3 ml) was added to a stirred, ice cold solution of (14) (0.1 g, 0.5 mmol) in carbon tetrachloride (15 ml) and the reaction mixture was allowed to warm to room temperature over 1h. Removal of the solvent *in vacuo* gave an oil (0.18 g) which was dissolved in ethanol (10 ml), potassium carbonate (0.2 g) was added and the mixture was stirred at room temperature for 4h. The mixture was diluted with dichloromethane (20 ml), filtered and the filtrate was concentrated *in vacuo* to give an oil consisting of (42) and (43) (0.13 g.) P.m.r: δ 6.8, br, NH; 5.9-4.1, m, $OC=CH$, OCH_2, $CH=CHBr$; 2.80, d, J 6Hz, CH_2N, 2.13, s, $CH_2C=CH$; 0.95, s, $C(CH_3)_2$. Mass spectrum m/e 275,273. $C_{11}H_{16}BrNO_2$ requires 275, 273. This oil was treated with sodium hydroxide in ethanol at room temperature and at 60° for 12h but it was recovered unchanged in both cases. The same result was obtained using potassium t-butoxide at 60° for 12h.

N-Allylcaprolactams

The following general procedure was used. A mixture of the lactam (2.9 mmol), sodium hydride (2.9 mmol) and dry benzene (40 ml) was stirred at room temperature under nitrogen until hydrogen evolution had ceased (c.3h). A solution of allyl bromide (0.5 ml, 5.8 mmol) in dry benzene (5 ml) was added over 30 min. and the solution was refluxed under nitrogen for 20h. The hot mixture was filtered, the residue washed with benzene and the combined filtrates were evaporated to yield the crude product. The following compounds were prepared in this manner.

Allyl bromide and 6-chloro-4,4-dimethyl-2,3,4,5-tetrahydro-1H-azepin-2-one gave 1-allyl-6-chloro-4,4-dimethyl-2,3,4,5-tetrahydro-1H-azepin-2-one (46) as a colourless oil b.p. 88-90°/0.02mm (88%) which darkened on standing (Found: C, 61.8; H, 7.5; N, 6.6. $C_{11}H_{16}ClNO$

requires C, 61.6; H, 7.7; N, 6.6%). ν_{max} (film) 1660cm^{-1}. P.m.r: δ 6.30, s, C=CH; 6.2-5.1, m, $CH=CH_2$; 4.10, d, J 6Hz, CH_2N; 2.40, 2.38, s, $CH_2C(CH_3)_2CH_2$; 1.16, s, $C(CH_3)_2$.

4,4-Dimethyl-2,3,4,5-tetrahydro-1H-azepin-2-one (44) was prepared according to the method of Ward *et al.*[73], m.p. 62-63° (lit.[73] 62-63°). Allyl bromide and (44) gave 1-allyl-4,4-dimethyl-2,3,4,5,-tetrahydro-1H-azepin-2-one (45) as a colourless oil b.p. 45-48°/0.01 mm (Found: C, 73.3; H, 9.9; N, 7.7. $C_{11}H_{17}NO$ requires C, 73.3; H, 9.6; N, 7.8%). ν_{max} (film) 1660cm^{-1}. P.m.r: δ 6.2-5.0, m, CH=CH, $CH=CH_2$; 4.19, d, J 6Hz, CH_2N; 2.33, s, CH_2CO; 1.96, d, J 7Hz, $CH_2C(CH_3)_2$; 1.09, s, $C(CH_3)_2$.

Attempted rearrangement of (45) and (46)

(i) A sealed ampoule containing (46) (0.1 g) and N,N-dimethylaniline (1 ml), under nitrogen, was heated at 200° for 30 min. The reaction mixture was cooled, diluted with dichloromethane (30 ml), washed with dilute hydrochloric acid (3 x 10 ml) and then water (2 x 10 ml). The organic layer was dried and evaporated to yield the starting lactam which was identified by t.l.c. and p.m.r. spectroscopy.

(ii) In an identical experiment the ampoule was heated at 270° for 60h. Work-up as above gave a brown oil whose p.m.r. spectrum was devoid of olefinic protons.

(iii) The sealed ampoule was heated at 180° for 8h. Work-up as above gave the starting material.

(iv) A solution of (45) (0.07 g, 0.4 mmol) and anhydrous zinc chloride (0.07 g, 0.5 mmol) in xylene (5 ml) was refluxed for 48h. The cooled reaction mixture was poured into sodium hydroxide (10%, 5 ml), the layers

were separated and the aqueous phase was extracted with dichloromethane (3 x 15 ml). The combined organic extracts were dried and evaporated to afford starting material (0.04 g, 57%). The aqueous phase was acidified with dilute hydrochloric acid, saturated with sodium chloride and extracted with dichloromethane to yield a complex, unidentified mixture (0.022 g).

Attempted preparation of the 4-phenylaminolactam (50)

(i) After treatment of (15) (0.01 g, 0.05 mmol) with aniline (0.05 g, 0.05 mmol) in dry chloroform (10 ml) according to the literature procedure[19] for 5 days only starting materials could be detected by t.l.c. and p.m.r. analysis.

(ii) Aniline (0.05 g, 0.5 mmol) and (15) (0.01 g, 0.5 mmol) in anhydrous benzene were refluxed with a trace of p-toluenesulfonic acid for 72h using a Dean Stark water separator. Removal of the solvent gave unchanged lactam.

(iii) Aniline (1.0 ml) and (15), (0.05 g, 0.25 mmol) were heated at 120°, under nitrogen, for 6h. The excess aniline was evaporated under reduced pressure to give a residue, which afforded only starting materials after preparative t.l.c. (ethyl acetate/dichloromethane 1:1). The p.m.r. spectrum of the residue before chromatography showed a new resonance, ascribed to (50), at δ 0.95 (s).

General procedure for the alkylation of 6,6-dimethylhexahydroazepine-2,4-dione (16).

6,6-Dimethylhexahydroazepine-2,4-dione (16) was prepared according to the method of Duong[18], m.p. 146-147° (lit.[18] 145.5-146.5°).

To a solution of the oxolactam (16) (2.5 mmol) and sodium methoxide (2.5 mmol) in dry methanol (30 ml) was added, at room temperature, the

alkyl halide (5.0 mmol) in portions with stirring. The reaction mixture was refluxed under nitrogen for 16h, and concentrated. Chloroform was added to the residue and the precipitated sodium halide removed by filtration. Evaporation of the chloroform yielded a crude product which was separated by column chromatography, to give both the mono- and dialkylated products.

(i) with allyl bromide. Elution with light petroleum/ethyl acetate (1:1) yielded 3,3-di(prop-2'-enyl)-6,6-dimethylhexahydroazepin-2,4-dione (54) (0.12 g, 17%), m.p. 115-116° after recrystallisation from light petroleum (Found: C, 71.6; H, 9.0; N, 5.8. $C_{14}H_{21}NO_2$ requires C, 71.5; H, 9.0; N, 5.6%). ν_{max} 3220, 3080, 1710, 1650cm^{-1}. P.m.r: δ 7.0, br, NH; 6.2-4.9, complex, 6H, $CH=CH_2$; 2.94, d, J 6Hz, CH_2N; 2.65, 2.52, both d, J 4Hz, CH_2-C=C; 2.35, s, CH_2CO; 1.05, s, $C(CH_3)_2$.

Further elution with light petroleum/ethyl acetate gave (15), m.p. 97-99°, the structure of which was confirmed by p.m.r. analysis and was identical with the product obtained by Claisen rearrangement of (14).

(ii) with but-2-enyl bromide. Elution with light petroleum/ethyl acetate (7:3) gave 3,3-di(but-2'-enyl)-6,6-dimethylhexahydroazepine-2,4-dione (55) (0.36 g; 54%) as white needles from hexane, m.p. 68.5-70° (Found: C, 72.9; H, 9.3; N, 5.5. $C_{16}H_{25}NO_2$ requires C, 73.0; H, 9.6; N, 5.3%). ν_{max} 3220, 1725, 1660cm^{-1}. P.m.r: δ 7.4, br, NH; 5.7-5.4, complex, 4H, CH=CH; 2.91, d, J 7Hz, CH_2N; 2.50, 2.40, 2 x br d, J 2Hz, CH_2-C=C; 2.35, s, CH_2CO; 1.63, d, J 4Hz, C=CH-CH_3; 1.05, s, $C(CH_3)_2$.

Further elution with light petroleum/ethyl acetate (1:1) gave 3-(but-2'-enyl)-6,6-dimethylhexahydroazepine-2,4-dione (52), which was recrystallised from light petroleum to give colourless needles (0.05 g, 24%), m.p. 97-107° (Found: C, 68.8; H, 9.0; N, 6.5. $C_{12}H_{19}NO_2$ requires C, 68.9; H, 9.1; N, 6.7%). ν_{max} 3250, 3140, 1720, 1680cm^{-1}. P.m.r: δ 7.3, br, NH; 5.50, m, -CH=CH; 3.8-2.3, complex, 7H, CH_2COCH, CH_2N, CH_2-C=C;

1.58, d, J 4Hz, -C=CH-C$\underline{H}_3$; 1.10, 1.00, two s, $C(CH_3)_2$. Some starting material (0.03 g, 20%) was also recovered.

(iii) with cinnamyl chloride. Elution with light petroleum/ethyl acetate (1:1) gave 3,3-di(3'-phenylprop-2'-enyl)-6,6-dimethylhexahydroazepine-2,4-dione (57) (0.15 g, 16%), which was recrystallised from light petroleum, m.p. 155-157° (Found: C, 80.4; H, 7.6; N, 3.4. $C_{26}H_{29}NO_2$ requires C, 80.6; H, 7.5; N, 3.6%). ν_{max} 3200, 1700, 1660, 1600cm^{-1}. P.m.r: δ 7.32, s, ArH, 6.8-6.0, m, 5H, NH, 2 x CH=CH; 3.0-2.7, three overlapping d, 6H, CH_2N, CH_2C=C, 2.33, s, CH_2CO; 1.00, s, $C(CH_3)_2$.

Elution with light petroleum/ethyl acetate (1:3) gave 3-(3'-phenylprop-2'-enyl)-6,6-dimethylhexahydroazepine-2,4-dione (53) (0.23 g, 34%), which was recrystallised from light petroleum, m.p. 128-132° (Found: C, 75.3; H, 7.9; N, 5.5. $C_{17}H_{21}NO_2$ requires C, 75.3; H, 7.8; N, 5.2%). ν_{max} 3400, 1720, 1670, 1650cm^{-1}. P.m.r: δ 7.30, s, ArH; 7.0-6.2, m, NH, -C$\underline{H}$=C$\underline{H}$; 3.85-2.7, m, 5H, C$\underline{H}_2$C$\underline{H}$, CH_2N; 2.42, s, CH_2CO; 1.05, 0.95, two s, $C(CH_3)_2$.

(iv) alkylation of 3-(2'-methylprop-2'-enyl)-6,6-dimethylhexahydroazepine-2,4-dione (29). To a solution of (29) (0.3 g; 1.43 mmol) and sodium methoxide (1.5 mmol) in methanol (10 ml) was added 2-methyl-3-chloropropene (1 ml) and the reaction mixture was stirred under nitrogen at reflux temperature for 24h. The reaction mixture was diluted with dichloromethane (40 ml), washed with saturated ammonium chloride (2 x 10 ml), dried, evaporated, and the crude mixture separated by preparative t.l.c. (ethyl acetate/dichloromethane 1:1).

The high R_f product was identified as 3,3-di(2'-methylprop-2'-enyl)-6,6-dimethylhexahydroazepine-2,4-dione (56), which was recrystallised from light petroleum (0.059 g, 16%), m.p. 77-80° (Found: C, 73.1: H, 10.0; N, 5.4. $C_{16}H_{25}NO_2$ requires C, 73.0; H, 9.6; N, 5.3%). ν_{max} 3400, 1700, 1660cm^{-1}. P.m.r: δ 6.5, br, NH; 4.73, m, 4H, C=C$\underline{H}_2$; 2.83, d,

J 7Hz, CH_2N; 2.60, 2.53, two s, 4H, CH_2-C=C; 2.30, s, CH_2CO; 1.73, s, C=C-CH_3; 1.00, s, $C(CH_3)_2$. This product was also obtained by the alkylation of 6,6-dimethylhexahydroazepine-2,4-dione using the above general method.

2.2

N-propylsuccinimide (61b)

This was prepared using the method of Rice *et al.*[58] b.p. 125-128°/16 mm (lit.[74] 136-137°/27 mm).

N-butylsuccinimide (61c)

This was prepared according to the method of Rice *et al.*[58] b.p. 62-63°/0.1 mm (lit.[58] 80-82°/0.5 mm) in 54% yield.

N-hexylsuccinimide (61d)

This was prepared using the method of Rice *et al.*[58] b.p. 78-81°/0.05 mm (lit.[58] 96-101°/0.5 mm) in 58% yield.

N-2-hydroxyethylsuccinimide (61h)

This compound was prepared according to the method of Nikolaev[61] m.p. 58-60° (lit.[61] 58°).

N-2-phenylethysuccinimide (61g)

This compound was prepared according to the method of Wojeik[62] m.p. 134-136° (lit.[62] 133-134°) in 89% yield.

Alkylation of succinimide

A typical experiment for the preparation of 26 and 27 is outlined below.

Succinimide (0.02 mol), potassium (0.7 g) and dry t-butyl alcohol (40 ml) were stirred at ~ 70° under nitrogen for 2.5h, the alkyl halide (0.02 mol) then added and refluxing continued for 48h. The butanol was removed *in vacuo*, the residue dissolved in dichloromethane (100 ml), filtered and concentrated to yield the crude product.

(i) Using this procedure, N-(2-cyanoethyl)-succinimide (61e) was prepared (72%) and recrystallised from benzene, m.p. 99-100° (Found: C, 55.2; H, 5.3. $C_7H_8N_2O_2$ requires C, 55.2; H, 5.3%). ν_{max} 2280, 1780, 1710cm^{-1}. P.m.r: δ 3.87, t, J 7Hz, CH_2N, 2.83, S, $OC(CH_2)_2$; 2.76, t, J 7Hz, CH_2CN.

(ii) Using the above procedure ethyl-3-succinimidopropionate (61f) was prepared (45%) b.p. 105-110/0.01 mm (Found: M, 199. $C_9H_{13}NO_4$ requires M, 199.) ν_{max} 1780, 1720cm^{-1}. P.m.r.: δ 4.18, q, J 7Hz, CH_2CH_3; 3.82, t, J 8Hz, CH_2N; 2.71, s, $OC(CH_2)_2$; 2.62, t, J 6Hz, CH_2CO_2; 1.2, t, J 8Hz, CH_3.

N-ethyl-cis-$\Delta^{5,6}$-tetrahydrophthalimide (70)

This was prepared using the method of Rice *et al.*[58] b.p. 85-90°/0.03 mm (lit.[58] 86-90°/0.03 mm).

N-ethyl-cis-hexahydrophthalimide (71)

This was prepared in 62% yield according to the method of Rice *et al.*[58] b.p. 80-84°/0.03 mm (lit.[58] 88-92°/0.03 mm).

Hexahydroazepin-2,5-dione (62a)

Using the method of Kanaoka *et al.*[26], this compound was isolated in 55% yield m.p. 137-139° (lit.[26] 140°).

6-Methylhexahydroazepin-2,5-dione (62b)

This was prepared using the method of Kanaoka[26] and is described below.

A degassed solution of N-propylsuccinimide (0.56 g, 4 mmol) in acetonitrile (400 ml) was irradiated for 3h. The solvent was removed *in vacuo*, excess starting material removed by kugelruhr distillation and

the remaining mixture separated by preparative t.l.c. (dichloromethane, 2% ethanol). The High R_f compound was identified as starting material, (0.31 g, 53%). The other two compounds were identified as (62b) (0.12 g, 21%), m.p. 117-120° (lit.[26] 118-120°), and succinimide (19%) as evidenced by p.m.r. and t.l.c. analysis.

This reaction was performed several times and in some experiments, the p.m.r. spectrum of the crude reaction mixture suggested the presence of a compound possessing olefinic protons, but it could not be isolated as it readily polymerised.

6-Ethylhexahydroazepin-2,5-dione (62c)

This was prepared using the method of Kanaoka,[26] m.p.84-86° (lit.[26] 85-87°) in only 7.2% yield. The p.m.r. spectrum of the crude reaction mixture indicated the presence of a compound with olefinic protons, however, due to the small amount present, it could not be isolated. The structure of this compound was postulated as (64c).

6-Butylhexahydroazepin-2,5-dione (62d)

N-Hexylsuccinimide (0.73 g; 4 mmol) in degassed acetonitrile (400 ml) was irradiated under nitrogen for 0.5h. The solvent was removed *in vacuo* and the oil distilled using a keigelruhr distillation apparatus and the residue separated using preparative t.l.c. (developing with ethyl acetate/dichloromethane; 1:1) gave (62d) (0.088 g; 12 l.) which was sublimed, 105-110°/0.05 mm, m.p. 57-60° (Found: M, 183.1260. $C_{10}H_{17}NO_2$ requires M, 183.1259). ν_{max} 3200, 3080, 1700, 1660cm^{-1}. P.m.r: δ 7.0, br, NH; 3.32, M, CH_2N; 2.59, M, $CHCOCH_2CH_2$, .1.5-0.85, M, $(CH_2)_3CH_3$.

A compound (0.04 g, 5.5%) with a slightly higher Rf was identified as (64d), but it could not be purified. ν_{max} 3200, 1705cm^{-1}. P.m.r: δ 5.5-5.0, m, CH=CH; 3.58, m, $CHNCH_2$; 2.61-0.91, m, CH_2CH_2CO; $(CH_2)_2CH_3$.

6-Phenylhexahydroazepin-2,5-dione (62g)

A solution of (66c) (0.4 g; 1.0 mmol) in degassed acetonitrile (100 ml) was irradiated under nitrogen for 0.5h. After removal of the solvent, preparative t.l.c. (using ethyl acetate-dichloromethane; 1:1, as developing solvent) gave three compounds. The starting imide (0.25 g; 60%) was identified by (t.l.c.) and p.m.r. spectroscopy. Succinimide (0.06 g, 15%) was identified by p.m.r. and m.p. 116-120° (lit.[74] 121°). The required product (67c) was obtained as a white solid (0.039 g; 10%) m.p. 154-156° (Found M, 203.0949. $C_{12}H_{13}NO_2$ requires M, 203.0946.) ν_{max} 3200, 1725, 1660cm^{-1}. P.m.r : δ 7.10, S, ArH; 6.14, br, NH; 3.67, t, J 7Hz, C<u>H</u>CH_2; 3.37, t, J 6Hz, CH_2N; 2.90-2.40, M, CH_2CH_2.

6-Hydroxyhexahydroazepin-2,5-dione (62h)

N-2-Hydroxyethylsiccinimide (0.57 g, 4.0 mmol) in degassed acetonitrile (400 ml) under nitrogen was irradiated for 0.5h. Removal of acetonitrile *in vacuo*, followed by the addition of chloroform yielded the required product (0.08 g; 15%), m.p. 159-163 (Found: M, 144.0663. $C_6H_9NO_3$ requires M+1, 144.0660.) ν_{max} 3200, 1720, 1660cm^{-1}. P.m.r. (CF_3CO_2H): δ 3.81-2.84, m, 4H, CH CH_2N; 2.63-2.21, m, 4H, CH_2CH_2.

Attempted photolysis of N-2-cyanoethylsuccinimide (61e)

A solution of (61e) (0.152 g; 1 mmol) in degassed acetonitrile (100 ml) under nitrogen was irradiated for 0.5h. The solvent was removed *in vacuo* to yield starting material, as evidenced by p.m.r. spectroscopy and t.l.c. analysis.

Table II shows the various solvent and reaction times under which the photolysis was attempted.

TABLE II. Attempted Photolysis of N-2-cyanoethyl succinimide.

Solvent	time h	result
Acetonitrile	1.5	no reaction
Dichloromethane	2.5	no reaction
Acetonitrile/deuteriumoxide	0.5	A
Methanol/HCl	20	B

A: No deuterium incorporation had occurred compared with a solution which was not irradiated.

B: This reaction is detailed below.

A solution of (61e) (1.14 g; 7.5 mmol) in degassed methanol (150 ml) containing 10 drops of concentrated hydrochloric acid was irradiated under nitrogen for 20h. The methanol was removed *in vacuo*, the residue dissolved in dichloromethane (80 ml), washed with water (2 x 10 ml), dried and solvent removed to yield an oil (1.13 g; 98%) which was chromatographed on silica. (Prior to chromatography, the p.m.r. spectrum of the crude product suggested all the starting material had reacted). Elution with light petroleum/ethyl acetate (1:1) gave (61e) (0.12 g). Further elution gave mixtures of various compounds. These mixtures when separated by preparative t.l.c. (dichloromethane/ethylacetate; 1:2) gave several compounds including (61e). On standing some of the isolated products were found to convert to the starting material as evidenced by p.m.r. spectroscopy.

Examination of the p.m.r. spectrum of the various products showed the existence of olefinic protons. No compounds could be purified but one which was isolated (3%) darkened on standing and showed m/e 166 ($C_8H_{10}N_2O_2$ requires 166) and this compound was ascribed the structure (67).

Photolysis of (61f)

A solution of (61f) (0.23 g; 1.3 mmol) in degassed acidified methanol (25 ml) was irradiated under nitrogen for 20h. The mixture was diluted with chloroform (50 ml), washed with water (10 ml), dried and concentrated to yield an oil (0.23 g). This was separated by preparative t.l.c., however only starting material and a large number of unidentified compounds were obtained. Again the various p.m.r. spectra indicated the existence of olefinic protons.

Photolysis of N-ethyl hexahydrophthalimide

N-ethylhexahydrophthalimide (0.9 g; 5.0 mmol) in degassed acidified methanol (100 ml) under nitrogen was irradiated for 20h. The methanol was removed *in vacuo*, residue dissolved in chloroform (80 ml), washed with water (10 ml) dried and concentrated to yield an oil (0.9 g) which was chromatographed on silica. However a variety of unidentified compounds was obtained. The p.m.r. spectra, although complex, suggested the existence of an NH proton which indicated that some form of photochemical reaction had occurred. The reaction was repeated in acetonitrile, irradiating for 3h, and again a complex mixture was obtained. Examination of the reaction mixture by t.l.c. indicated several products and no starting material.

Photolysis of N-ethyl-cis-$\Delta^{5,6}$-tetrahydrophthalimide

N-Ethyl-cis-$\Delta^{5,6}$-tetrahydrophthalimide (0.18 g; 1 mmol) in degassed acetonitrile (100 ml) under nitrogen was irradiated for 0.5h. The solvent was removed and the crude reaction mixture dissolved in ether and the precipitated solid collected and identified as (74), m.p. 185 dec. (Found: M, 358. $C_{20}H_{26}N_2O_4$ requires M, 358). ν_{max} 1860, 1690cm^{-1}. The p.m.r. spectrum was complex but consistent with the structure (74).

5-Hydroxy-6-methylhexahydroazepin-2-one (65)

6-Methylhexahydroazepin-2,5-dione (0.11 g, 0.8 mmol) was hydrogenated in the presence of platinim oxide (0.05 g) in ethanol (15 ml) until the theoretical amount of hydrogen had been consumed. The reaction mixture was filtered through celite and the celite washed with ethanol (2 x 5 ml). The ethanol extracts were concentrated *in vacuo* to yield an oil (0.09 g). This material was distilled to give (65) (0.06g, 56%), which was purified by sublimation 115-118°/0.05 mm, m.p. 75-78°, 98-101° (Found: C, 59.1; H, 9.2; N, 9.5. $C_7H_{13}NO_2$ requires C, 58.7; H, 9.1; N, 9.8%). ν_{max} 3300, 1660cm^{-1}. P.m.r: δ 6.32, br, NH; 4.00-2.51, m, C<u>H</u>O<u>H</u>, CH_2N; 2.41-1.71, m, C<u>H</u>CH_3, CH_2CH_2; 0.97, d, J 7Hz, $CHCH_3$.

WORK DESCRIBED IN PART II

5,6-Dimethoxy-isobenzofuran-1(3H)-one

This was prepared according to the method of Ikeda[101] m.p. 153-155° (lit.[101] 154-155°) in 42% yield.

4,5-Dimethoxyphthalic anhydride (35b)

This was prepared according to the method of Ikeda[101] m.p. 176-178° (lit.[101] 175-177°).

Triphenyl-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-phosphonium bromide (36)

This was prepared using the procedure of Howe[69] m.p. 254-256° (lit.[69] 258-260°) in 60% yield.

Triphenyl-(5,6-dimethoxy-3-oxo-1,3-dihydraisobenzofuran-1-yl)-phosphonium bromide (37)

3-Bromo-5,6-dimethoxyphthalide was prepared by treating 5,6-dimethoxyphthalide (1.0 g, 5.2 mmol) with N-bromosuccinimide (0.92 g, 5.2 mmol) in carbon tetrachloride (40 ml) in an anhydrous atmosphere, at reflux temperature, while irradiating with a 100 watt globe, until all the N-bromosuccinimide was consumed. The reaction mixture was cooled and filtered. The filtrate was concentrated *in vacuo* and the solid collected (1.3 g, 85%). P.m.r: δ 7.25, s, ArH; 7.15, s, ArH; 6.90, s, ArCH; 4.95, s, OCH_3; 4.90, s, OCH_3. This material was used directly in the next step.

A solution of the above 3-bromophthalide (0.5 g, 1.8 mmol) and triphenylphosphine (0.48 g, 1.8 mmol) in benzene (30 ml) was refluxed under an atmosphere of nitrogen for 72h. The precipitated salt was collected and washed with acetone (3x10 ml) to give (37) (0.7 g, 72%). A small sample was recrystallised from acetonitrile to yield colourless needles, m.p. 226-227° (Found: C, 62.6; H, 4.6. $C_{28}H_{24}BrO_4P$ requires C, 62.8;

H, 4.5%). ν_{max} 1780 cm^{-1}. P.m.r: δ 8.21-7.38, m, 16H, ArH; 7.08, s, 1H, ArH; 6.50, br s, ArCH; 3.90, s, OCH_3; 3.58, s, OCH_3.

$\Delta^{3,3'}$-Biphthalide (30)

This was prepared using the method of Ramirez[62] m.p. 350-352° (lit.[62] 352-354°), but yields never approached those quoted.

Attempted Preparation of (41)

A solution of (35b) (0.3 g, 0.24 mmol) and triethyl phosphite (3 ml) was heated at reflux temperature for 24h under nitrogen, after which time t.l.c. showed only starting material.

After 60h, the mixture was worked up as prescribed[62] to yield polymeric material.

E-$\Delta^{3,3'}$-Biphthalides (38)-(41)

A typical preparation of a substituted biphthalide is described below.

(i) A solution of 4,5-dimethoxyphthalic anhydride (2.0 g, 9.6 mmol), (37) (4.95 g, 9.6 mmol) and triethylamine (0.97 g, 9.6 mmol) in dichloromethane (100 ml) was stirred at room temperature under nitrogen. After 10h, dichloromethane (200 ml) was added to the reaction mixture and then

washed with brine (2 x 50 ml). The brine was extracted with dichloromethane until no colour remained in the aqueous phase. The combined organic phases were dried and evaporated to afford a yellow solid which was refluxed with ether (100 ml) and filtered whilst hot. Recrystallisation of the solid from xylene afforded E-5,6-dimethoxy-$\Delta^{3,3'}$-biphthalide (38) as bright yellow needles (2.8 g, 90%), m.p. 289-290° (Found: C, 66.8; H, 3.8. $C_{18}H_{12}O_6$ requires C, 66.7; H, 3.7%). ν_{max} 1780, 1600 cm^{-1}. P.m.r (CF_3CO_2H): δ 8.41-7.48, m, ArH; 4.22, s, OCH_3; 4.16, s, OCH_3.

(ii) Using the above procedure, E-6-Nitro-$\Delta^{3,3'}$-biphthalide (39) was prepared as an orange powder (3.2 g, 90%), m.p. 251-253° (Found: C, 62.5; H, 2.4; N, 4.7. $C_{16}H_{17}NO_6$ requires C, 62.1; H, 2.3; N, 4.7%). ν_{max} 1780cm^{-1}. P.m.r. (d_6DMSO): δ 8.48-7.78, m, ArH.

(iii) E-6-Methyl-$\Delta^{3,3'}$-biphthalide (40a) and E-5-methyl-$\Delta^{3,3'}$-biphthalide (40b) were prepared as an inseparable mixture by the prescribed method, (2.5 g, 76%), m.p. 260-267° (Found: C, 73.0; H, 3.5. $C_{17}H_{10}O_4$ requires C, 73.4; H, 3.6%). ν_{max} 1780 cm^{-1}. P.m.r: δ 8.25-7.40, m, ArH; 2.60, s, CH_3; 2.58, s, CH_3.

(iv) E-5,5',6,6'-Tetramethoxy-$\Delta^{3,3'}$-biphthalide (41) requires 12h at reflux temperature to be formed in high yield. The product was purified by boiling in acetic acid and collecting the insoluble material (2.6 g, 70%), m.p. > 350° (Found: C, 62.3; H, 4.5. $C_{20}H_{16}O_8$ requires C, 62.5;

H, 4.2%). ν_{max} 1780, 1610 cm^{-1}. No p.m.r could be obtained because of the low solubility of the compound in all the available solvents.

Preparation of the 4-(3-Oxo-1,3-dihydroisobenzofuran-1-yl)-phthalazin-1(2H)-ones, (31), (42), (44), (46).

A typical preparation of a phthalidylphthalazinone is detailed below.

(i) Hydrazine hydrate (0.095 g, 1.9 mmol) in ethanol (20 ml) was added dropwise over 30 min. to a stirred refluxing suspension of biphthalide (0.5 g, 1.9 mmol) in ethanol (60 ml). The reaction mixture was then refluxed for a further 14h and stripped of solvent to yield 4-(3-oxo-1,3-dihydro-isobenzofuran-1-yl)-phthalazin-1(2H)-one (31), which afforded white needles (0.34 g, 65%) from ethyl acetate, m.p. 230-231.5° (Found: C, 68.9; H, 3.5; N, 10.1. $C_{16}H_{10}N_2O_3$ requires C, 69.1; H, 3.6; N, 10.1%). ν_{max} 3140, 1780, 1675 cm^{-1}. P.m.r (d_6DMSO): δ 10.2, br, NH; 8.41-7.63, m, ArH; 7.33, s, ArCH;

(ii) 4-(5,6-Dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-phthalazin-1(2H)-one (44) was prepared using the above procedure and recrystallised from acetic acid (0.38 g, 73%), m.p. 291-293° (Found: M, 338.0899. $C_{18}H_{14}N_2O_5$ requires M, 338.0903). ν_{max} 3250, 1750, 1670 cm^{-1}. P.m.r (d_6DMSO/CF_3CO_2H, 1:1): δ 8.33-7.51, m, 7H, ArH; 7.20, s, ArCH; 4.15, s, OCH_3; 4.05, s, OCH_3.

(iii) Treatment of (40) with hydrazine hydrate as described above afforded 7-methyl-4-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-phthalazin-1(2H)-one (46a) as a white solid (0.32 g, 95%) which was recrystallised from ethanol/water, m.p. 195-204°, 214-225° (Found: C, 69.9; H, 4.1; N, 9.6. $C_{17}H_{12}N_2O_3$ requires C, 69.7; H, 4.4; N, 9.2%). ν_{max} 3200, 1775, 1670 cm^{-1}. P.m.r: δ 8.41-7.16, m, ArH; 6.75-6.60, four s, 1H, ArCH; 2.55-2.38, m, 3H, $ArCH_3$. The p.m.r spectrum indicated a mixture of four isomers, but there

was only one spot by t.l.c.

(iv) 6,7-Dimethoxy-4-(5,6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-phthalazin-1(2H)-one (42) was prepared (0.38 g, 96%) but 10 equivalents of hydrazine hydrate were required. The product was recrystallised from acetic acid, m.p. 287-289° (Found: M, 398.1120. $C_{20}H_{18}N_2O_7$ requires M, 398.1114). ν_{max} 3250, 1740, 1670, 1610 cm^{-1}. P.m.r (CF_3CO_2H): δ 8.00, s, ArH; 7.63, s, ArH; 7.55, s, ArH; 7.20, s, ArH; 7.05, s, ArCH, 4.20, 4.18, 4.05, 4.02, four s, OCH_3.

Reaction of (39) with hydrazine hydrate.

(i) Hydrazine hydrate (0.085 g, 1.7 mmol) in ethanol (20 ml) was added dropwise over 1h to a stirred refluxing suspension of (39) (0.5 g, 1.6 mmol) in ethanol (50 ml). Stirring at reflux temperature was continued for 24h and the mixture cooled and concentrated *in vacuo*. Upon the addition of ethanol a solid precipitated (0.13 g, 27%) which could not be purified by conventional methods such as chromatography and recrystallisation. However, from its p.m.r and i.r spectra the product was identified as 3-nitro-8H-[1,2-b]-isoindole-2,3-benzodiazepin-5(6'H),8,13(12bH)-trione (53) (Found: M, 339. $C_{16}H_9N_3O_6$ requires M, 339). ν_{max} 1720, 1690, 1680 cm^{-1}. P.m.r (d_6DMSO): δ 11.2, br s, NH; 8.45, br s, ArH; 8.21-7.60, m, 6H, ArH; 4.81, s, ArCH.

The filtrate was concentrated and by fractional crystallisation, 6-nitrophthalide (0.052 g) was obtained, m.p. 140-143° (lit.[102] 145°). The filtrate showed a further four compounds by t.l.c.

(ii) The reaction was repeated as above. Examination of the reaction mixture by t.l.c. (dichloromethane) suggested the existence of 6-nitrophthalide, phthalazin-2,4-dione (52a) and several other compounds. Fractional crystallisation provided an enriched sample of phthalazin-2,4-dione (0.24 g) as suggested by, i.r., ν_{max} 3100, 1660, 1600 cm^{-1} and p.m.r

spectroscopy. Further purification of the filtrate by preparative t.l.c. (dichloromethane) gave 6-nitrophthalide (0.1 g) m.p. 140-142° (lit.[102] 145°). No other material could be identified.

Preparation of 2-Methyl-4-(3 -oxo-1 ,3 -dihydroisobenzofuran-1 -yl)-phthalazin-1(2H)-ones. (32), (43), (45), (47), and (48).

A typical experiment is described below.

(i) A solution of methyl hydrazine (0.10 g, 2.2 mmol) in ethanol (25 ml) was added dropwise over 45 min to a stirred refluxing suspension of biphthalide (0.5 g, 1.9 mmol) in ethanol (60 ml). The reaction mixture was stirred at reflux temperature for 10h, cooled and evaporated to yield 2-methyl-4-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-phthalazin-1(2H)-one (32) (0.43 g, 86%). This material was essentially pure and a small amount was recrystallised from ethanol, m.p. 187-189° (Found: C, 69.6; H, 4.4; N, 9.5. $C_{17}H_{12}N_2O_3$ requires C, 69.9; H, 4.1; N, 9.6%). ν_{max} 1775, 1670, 1650 cm^{-1}. P.m.r: δ 8.52, m, ArH_8; 8.21-7.45, m, 7H, ArH; 6.83, s, ArCH; 3.83, s, NCH_3.

(ii) Using the above procedure, 4-(5,6-dimethoxy-3-oxo-1,3-dihydro-isobenzofuran-1-yl)-2-methylphthalazin-1(2H)-one (45) was prepared and recrystallised from ethanol as colourless needles (0.28 g, 86%), m.p. 259-261° (Found: C, 64.9; H, 4.6; N, 8.0. $C_{19}H_{16}N_2O_5$ requires C, 64.8; N, 4.6; N, 8.0%). ν_{max} 1780, 1670 cm^{-1}. P.m.r: δ 8.41, m, 1H, ArH_8; 7.85-7.50, m, 3H, ArH; 7.31, s, $ArH_{4'}$; 6.85, s, $ArH_{7'}$; 6.56, s, ArCH; 4.00, s, OCH_3; 3.94, s, OCH_3; 3.75, s, NCH_3.

(iii) Using the above method 6,7-dimethoxy-4-(5,6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-2-methylphthalazin-1(2H)-one (43) was prepared (0.47 g, 92%) but 10 equivalents of methylhydrazine were required. A small sample was recrystallised three times from acetic acid, m.p. 277-279° (Found: M, 412.1278. $C_{21}H_{20}N_2O_7$ requires M, 412.1270). ν_{max} 1760,

1665, 1610 cm^{-1}. P.m.r (CF_3CO_2H): δ 8.05, s, ArH; 7.65, s, ArH; 7.60, s, ArH; 7.25, s, ArH; 7.05, s, ArCH; 4.31-4.01, five overlapping s, 15 H, four OCH_3, NCH_3.

(iv) Using the above procedure treatment of (39) with methyl hydrazine afforded three products by t.l.c. (dichloromethane). Fractional crystallisation of the residue after work up afforded 2-methyl 7-nitro-4-(3-oxo-1,3-dihydroisobenzofuran-1'-yl)-phthalazin-1(2H)-one (48) which was recrystallised from ethanol as white needles (0.14 g, 26%), m.p. 256-258° (Found: C, 60.6; H, 3.4; N, 12.2. $C_{17}H_{11}N_3O_5$ requires C, 60.5; H, 3.3; N, 12.5%). (m/e 337 ($C_{17}H_{11}N_3O_5$), 133 (100%) ($C_8H_5O_2$)). ν_{max} 1780, 1650 cm^{-1}. P.m.r (d_6DMSO): δ 8.98, d, J 1Hz, 1H, ArH_8; 8.85-8.43, m, 2H, ArH; 8.20-7.61, m, ArH', 7.50, s, ArCH; 3.71, s, NCH_3.

Further fractional crystallisation yielded 2-methylphthalazin-2,4-dione (52b) (0.06 g) m.p. 238-240° (lit.[104] 239-240°). Analysis of the mother liquor by p.m.r spectroscopy and t.l.c. indicated the presence of (48), (52b) and 6-nitrophthalide.

(i) 7-Methyl-4-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-phthalazin-1(2H)-one (47a)* was prepared by the above procedure (0.28 g, 96%) which was recrystallised from ethanol/water, m.p. 163-173°, 180-189° (Found: C, 70.5; H, 4.8; N, 9.1. $C_{18}H_{14}N_2O_3$ requires C, 70.6; H, 4.6; N, 9.1%). ν_{max} 1770, 1650 cm^{-1}. P.m.r: δ 8.35, m, 1H, ArH; 8.06-7.11, m, 6H, ArH; 6.71, m, ArCH; 3.68, m. NCH_3; 2.42, m. $ArCH_3$.

*This is only one of the 4 inseparable isomers. The others are isomeric at C6, C5' and C6'. The p.m.r. spectrum although complex because of the mixture of products confirmed the existence of the 4 isomers. The 4 isomers could not be separated by conventional methods such as chromatography or fractional crystallisation.

Alkylation of (31)

(i) A mixture of (31) (0.16 g, 0.61 mmol), potassium carbonate (1.6 g) and methyl iodide (1 ml) in acetone (25 ml) was stirred at reflux temperature under nitrogen for 48h. The mixture was cooled, diluted with dichloroethane (50 ml), filtered and the filtrate evaporated to dryness. The resulting brown oil (0.24 g) was purified by preparative t.l.c. (dichloromethane). The middle Rf compound (after three plates) was identified as 2-methyl-4-(1-methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)-phthalazin-1(2H)-one (57) which was recrystallised from ethyl acetate (0.06 g, 34%), m.p. 184-185° (Found: C, 70.4; H, 4.6; N, 8.9. $C_{18}H_{14}N_2O_3$ requires C, 70.6; H, 4.6; N, 9.1%). ν_{max} 1760, 1650 cm^{-1}. P.m.r: δ 8.57-8.18, m, 2H, ArH; 8.05-7.45, m, 6H, ArH; 3.78, s, NCH_3; 2.10, s, CCH_3. No other material was identifiable.

(ii) A mixture of (31) (0.15 g, 0.57 mmol), potassium carbonate (1.5 g) and methyl iodide (0.4 ml) in acetone (40 ml) was stirred at reflux temperature for 8h after which time, no starting material remained by t.l.c. The mixture was cooled, diluted with dichloromethane (60 ml), filtered and the filtrate concentrated *in vacuo* to yield an orange oil (0.21 g). This material was separated by preparative t.l.c. (ethylacetate/dichloromethane, 3:7) to give two compounds. The high Rf compound was identified as 4-(2-methoxycarbonylbenzoyl)-2-methylphthalazin-1(2H)-one (58) (0.04 g, 22%), which was purified by sublimation, 98-100°/2 mm, m.p. 136-138° (Found: C, 67.2; H, 4.6; N, 8.4. $C_{18}H_{14}N_2O_4$ requires C, 67.1; H, 4.4; N, 8.7%). ν_{max} 1715, 1695, 1660 cm^{-1}. P.m.r: δ 9.10, m, 1H, ArH; 8.51, m, 1H, ArH; 8.14-7.51, m, 6H, ArH; 3.72, s, OCH_3; 3.66, s, NCH_3.

The low Rf product was identified as (57) (0.06 g, 22%) by comparison of the p.m.r. spectrum with the sample characterised above.

(iii) A mixture of (31) (0.2 g, 0.72 mmol), potassium carbonate (2.0 g) and methyl iodide (0.25 ml) in acetone (70 ml) was stirred at room temperature for 14h. This was worked up as above to afford a brown oil (0.23 g). This oil was purified by preparative t.l.c. (ethyl acetate/ dichloromethane, 1:4) to give a pure sample of (58), m.p. 135-138°. (32) and (57) were also present as evidenced by p.m.r. spectroscopy but they could not be separated.

Conversion of (58) to (32)

Sodium borohydride (c.0.015 g) was added to an ice cold solution of (58) (0.02g, 0.06 mmol) in methanol (3 ml) and the reaction mixture stirred between 0°-5° for 2h. 10% Sodium hydroxide (2 ml) was added and the mixture stirred at ambient temperature for 6h. The mixture was acidified and then dissolved in dichloromethane (20 ml), the solution washed with brine (5 ml), dried and evaporated to yield a solid which was identified as (32) by comparison of the p.m.r. spectrum with that of an authentic sample.

Alkylation of (44)

A mixture of (44) (0.1 g, 0.3 mmol), potassium carbonate (1.0 g) and methyl iodide (0.3 ml) in acetone (20 ml) was stirred at ambient temperature under nitrogen for 16h. The mixture was diluted with dichloromethane (60 ml), filtered and the filtrate concentrated *in vacuo* to yield a white solid (0.11 g). The mixture was purified by preparative t.l.c. (ethyl acetate/dichloromethane, 1:1) to give (45) (0.075 g, 69%) which was identified by the comparison of the p.m.r. spectrum with an authentic sample.

Alkylation of (32)

A mixture of (32) (0.1 g, 0.3 mmol), potassium carbonate (1.0 g) and methyl iodide (0.5 ml) in acetone (20 ml) was stirred at reflux temperature for 18h. The reaction mixture was worked up as above to give a brown oil (0.11 g) which was purified by preparative t.l.c. (ethyl acetate/dichloromethane, 1:4) to give a mixture of (32) and (57) (20%) by p.m.r. spectroscopy.

Alkylation of (31)

(i) A solution of (31) (0.1 g, 0.36 mmol), potassium carbonate (1.0 g) and ethyl iodide (0.5 ml) in acetone (25 ml) was stirred at reflux temperature for 24h. The reaction mixture was cooled, diluted with dichloromethane (40 ml), filtered and the filtrate concentrated *in vacuo* to afford an oil (0.11 g). Examination of the mixture by p.m.r. spectroscopy indicated several products as there were at least three signals in the region δ 4.2 attributable to NCH_2. Exhaustive attempts to separate the products by normal chromatographic techniques were unsuccessful.

(ii) A solution of (31) (0.1 g, 0.36 mmol), potassium carbonate (1.0 g) and ethyl iodide (0.5 ml) in acetone (25 ml) was stirred at room temperature for 6h. The mixture was diluted with ether (60 ml), filtered and the filtrate concentrated *in vacuo* to yield an oil which was separated by preparative t.l.c. (dichloromethane). The middle Rf compound was identified as 2-ethyl-4-(3-oxo-1,3-dihydroisobenzofuran-1 -yl)-phthalazin-1(2H)-one (60) (0.54 g, 54%). A small sample was purified by sublimation, 180-185°(block)/0.2 mm, m.p. 128-130° (Found: C, 70.7; H, 5.0; N, 8.8. $C_{18}H_{14}N_2O_3$ requires C, 70.6; H, 4.6; N, 9.1%). ν_{max} 1770, 1660 cm^{-1}. P.m.r: δ 8.51, m, ArH_8; 8.16-7.41, m, ArH; 6.78, s, ArCH; 4.17, q, J 6Hz, NCH_2; 1.30, t, J 6Hz, CH_2CH_3.

Alkylation of (42)

A mixture of (42) (0.13 g, 0.33 mmol), potassium carbonate (1.3 g), and ethyl iodide (1.0 ml), in acetone (50 ml) was stirred at reflux temperature under nitrogen for 48h. The mixture was then cooled, diluted with dichloromethane (50 ml), filtered and the filtrate concentrated *in vacuo* to yield 6,7-dimethoxy-4-(5,6-dimethoxy-3 -oxo-1 ,3 -dihydroisobenzofuran-1-yl)-2-ethylphthalazin-1(2H)-one (63) (0.1 g, 71%) which was recrystallised from ethyl acetate, m.p. 266-269° (Found: M, 426.1432. $C_{22}H_{22}N_2O_7$ requires M, 426.1427). ν_{max} 1770, 1660, 1610 cm^{-1}. P.m.r: δ 7.69, s, ArH; 7.32, s, ArH; 6.90, s, ArH; 6.82, s, ArH; 6.53, s, ArCH; 4.24, 9, J 6Hz, NCH_2; 4.00, 3.97, 3.88, 3.81, s, OCH_3; 1.32, t, J 6Hz, CH_2CH_3.

4-(3'-Oxo-1',3'-dihydroisobenzofuran-1'-ylidene)-3-penylphthalazin-1(2H)-one (64).

Phenylhydrazine (0.11 g, 0.1 mmol) in xylene (5 ml) was added to a refluxing solution of biphthalide (0.25 g, 0.1 mmol) in xylene (20 ml) and the reaction mixture refluxed under nitrogen for 72h. On cooling, the precipitated solid was collected and recrystallised twice from xylene to give (64) (0.14 g, 40%) as pale yellow needles, m.p. 279-284°, 290-295° (Found: M, 354.1009. $C_{22}H_{14}N_2O_2$ requires M, 354.1004). ν_{max} 3200, 1780, 1660 cm^{-1}. P.m.r (CF_3CO_2H): δ 8.89-6.91, m, ArH.

1-Chlorophthalazine (13)

This was prepared according to the method of Atkinson and Brown[103] m.p. 112-113° (lit.[103] 109-111) in 80% yield.

4-Chloro-2-methylphthalazin-1(2H)-one (69)

A suspension of 4-chlorophthalazin-1(2H)-one (2.0 g, 11.1 mmol),

potassium carbonate (10 g) and methyl iodide (1.5 ml) in acetone (80 ml) was stirred at reflux temperature in an anhydrous atmosphere for 16h. The mixture was cooled, diluted with dichloromethane (100 ml), filtered and the filtrate concentrated *in vacuo* to give (69) which was recrystallised from ethanol (1.4 g, 65%) m.p. 125-127° (lit.[104] 128-129°).

1-Methoxyphthalazine-3-methiodide (71)

This was prepared according to the method of Ikeda *et al.*[105] m.p. 148-151° (lit.[105] 158-160) in 70% yield. P.m.r: δ 11.59, s, ArH_4; 9.11-7.97, m, 4H, ArH; 4.76, s, NCH_3; 4.40, s, OCH_3.

1-Bromophthalazine (73)

This was prepared by the method of Orphanos[106], m.p. 98-101° (lit.[106] 100°). This compound darkened on exposure to light. The new, dark orange compound, assigned the structure (77) was insoluble in most organic solvents and a satisfactory p.m.r. spectrum could not be obtained. Due to the nature of (77) a satisfactory molecular ion could not be obtained.

Attempted preparation of (66)

Several attempts were made to convert (31) to (66). Initial results suggested that compound (66) was very reactive and therefore no attempt to isolate (66) was made. Thus, the reduction was attempted on the crude reaction mixture.

(i) Phosphoryl chloride (2.0 ml) and (31) (0.25 g, 0.98 mmol) were heated at gentle reflux for 20 min. The mixture was poured into ice (10 g) and carefully basified with 20% sodium hydroxide. The precipitated solid (0.22 g) was collected and identified as starting material.

(ii) Phosphoryl chloride (2 ml) and (31) (0.25 g, 0.98 mmol) were gently refluxed for 1h. The phosphoryl chloride was removed under reduced pressure and the residual oil washed with light petroleum (2 x 5 ml), dissolved in methanol (5 ml) cooled to 0° and basified by the gradual addition of methanolic ammonia. The mixture was poured into water (10 ml) and extracted with dichloromethane (3 x 15 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness to yield 1-methoxy-4-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-phthalazine (68) (0.12 g, 42%), m.p. 174-176° (Found: M, 292.0848. $C_{17}H_{12}N_2O_3$ requires M, 292.0848). ν_{max} 1780 cm^{-1}. P.m.r: δ 8.40-7.49, m, 8H, ArH; 6.15, s, Ar CH; 4.28, s, OCH_3.

(iii) Phosporylchloride (1.3 ml) and (31) (0.13 g,0.45 mmol) were heated at gentle reflux for 1h. The phosphoryl chloride was removed *in vacuo* and the residual red gum dissolved in methanol (10 ml). Palladium chloride (0.16 g, 0.9 mmol) was added and then sodium borohydride (0.19 g, 4.5 mmol) was added in small portions at 0°. Stirring was continued for 1h and the mixture then poured into 10% hydrochloric acid (5 ml), basified with 10% sodium hydroxide and extracted with dichloromethane (4 x 25 ml), dried and concentrated *in vacuo* to yield an oil (0.1 g), the p.m.r. spectrum of which was devoid of aromatic protons. Analysis of the oil by t.l.c. and p.m.r. spectroscopy suggested reduction and polymerization had occurred.

(iv) Phosphorus pentachloride (0.2 g), phosphoryl chloride (1 ml) and (31) (0.12 g, 0.43 mmol) were heated at gentle reflux for 1.5h. The solution was poured onto ice (5 g) and brought to neutrality with 5% sodium carbonate and the precipitate collected (0.2 g). This solid (0.2 g) was dissolved in ethanol (20 ml) and hydrogenated over palladium on carbon at room temperature and at atmospheric pressure. The reaction mixture was filtered through celite, and the celite washed with warm ethanol (10 ml). The filtrate was concentrated *in vacuo* to yield unidentified material (0.13 g).

Reaction of the anion of Phthalide with various Electrophilic species.

Several attempts to effect nucleophilic substitution by the anion of phthalide on various electrophilic species proved unsuccessful. An example of these reactions is described below.

A solution of phthalide (0.16 g, 0.12 mmol) in dry tetrahydrofuran (10 ml) was added to a solution of lithium isopropylcyclohexylamide; [prepared by treating N-isopropylcyclohexylamine (0.17 g, 0.12 mmol) in dry tetrahydrofuran (10 ml) with n-butyl lithium (0.12 mmol) in hexane (1.0 ml) at -5° under an atmosphere of nitrogen], at -78° under a nitrogen atmosphere. After 10 min. (13) (0.2 g, 0.12 mmol) in dry tetrahydrofuran (15 ml) was added over 10 min. to yield a deep red coloured solution. The mixture was stirred at -78° for a further 1.5h, and then at room temperature for 24h. Saturated ammonium chloride (10 ml) was added and the organic phase separated. The aqueous phase was washed with dichloromethane (3 x 20 ml) and the combined organic extracts dried and concentrated *in vacuo* to give a brown oil (0.32 g, 88%). This mixture was separated by preparative t.l.c. (3 x ethyl acetate/dichloromethane, 1:1) to give phthalide (0.03 g, 18%), (13) (0.055 g, 28%) and polymeric material.

Other examples are given in Table IV.

2-Formyl-5-methoxy-benzoic acid

This was prepared using the procedure of Blair [108] *et al*, m.p. $149-151^{\circ}$ (lit.[108] $151-153^{\circ}$).

5,6-Dimethoxy-2-formylbenzoic acid (opianic acid).

This was prepared using the procedure of Blair[108] *et al*, m.p. $143-145^{\circ}$ (lit.[22] 146°).

TABLE IV. Reaction of the anion of Phthalide with various Electrophilic Species.

Base	Electrophile	Result
Potassium t-Butoxide[a]	(13)	Polymer
Lithium Diisopropylamide	(13)	Polymer
Sodium Methoxide[a]	(71)	Polymer[b]
Potassium t-Butoxide[a]	(71)	Polymer[c]
Sodium Methoxide[a]	(69)	Starting material
Potassium t-Butoxide[a]	(70)	Starting material

a: This was carried out using similar conditions to those of Tippett.[16]

b: 28% of the starting 1-chlorophthalazine was recovered.

c: 23% of a product identified as 4-methoxy-2-methylphthalazin-1(2H)-one, m.p. 87-90° (lit.[107] 93°).

Preparation of the 2-Formylbenzoates (75), (84), (85)

A typical experiment is described below.

A mixture of the phthalaldehydic acid (17 mmol), methyl iodide (5 ml) and potassium carbonate (10 g) in acetone (80 ml) was stirred, under anhydrous conditions, at reflux temperature for 12h. The mixture was cooled, diluted with dichloromethane (100 ml), filtered and the filtrate concentrated *in vacuo* to give the methylbenzoate.

(i) Using the above procedure methyl-2-formylbenzoate (75) was prepared (85%) b.p. 144-148°/18 mm (lit.[109] 136-138°/13 mm).

(ii) Using the above procedure, methyl-2-formyl-5-methoxybenzoate (84) was prepared (91%), b.p. 175-180°(block)/15 mm (Found: C, 62.1; H, 5.4. $C_{10}H_{10}O_4$ requires C, 61.9, H, 5.2%). ν_{max} 1715, 1680, 1600 cm^{-1}. P.m.r: δ 10.23, s, ArCHO; 7.80, d, J 8Hz, ArH_3; 7.26, d, J 3Hz, ArH_6; 6.97, dd, J 8Hz 3Hz, ArH_4; 3.93, s, OCH_3; 3.87, s, OCH_3.

(iii) Methyl-2-formyl-5,6-methylenedioxybenzoate (85) was prepared (74%) using the general procedure described above, b.p. 123-126°(block)/0.05 mm (Found: C, 58.2; H, 4.2. $C_{10}H_8O_5$ requires C, 57.7; H, 3.9%). ν_{max} 1710, 1680, 1615 cm^{-1}. P.m.r: δ 9.98, s, ArCHO; 7.43, d, J 8Hz, ArH; 6.90, d, J 8Hz, ArH; 6.07, s, OCH_2O, 3.93, s, OCH_3.

Attempted preparation of (67)

Butyl lithium (1.9 mmol) in hexane (1.0 ml) was added to a solution of bromophthalazine (0.4 g, 1.9 mmol) in dry tetrahydrofuran (30 ml) at -78° under a nitrogen atmosphere. After 3 min. (75) (0.29 g, 1.9 mmol) in dry tetrahydrofuran (10 ml) was added to the deep red coloured solution and the reaction mixture allowed to warm to room temperature over 10h. The reaction mixture was poured into saturated ammonium chloride (5 ml) and separated. The aqueous phase was extracted with dichloromethane (2 x 30 ml) and the combined extracts were dried (Na_2SO_4) and evaporated to dryness to yield a black tar (0.65 g). Examination of the p.m.r. spectrum exhibited a signal at about δ 1.11 which suggested a butyl group in the product.

Attempted preparation of (67)

Butyl lithium (6.1 mmol) in hexane (3.2 ml) was added to a solu-

tion of (13) (1.0 g, 6.1 mmol) in dry tetrahydrofuran (30 ml) under an atmosphere of nitrogen at -78°. After 2 min. (75) (0.92 g, 6.1 mmol) in dry tetrahydrofuran (15 ml) was added to the blood red solution and the reaction mixture allowed to warm to room temperature overnight. The reaction mixture was quenched with 10% hydrochloric acid (10 ml) and extracted with dichloromethane (3 x 40 ml). The combined organic extracts were dried and concentrated *in vacuo* to yield a red oil (2.2 g) which was chromatographed on silica. Elution with ethyl acetate/light petroleum (1:1) gave a white solid (1.1 g, 51%) which was identified as 4-butyl-1-chloro-3-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-3,4-dihydrophthalazine (78) and yielded colourless needles from ethanol, m.p. 160.5-163° (Found: C, 67.5; H, 5.6; N, 7.6. $C_{20}H_{19}ClN_2O_2$ requires C, 67.7; H, 5.4; N, 7.9%). ν_{max} 1780 cm^{-1}. P.m.r: δ 7.90-7.07, m, 8H, ArH; 6.70, s, ArCHO; 4.47, t, J 6Hz, ArCHN; 2.03-0.68, m, C_4H_9. ^{13}C N.m.r: 170.6; 145.5; 138.2; 135.2; 134.8; 134.5; 131.9; 131.1; 130.3; 128.9; 126.2; 125.6; 124;6; 124.4; 124.0; 96.3; 61.6; 33.4; 27.2; 22.7 ppm. The p.m.r. and ^{13}C n.m.r. represent only 1 set of the observed signals of the diastereoisomers.

The compound (78) when treated with either sodium hydride, potassium t-butoxide, or sodium methoxide, gave a gross mixture of products as evidenced by t.l.c. and p.m.r. spectroscopy.

2-Benzoyl-1-cyano-1,2-dihydrophthalazine (83)

Phthalazine was prepared in 85% yield using the method of Hirsch[117] m.p. 88-90° (lit.[118] 90°) and then used to prepare (83), m.p. 160-162° (lit.[81] 163-164°) in 42% yield according to the procedure of Popp.[81]

Preparation of the Phthalidylphthalazines (67), (86)-(88)

The general procedure used to prepare these compounds is described below.

Saturated sodium hydroxide (2 ml) was added to a vigorously stirred solution of the 2-formylbenzoate (1.1 mmol), (83) (1.1 mmol) and benzyltriethylammonium chloride (0.4 mmol) in dry dichloromethane (15 ml) under nitrogen and the reaction mixture stirred at 20° for 3h. Water (5 ml) was then added and extracted with dichloromethane (5 x 15 ml). The combined extracts were dried (Na_2SO_4), filtered and evaporated to dryness to yield an oil*. This oil was dissolved in methanol (5 ml) and 15% sodium hydroxide (5 ml) and the solution refluxed for 30 min. and extracted with dichloromethane (5 x 15 ml). The aqueous phase was acidified with concentrated hydrochloric acid and refluxed for 30 min. The solution was basified with solid sodium carbonate and extracted with dichloromethane (5 x 15 ml). The combined organic extracts were dried (Na_2SO_4), filtered and the filtrate concentrated *in vacuo* to yield the phthalidylphthalazine as a white solid which was recrystallised from ethanol.

* The p.m.r. spectrum before hydrolysis indicated the presence of phthalazine and 1-cyanophthalazine.

(i) Using the above method, 1-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-phthalazine (67) was prepared (40%) as an apricot coloured powder, m.p. 186-188° (Found: C, 72.9; H, 4.2; N, 10.6. $C_{16}H_{10}N_2O_2$ requires C, 73.3; H, 3.8; N, 10.7%). ν_{max} 1760 cm^{-1}. P.m.r: δ 9.37, s, ArH_4; 7.98-7.48, m, 8H, ArH; 7.20, s, ArCH.

(ii) 1-(5-Methoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-phthalazine (86) was prepared (23%), using the above procedure, as an apricot coloured powder, m.p. 169-171° (Found: C, 67.0; H, 4.5; N, 9.6. $C_{17}H_{12}N_2O_3$ requires C, 69.9; H, 4.2; N, 10.0%). ν_{max} 1760 cm^{-1}. P.m.r: δ 9.30, s, ArH_4; 8.10-7.60, m, 4H, ArH; 7.48-7.10, m, 3H, ArH'; 7.01, s, ArCH; 3.87, s, OCH_3. When the p.m.r. spectrum was repeated in d_4 methanol, the signal at δ 9.30 was reduced in its integral value. It suggested the presence of a small amount of (91a).

(iii) By following the above procedure but substituting opianic acid for the 2-formylbenzoate and benzene for dichloromethane, 1-(4,5-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-phthalazine (88) was obtained as a white powder (20%), m.p. 181-182° (Found: C, 67.1; H, 4.4; N, 8.7. $C_{18}H_{14}N_2O_4$ requires C, 66.9; H, 4.5; N, 8.6%). ν_{max} 1770 cm^{-1}. P.m.r: δ 9.30, s, ArH_4; 7.92-7.57, m, 4H, ArH; 7.06, s, 3H, ArH'; 6.94, s, ArCH; 4.14, s, OCH_3; 3.86, s, OCH_3.

(iv) 1-(4,5-Methylenedioxy-3-oxo-1,3-isobenzofuran-1-yl)-phthalazine (87) was prepared following the above procedure and isolated as a fawn coloured powder (23%), m.p. 193-195° (Found: M, 306.0536. $C_{17}H_{10}N_2O_4$ requires M, 306.0541). ν_{max} 1760 cm^{-1}. P.m.r: δ 9.41, s, ArH_4; 7.91-7.72, m, 4H, ArH; 7.03, s, ArCH; 7.01, d, J 7Hz, ArH_6; 6.83, d, J 7Hz, ArH_7; 6.13, s, OCH_2O.

2.2

Cinnolin-4(1H)-one (19)

To a stirred solution of o-aminoacetophenone (2.0 g, 14.8 mmol) in concentrated hydrochloric acid (75 ml) and water (12 ml) was added sodium nitrite (1.2 g, 17.4 mmol) in water (3 ml) over a period of 45 min maintaining the temperature between -5° and -10°C during the addition. The reaction mixture was stirred at 0° for 1h and then at 80° for 48h. The mixture was then concentrated to c, 0.2 volume, cooled and the precipitate collected. This was dissolved in 10% sodium hydroxide and re-precipitated with concentrated hydrochloric acid to yield 4-hydroxycinnoline (0.75 g, 35%), m.p. 233-234° (lit.[88] 236-237°).

6,7-Dimethoxycinnolin-4(1H)-one (92)

This was prepared in 85% yield according to the method of Castle and Kruse[110] m.p. 304-305.5° (lit.[110] 305-306°).

6,7-Methylenedioxycinnolin-4(1H)-one (93)

3,4-Methylenedioxyacetophenone m.p. 85-87° (lit.[113] 87°) was prepared according to the method of Mathur *et al.*[113] 4,5-Methylenedioxy-2-nitroacetophenone was prepared using the method of Simpson[114] as pale yellow needles from ethanol (80%) m.p. 177-120° (Found: C, 51.7; H, 3.4; N, 6.5. $C_9H_7NO_5$ requires C, 51.7; H, 3.4; N, 6.7%). ν_{max} 1710 cm^{-1}. P.m.r: δ 7.33, s, ArH; 6.60, s, ArH; 6.07, s, OCH_2O; 2.40, s, $COCH_3$. This compound was reduced quantitatively to 2-amino-6,7-methylenedioxyacetophenone using the method of Simpson[114]. P.m.r: δ 6.95, s, 1H, ArH; 6.03, s, 1H, ArH, 5.77, s, OCH_2O; 5.00, br, NH_2; 2.40, s, $COCH_3$.

6,7-Methylenedioxycinnolin-4(1H)-one (93) was prepared, using the method of Castle and Kruse[110], as fawn needles (95%) from acetic acid m.p. 320° (dec) (Found: C, 56.9; H, 3.4; N, 14.7. $C_9H_6N_2O_3$ requires C, 56.9; H, 3.2; N, 14.7%). ν_{max} 3200, 1620, 1600, 1550 cm^{-1}. P.m.r(d_6DMSO):

δ 7.65, s, 1H, ArH; 7.39, s, 1H, ArH; 7.05, s, 1H, ArH; 6.25, s, OCH_2O.

4-Hydroxy-6-methylcinnoline-3-carboxylic acid (94)

This was prepared in 25% yield according to the method of Barber *et al.*[88] m.p. 262-264° (lit.[88] 269°).

4-Chloro-6,7-dimethoxycinnoline (124)

This was prepared according to the procedure of Castle and Kluse,[110] m.p. 193-195° (lit.[110] 195-196°) in 82% yield.

4-Methoxycinnoline (104)

This was prepared according to the procedure of Albert and Barlin,[111] m.p. 124-126° (lit.[111] 127-128°) in 80% yield. When a small quantity was dissolved in chloroform and exposed to the light for 5 days and although the p.m.r. spectrum was complex, it indicated that demethylation had occurred. P.m.r: δ 7.92-6.78, m, 15H, ArH; 3.81, s, 2H, OCH_3.

4,6,7-Trimethoxycinnoline

Preparation of this compound according to the method of Castle[112] *et al.* yielded the required product as was confirmed by an examination of its p.m.r. spectrum, m.p. 206-209° (lit.[112] 210 dec). P.m.r: δ 8.85, s, 1H, ArH_3; 7.68, s, ArH_5; 7.29, s, ArH_8; 4.10, 4.06, s, 9H, OCH_3. However, after storing for 2 weeks, examination of the p.m.r. and i.r. showed it to be a different compound, with a greatly decreased solubility. The product is suggested to have the structure (121). ν_{max} 3300, 1590 cm^{-1}. P.m.r: δ 9.21, br, NH; 7.81, s, ArH; 7.35, s, ArH; 4.20, 4.15, 4.10, three s, 3 x OCH_3. A satisfactory mass spectrum could not be obtained.

6,7-Dimethoxy-1-methylcinnolin-4(1H)-one (103)

6,7-Dimethoxy-4-hydroxycinnoline (0.1 g, 0.49 mmol), potassium carbonate (1.5 g) and methyl iodide (0.5 ml) in acetone (30 ml) were stirred at room temperature for 12h. The mixture was poured into dichloromethane (50 ml), filtered and concentrated *in vacuo* to yield a dark green oil (0.12 g). This material was separated by preparative t.l.c. (3 x ethyl

acetate) to yield the required product (0.054 g, 50%), m.p. 195-196° (lit.[115] 209-210°). The p.m.r. spectrum was identical to that published[91].

1-Methylcinnolin-4(1H)-one (22)

4-Hydroxycinnoline (0.1 g, 0.68 mmol), potassium carbonate (1.0 g), and methyl iodide (0.3 ml) in acetone (15 ml) were stirred at room temperature for 8h. The mixture was diluted with dichloromethane (25 ml), filtered and filtrate stripped of solvent to yield an oil (0.11 g). This was separated by preparative t.l.c. (ethyl acetate) to give (22) (0.43 g, 38%), m.p. 113-115° (lit.[52] 114-116°).

6-Methoxyisobenzofuran-1(3H)-one

This compound m.p. 118-120° (lit.[20] 120°) was prepared by the method of Chakravati and Perkin[20].

3-Bromoisobenzofuran-1(3H)-one (7)

This compound m.p. 78-79° (lit.[90] 78-80°) was prepared in 72% yield by the method of Koten[90].

3-Bromo-6-methoxyisobenzofuran-1(3H)-one (96) and 3-Bromo-6,7-dimethoxy-isobenzofuran-1(3H)-one (97)

These two compounds were prepared using the method of Koten. (96) was prepared as a white solid (79%) m.p. 96-99°. P.m.r: δ 7.55-7.25, m, ArH; ArCH; 3.90, s, OCH_3. (97) was prepared as a white solid (85%) m.p. 83-86°. P.m.r: δ 7.40-7.20, m, ArH, ArCH; 4.15, s, OCH_3; 3.90, s, OCH_3.

2-Formyl-5,6-methylenedioxybenzoic acid (98)

This acid m.p. 164-166° (lit.[30] 164-164.5°) was prepared according to the method of Ziegler and Fowler[30]. The precursor imine (from piperonal and cyclohexylamine, m.p. 64-66° (lit.[116] 65-66°) was prepared by the

procedure of Baddar and Iskander[116] and its p.m.r. spectrum was identical with that published.[30]

3-Chloro-6,7-methylenedioxyisobenzofuran-1(3H)-one (99)

A suspension of 6,7-methylenedioxyphthalaldehydic acid (0.4 g, 2.2 mmol) in benzene (3 ml) and thionyl chloride (2 ml) was stirred at reflux temperature in an anhydrous atmosphere for 1.5 h. The solvent was removed *in vacuo* to afford a white solid (0.43 g, 91%), m.p. 124-127° (Found: M, 211.9877. $C_9H_5ClO_4$ requires M, 211.9876). ν_{max} 1780 cm^{-1}. P.m.r: δ 7.05-6.95, m, ArH, ArCH; 6.12, s, OCH_2O.

Attempted condensation of 6,7-Dimethoxycinnolin-4(1H)-one and phthalaldehydic acid.

(i) A suspension of 6,7-Dimethoxy-4-hydroxycinnoline (0.1 g, 0.5 mmol) and phthalaldehydic acid (0.073 g, 0.5 mmol) in acetone (25 ml) with a catalytic amount of p-toluenesulfonic acid was stirred at reflux temperature for 24h. After this time t.l.c. showed only starting materials to be present.

(ii) A solution of 6,7-Dimethoxy-4-hydroxycinnoline (0.05 g, 0.25 mmol) and phthalaldehydic acid (0.04 g, 0.27 mmol) in dimethylformamide (5 ml) with a trace of p-toluenesulfonic acid was refluxed under nitrogen for 36h. The reaction mixture was poured into dichloromethane (60 ml), washed with water (5 x 10 ml), dried, filtered and concentrated *in vacuo* to give unchanged starting materials as evidenced by t.l.c. and p.m.r. spectroscopy.

(iii) A solution of (92) (0.05 g, 0.25 mmol) and (95) (0.05 g, 0.25 mmol) [from (6) and trifluroacetic anhydride] in benzene (10 ml) was heated at reflux for 6h. The solvent was removed *in vacuo* and the starting materials were recovered.

Attempted condensation of 6-Methyl-4-hydroxycinnoline-3-carboxylic acid (94) and phthalaldehydic acid.

(i) Phthalaldehydic acid (0.074 g, 0.5 mmol) and (94) (0.1 g, 0.5 mmol) and a trace of p-toluenesulfonic acid in benzene (20 ml) were refluxed in a Dean Stark water separator apparatus. After refluxing for 24h, the precipitated solid was collected and identified as (94).

(ii) A mixture of phthalaldehydic acid (0.074 g, 0.5 mmol) and (94) (0.1 g, 0.5 mmol) in dry dimethoxy ethane (20 ml) in the presence of 10% Triton B (0.11 g, 1.0 mmol) was refluxed for 24h. However only starting materials were present according to t.l.c.

Preparation of 1-(3-Oxo-1,3-dihydroisobenzofuran-1-yl)-cinnolin-4(1H)-ones (102), (109)-(117).

A typical reaction used to prepare the phthalidylcinnolinones is described below.

(i) A solution/suspension of 6,7-dimethoxy-4-hydroxycinnoline (0.3 g, 1.45 mmol) and sodium hydride (0.085 g, 1.7 mmol) in dry tetrahydrofuran (160 ml) was stirred at room temperature (20°) under a blanket of nitrogen for 12h. 3-Bromo-6-methoxyphthalide (96) (0.35 g, 1.45 mmol) in dry tetrahydrofuran (30 ml) was added dropwise and the reaction mixture stirred at room temperature under nitrogen for 24h and then heated at reflux for 24h. The reaction mixture was filtered and the filtrate absorbed directly onto silica. The material was chromatographed on silica and eluted with 250 ml aliquots of the following solvent mixtures: light petroleum; light petroleum/dichloromethane, 9:1, 4:1, 1:1, 1:3; dichloromethane; dichloromethane/ethyl acetate 19:1, 9:1, 4:1, 7:3, 1:1, 1:3; ethyl acetate. Elution with dichloromethane/ethyl acetate 1:1 gave 6,7-dimethoxy-1-(5-methoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-cinnolin-

4(1H)-one (112) and was recrystallised from acetic acid (0.25 g, 53%), m.p. 283-283.5° (Found: C, 62.0; H, 4.4; N, 7.6. $C_{19}H_{16}N_2O_6$ requires C, 62.0; H, 4.5; N, 7.5%). ν_{max} 1785, 1640, 1610 cm^{-1}. P.m.r (d_6DMSO): δ 8.30, s, ArH_8; 7.75-7.45, m, 6H, ArH, ArCH; 4.05, s, OCH_3; 3.97, s, 6H, OCH_3.

The yield of the phthalidylcinnolinone was noticeably higher when the appropriate 3-bromophthalide was prepared just prior to use. The majority of these compounds were obtained as powders and only a small number could be induced to crystallise. Therefore, accurate mass spectrum are quoted if a satisfactory analysis could not be obtained. Because of their low solubility the majority of p.m.r. and ^{13}C n.m.r. spectra were recorded in deuterated dimethylsulfoxide or trifluoro acetic acid.

(ii) 1-(3-Oxo-1,3-dihydroisobenzofuran-1-yl)-cinnolin-4(1H)-one (109) was prepared (48%) as described above and recrystallised from ethanol, m.p. 235-236° (Found: M, 278.0682. $C_{16}H_{10}N_2O_3$ requires M, 278.0691). ν_{max} 1780, 1625, 1610 cm^{-1}. P.m.r: δ 8.39, dd, J 9Hz 1Hz, 1H, ArH_8; 8.10-7.32, m, ArH, ArCH.

(iii) 1-(5-Methoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-cinnolin-4(1H)-one (110) was prepared (65%) by the prescribed method and recrystallised from ethanol, m.p. 207-209° (Found: C, 65.6; H, 4.4; N, 8.8. $C_{17}H_{12}N_2O_4$ requires C, 66.2; H, 3.9; N, 9.1%), (Found: M, 308.0794. $C_{17}H_{12}N_2O_4$ requires M, 308.0797). ν_{max} 1780, 1645, 1610 cm^{-1}. P.m.r: δ 8.39, d, J 8Hz, 1H, ArH_8; 8.00-7.30, m, 8H, ArH, ArCH; 3.98, s, OCH_3.

(iv) 1-(4,5-Dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-cinnolin-4(1H)-one (111) was prepared (64%) by the prescribed procedure, and recrystallised from ethanol, m.p. 255-237° (Found: C, 63.7; H, 4.3; N, 8.0. $C_{18}H_{14}N_2O_5$ requires C, 63.9; H, 4.2; N, 8.3%). ν_{max} 1760, 1620, 1600 cm^{-1}. P.m.r: δ 8.25, dd, J 7Hz 1Hz, 1H, ArH_8; 7.80-7.30, m, 5H, ArH; 7.17, d,

d, Jab 7Hz, 1H, ArH'; 7.03, d, Jab 7Hz, 1H, ArH'; 4.17, s, OCH_3; 3.93, s, OCH_3. Elution with dichloromethane/ethyl acetate (2:1) gave 6,6',7,7'-tetramethoxy-$\Delta^{3,3}$-biphthalide (34) (6.1%), m.p. 308-311° (lit.[66] 305°).

(v) 6,7-Dimethoxy-1-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-cinnolin-4(1H)-one (102) was prepared (47%) using the method above, and recrystallised from acetic acid, m.p. 265-267° (Found: M, 338.0908. $C_{18}H_{14}N_2O_5$ requires M, 338.0903). ν_{max} 1780, 1625, 1615 cm^{-1}. P.m.r (d_6DMSO): δ 8.45, s, ArH_8, 8.31-7.59, m, 7H, ArH, ArCH; 4.07, s, OCH_3; 3.98, s, OCH_3.

(vi) 6,7-Dimethoxy-1-(4,5-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-cinnolin-4(1H)-one (113) was prepared (31%) by the prescribed procedure, and recrystallised from ethanol, m.p. 249-251° (Found: C, 60.1; H, 4.9; N, 7.0. $C_{20}H_{18}N_2O_7$ requires C, 60.3; H, 4.6; N, 7.0%). ν_{max} 1780, 1625, 1600 cm^{-1}. P.m.r: δ 7.56, s, ArH_8; 7.53, s, ArH; 7.43, s, ArH; 7.2, d, Jab 8Hz, $ArH_{6'}$; 7.06, d, Jab 8Hz, $ArH_{7'}$; 6.9, s, ArCH; 4.10-3.96, four s, 12H, OCH_3.

(vii) 6,7-Methylenedioxy-1-(3-oxo,1,3-dihydroisobenzofuran-1-yl)-cinnolin-4(1H)-one (114) was prepared (39%) by the method described above and recrystallised from acetic acid, m.p. 284-285° (Found: C, 63.5; H, 3.3; H, 8.4. $C_{17}H_{10}N_2O_5$ requires C, 63.4; H, 3.1; N, 8.7%). ν_{max} 1780, 1640, 1630, 1600 cm^{-1}. P.m.r (d_6DMSO): δ 8.32, s, ArH_8; 8.17-7.70, m, 4H, ArH; 7.9, s, 1H, ArH; 7.65, s, 1H, ArH; 7.5, s, 1H, ArCH; 6.35, s, OCH_2O.

(viii) 1-(5-Methoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-6,7-methylenedioxycinnolin-4(1H)-one (115) was prepared (25%) according to the prescribed method and recrystallised from acetic acid m.p. 270-272° (Found: C, 61.1; H, 3.8; N, 7.8. $C_{18}H_{12}N_2O_6$ requires C, 61.4; H, 3.4; N, 7.6%). ν_{max} 1785, 1625, 1600 cm^{-1}. P.m.r (d_6DMSO): δ 8.25, s, ArH_8; 7.87, s, 1H, ArH; 7.76-7.40, m, 5H, ArH, ArCH; 6.35, s, OCH_2O; 3.95, s, OCH_3.

(ix) 1-(4,5-Dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-6,7-methylenedioxycinnolin-4(1H)-one (117) was prepared (44%) using the general method and recrystallised from acetic acid m.p. 288.5-290° (Found: C, 59.4; H, 4.0; N, 7.2. $C_{19}H_{14}N_2O_7$ requires C, 59.7; H, 3.7; N, 7.3%). ν_{max} 1780, 1625 cm^{-1}. P.m.r (CF_3CO_2H): δ 8.51, s, ArH_8; 7.99, s, 1H, ArH; 7.67, s, 2H, ArH, ArCH; 7.43, d, Jab 10Hz, $ArH_{6'}$; 7.30, d, Jab 10Hz, $ArH_{7'}$; 6.33, s, OCH_2O; 4.23, s, OCH_3; 4.03, s, OCH_3.

(x) 6,7-Methylenedioxy-1-(4,5-methylenedioxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-cinnolin-4(1H)-one (116) was prepared (30%) using the general method and recrystallised from acetic acid, m.p. 280-281.5° (Found: M, 366.0488. $C_{18}H_{10}N_2O_7$ requires M, 366.0488). ν_{max} 1780, 1630 cm^{-1}. P.m.r (d_6 DMSO): δ 7.87, s, ArH_8; 7.67, s, 1H, ArH; 7.53, s, 1H, ArH; 7.43, s, 2H, ArH, ArCH; 7.08, d, Jab 10Hz, $ArH_{6'}$; 6.93, d, Jab 10Hz, $ArH_{7'}$; 6.27, s, OCH_2O; 6.17, s, OCH_2O.

Attempted preparation of (115)

When exploratory reactions were first attempted, the reaction between 4-hydroxy-6,7-methylenedioxycinnoline and 3-bromo-6-methoxyphthalide gave a product with properties to be expected of the O-alkylated product.

A suspension of 4-hydroxy-6,7-methylenedioxycinnoline (0.1 g, 0.53 mmol) in dry tetrahydrofuran (40 ml) was stirred with sodium hydride (0.03 g, 0.7 mmol) under an atmosphere of nitrogen for 15h. 3-Bromo-6-methoxyphthalide (0.12 g, 0.53 mmol) in dry tetrahydrofuran (25 ml) was added dropwise and the reaction mixture stirred at room temperature for 24h and then at reflux temperature for 4h. The reaction mixture was cooled, poured into brine (25 ml) and separated. The aqueous phase was extracted with dichloromethane (3 x 25 ml) and the combined organic extracts were dried, filtered and the solvent removed *in vacuo* to yield

a yellow solid (0.1 g, 53%) which was identified as O-(5-methoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-6,7-methylenedioxycinnoline (126), m.p. 208-210° (Found: M, 352.0692. $C_{18}H_{12}N_2O_6$ requires M, 352.0695). ν_{max} 1820, 1610, 1590 cm^{-1}. P.m.r (d_6DMSO): δ 8.42, s, ArH_3; 7.72, s, ArH_5; 7.71-7.21, m, 3H, ArH'; 7.38, s, ArCH; 7.14, s, ArH_8; 6.25, s, OCH_2O; 3.87, s, OCH_3. When a small sample was heated in tetrahydrofuran, the i.r. spectrum showed new absorbances, although only weak, at 1780 and 1640 cm^{-1}.

3-(2-Acetylphenylamino)-isobenzofuran-1(3H)-one (120)

2-Aminoacetophenone (1.0 g, 7.4 mmol) and phthalaldehydic acid (1.11 g, 7.4 mmol) in acetone (40 ml), with a crystal of p-toluene-sulfonic acid were refluxed for 3h. The acetone was removed *in vacuo* to afford a white solid which yielded colourless needles from ethanol (1.6 g, 80%), m.p. 126-128° (Found: C, 71.8; H, 4.9; N, 5.3; $C_{14}H_{13}NO_3$ requires C, 71.9; H, 4.9; N, 5.2%). ν_{max} 1760, 1640 cm^{-1}. P.m.r: δ 7.90-7.31, m, 6H, ArH; 7.19, s, ArCH; 7.07-6.78, m, 3H, ArH, NH; 2.60, s, $COCH_3$.

Attempted preparation of (123)

(i) To an ice cold solution of (120) (0.8 g, 3.0 mmol) in dichloromethane (40 ml) and acetic acid (15 ml) was added sodium nitrite (0.57 g, 8.2 mmol) over 5 min. The reaction mixture was stirred at room temperature for 1h, washed with 10% sodium bicarbonate (4 x 30 ml) and brine (2 x 30 ml), dried, filtered and the solvent removed *in vacuo* to afford the starting material (0.71 g, 89%).

(ii) Ethyl nitrite (0.2 g, 3.4 mmol) was added to an ice cold solution of (120) (0.2 g, 0.8 mmol) in acetic acid (5 ml) and stirred at room temperature for 24h. The reaction mixture was stripped of solvent to afford a pale yellow solid, which was separated by preparative t.l.c.

(ethyl acetate/dichloromethane, 1:1) to give starting material (0.16 g, 80%) and 4-hydroxycinnoline (0.02 g) identified by t.l.c. and p.m.r. spectroscopy.

Reaction of (124) with Phthalaldehydic acid

4-Chloro-6,7-dimethoxycinnoline (0.23 g, 1.0 mmol), phthalaldehydic acid (0.15 g, 1.0 mmol) and triethylamine (3 ml) were heated under nitrogen at 40° for 24h, after which time t.l.c. and p.m.r. spectroscopy suggested only starting materials.

2.3

Attempted preparation of o-Aminostyrene

(i) An attempt to dehydrate o-aminophenethan-1-ol using the method of Lesniak[119] gave a low yield of a mixture of o-aminostyrene and o-ethylphenylamine as evidenced by p.m.r. spectroscopy. The two compounds could not be separated by spinning band distillation.

(ii) An attempt to prepare o-aminostyrene by the method of Sabetay[120] proved unsuccessful. Nitration of phenethanol proved extremely troublesome and in our hands we were unable to prepare o-nitrophenethan-2-ol.

(iii) The method of Plevyak[95] was followed, but palladium chloride substituted for palladium acetate, however, it failed to give any of the required o-aminostyrene and only the starting o-bromoaniline was recovered.

o-Aminostyrene (130)

o-Nitrocinnamic acid (134) was prepared according to the procedure of Wiley[96], m.p. 145-147° (lit.[121] 143°).

The procedure described below was found to be general for the decarboxylation of the nitrocinnamic acids.

o-Nitrocinnamic acid (5 g, 0.026 mol) and copper bronze powder (2.5 g) were thoroughly mixed and placed in a cold finger apparatus. The mixture was heated with a flame until carbon dioxide evolution had ceased. The crude product was purified by chromatography to yield o-nitrostyrene (135) (1.4 g, 33%). P.m.r: δ 7.86-6.87, m, 5H, ArHCH; 5.83-5.20, m, $CH=CH_2$. This product was not purified but used directly in the next step.

o-Aminostyrene was prepared by the reduction of o-nitrostyrene according to the procedure of Boyer[97] in 89% yield. P.m.r: δ 7.23-6.52, m, SH, ArH CH; 5.70-5.14, m, $CH=CH_2$; 3.78, br, NH_2. This compound was pure

by p.m.r. spectroscopy and t.l.c. and was used directly for further reactions.

4,5-Dimethoxy-2-nitrostyrene (138)

4,5-Dimethoxy-2-nitrocinnamic acid (136) was prepared according to the procedure of Wiley[96], m.p. 282-285° (lit.[122] 285°).

(138) was prepared by the decarboxylation of (136) using the prescribed method and recrystallised from ethanol (69%), m.p. 91-93° (Found: C, 57.4; H, 5.4; N, 6.4. $C_{10}H_{11}NO_4$ requires C, 57.4; H, 5.3; N, 6.2%). ν_{max} 1610 cm^{-1}. P.m.r: δ 7.47, s, ArH; 7.32-7.11, m, $\underline{CH}=CH_2$; 6.87, s, ArH; 5.70-5.27, m, $CH=\underline{CH_2}$; 3.94, two s, two OCH_3.

4,5-Dimethoxy-2-ethenylaniline (140)

An adaption of the method of Boyer[97] was used to prepare (140). A solution of (138) (2.0 g, 9.6 mmol) in ether (20 ml) was added to a stirred suspension of aluminium almalgam (1.2 g) in ether (40 ml), at the same time adding water (1.2 ml), and refluxed for 1.5h. The mixture was cooled, filtered through celite and the residue washed with ether (2 x 30 ml). The filtrate was dried (Na_2SO_4), filtered and evaporated to dryness to yield (140) as an oil (1.45 g, 65%). The N-acetate was recrystallised from ethanol, m.p. 181-183° (Found: C, 64.9; H, 7.2; N, 6.2. $C_{12}H_{15}NO_3$ requires C, 65.1; H, 6.8; N, 6.3%). N-acetate ν_{max} 3300, 1680, 1640, 1620 cm^{-1}. P.m.r: δ 6.83-6.40, m, $\underline{CH}=CH_2$; 6.70, s, ArH; 6.10, s, ArH; 5.53-5.00 m, $CH=\underline{CH_2}$; 3.70, s, two OCH_3. N-acetate P.m.r: δ 7.30, s, ArH; 7.21-6.80, br, NH; 6.81, s, ArH; 6.76-6.42, m, $\underline{CH}=CH_2$; 5.68-5.16, m, $CH=\underline{CH_2}$; 3.86, s, two OCH_3; 2.17, s, $COCH_3$.

2-Ethenyl-4,5-methylenedioxyaniline (141)

4,5-Methylenedioxy-2-nitrostyrene (139) was prepared (36%) by the decarboxylation of 4,5-methylenedioxy-2-nitrocinnamic acid using the method above. P.m.r: δ 7.81-7.31, m, $C\underline{H}=CH_2$; 7.30, s, ArH; 6.84, s, ArH; 6.00, s, OCH_2O; 5.63-5.22, m, $CH=C\underline{H_2}$. This was not purified but used directly in the next step.

Reduction of (139), as described to reduce (138), afforded (141) (74%) as an oil which was characterised as the N-acetate. The acetate yielded needles from ethanol, m.p. 155-156° (Found: C, 64.4; H, 5.4; N, 6.9. $C_{11}H_{11}NO_3$ requires C, 64.4; H, 5.4; N, 6.8%). N-acetate ν_{max} 3300, 1680, 1660, 1635 cm^{-1}. P.m.r: δ 6.73, s, ArH; 6.70-6.23, m, $C\underline{H}=CH_2$; 6.17, s, ArH; 5.77, s, OCH_2O; 5.53-5.03, m, $CH=C\underline{H_2}$; 3.48, s, NH_2. N-acetate P.m.r: δ 7.10, s, ArH, 7.09-6.8, br, NH; 6.84, s, ArH; 6.73-6.40, m, $C\underline{H}=CH_2$; 5.90, s, OCH_2O; 5.60-5.01, m, $CH=C\underline{H_2}$; 2.13, s, $COCH_3$.

2-Methyl-2,1-borazanaphthalene (24)

This was prepared according to the method of Dewar[94], m.p. 72-74° (lit.[94] 73-74°) in 48% yield.

2-Phenyl-2,1-borazanapthalene (128)

This was prepared according to the method of Dewar[94], m.p. 137-139° (lit.[94] 137.5-139°) in 70% yield.

6,7-Dimethoxy-2-phenyl-2,1-borazanaphthalene (131a)

Phenylboron dichloride (0.35 g, 2.2 mmol) was added under nitrogen to a solution of (140) (0.4 g, 2.2 mmol) in benzene (20 ml) at 0°. After stirring for 30 min. at 0°, the reaction mixture was refluxed for 1.5h. The mixture was then poured into 10% sodium hydroxide (5 ml), separated

and the aqueous phase extracted with dichloromethane (2 x 10 ml). The combined organic extracts were dried and evaporated to dryness to yield an oil (0.6 g) which was separated by preparative t.l.c. (light petroleum/ether, 2:1). The only compound which could be identified was (131a) (0.03 g, 5%) (Found: M, 265. $C_{16}H_{16}BNO_2$ requires M, 265). P.m.r: δ 8.21-7.25, m, 8H, ArH; 6.92, s, ArH_5; 6.77, s, ArH_8; 3.91, two OCH_3. No further work was undertaken to increase the yield because the attempted alkylation of (24) and (128) was unsuccessful.

1-Methyl-2-phenyl-2,1-borazanaphthalene (142)

Methyl lithium (0.55 mmol) in ether (0.6 ml) was added to a solution of (128) (0.1 g, 0.55 mmol) in dry tetrahydrofuran (10 ml) under nitrogen at 20°. Methyl iodide (1 ml) was added after 15 min. and the mixture heated at reflux temperature for 18h. The mixture was poured into brine (10 ml) and extracted with ether (3 x 15 ml). The combined extracts were dried and concentrated *in vacuo* to yield an oil which was separated by preparative t.l.c. (light petroleum/ether; 9:1) to give (142) as a white solid (0.062 g, 60%) which was sublimed, 110-115°/20 mm, m.p. 63-64° (Found: C, 82.5; H, 6.7. $C_{15}H_{14}BN$ requires C, 82.2; H, 6.4%). ν_{max} 1605 cm^{-1}. P.m.r: δ 7.75, d, J 11Hz, ArH_4; 7.50-6.91, m, 9H, ArH; 6.74, d, J 11Hz, ArH_3; 3.58, s, NCH_3.

Attempted alkylation of (124) and (128)

An example of the attempted alkylation of (24) and (128) is given below. Other attempts are shown in Tables V and VI.

(i) Methyl lithium (0.35 mmol) in ether (0.32 ml) was added under nitrogen to a solution of (24) (0.05 g, 0.35 mmol) in dry benzene (5 ml). After 15 min. methyl-2-formyl-5-methoxybenzoate (0.07 g, 0.35 mmol) in benzene (2 ml) was added to yield a yellow solution and stirred at 20°

for 30 min. and then at reflux temperature for 6h. The mixture was poured into water (5 ml), separated and extracted with ether (3 x 15 ml). The combined organic extracts were dried and concentrated *in vacuo* to yield (24) (83%).

(ii) Methyl lithium (1.0 mmol) in ether (0.52 ml) was added to a solution of (128) (0.2 g, 1.0 mmol) in benzene (20 ml) under an atmosphere of nitrogen at 20°. After 15 min. 3-bromo-6-methoxyphthalide (0.25 g, 1.0 mmol) in benzene (10 ml) was added and the mixture stirred at ambient temperature for 20h and then at reflux temperature for 1h. The mixture was poured into water (5 ml), extracted with ether (3 x 15 ml), combined extracts dried and concentrated *in vacuo* to give an oil which was separated by preparative t.l.c. (light petroleum/ether, 9:1) to give (128) (70%) as confirmed by its p.m.r. spectrum. No other material could be identified.

1- [(2-Bromophenyl)methyl]-2-methyl-2,1-borazanaphthalene (148)

Methyl lithium (0.7 mmol) in ether (0.8 ml) was added to a stirred solution of (24) (0.1 g, 0.7 mmol) in dry benzene (10 ml) under an atmosphere of nitrogen at 20°. After 25 min. o-bromobenzyl chloride (0.144 g, 0.7 mmol) in benzene (2 ml) was added and the mixture heated at reflux temperature for 18h. The mixture was poured into water (10 ml), separated and the aqueous phase extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried and evaporated to dryness to yield an oil (0.19 g) which was purified by preparative t.l.c. (light petroleum) to yield (148) as an oil (0.075 g, 37%). Because there was only a small amount, this oil was not distilled but used directly in the next step. (Found: M, 310.0522. $C_{16}H_5BBrN$ requires M, 310.0518). ν_{max} 1605 cm^{-1}. P.m.r: δ 7.70, d, J 11Hz, ArH_4; 7.46-6.83, m, ArH; 6.67, d, J 11Hz, ArH_3; 5.32, s, $ArCH_2$; 0.78, s, BCH_3.

TABLE V. Attempted Alkylation of 2-Methyl-2,1-borazanaphthalene.

Electrophile	Solvent	Base	Temperature °C	Time (h)	Result
3-Bromophthalide	Benzene	Methyl Lithium	20°; 80°	24; 1	I (50%)[a]
Methyl-2-formyl-5-methoxybenzoate	THF	Methyl Lithium	20°; 68°	0.5; 6	I (86%)[a]
3-Bromo-6-methoxy phthalide	THF	Methyl Lithium	20°	5	I (82%)[a]
o-Chlorobenzyl bromide	Benzene	Methyl Lithium	80°	8	I (88%)[b]

I: 2-Methyl-2,1-borazanaphthalene (quantity recovered).

a: remaining material was unidentified.

b: o-Chlorotoluene recovered as evidenced by p.m.r. spectroscopy.

TABLE VI: Attempted Alkylation of 2-Phenyl-2,1-borazanaphthalene.

Electrophile	Solvent	Base	Temperature °C	Time (h)	Result
Methyl-2-formyl-benzoate	THF	Methyl Lithium	25°	24	I (78%)
	Benzene	Methyl Lithium	25°	24	I (72%)
3-Bromo-6-methoxy-phthalide	Benzene	Methyl Lithium	25°; 80°	20 ; 1	I (70%)
Methyl Iodide	Benzene	Methyl Lithium	80°	18	(142) (60%).

I: 2-Phenyl-2,1-borazanaphthalene (quantity recovered).

Attempted Carboxylation of (148)

Butyl lithium (0.23 mmol) in hexane (0.25 ml) was added to a solution of (148) (0.07 g, 0.23 mmol) in dry tetrahydrofuran (10 ml) at -78° under an atmosphere of nitrogen. After 15 min. dry carbon dioxide was bubbled into the pale yellow solution for 10 min., and the reaction mixture allowed to warm to room temperature over 30 min. The mixture was acidified with 10% hydrochloric acid and extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried and concentrated *in vacuo* to yield an oil which was separated by preparative t.l.c. (2 x light petroleum). The low Rf compound was obtained as an oil (0.019 g) and identified as 1-benzyl-2-butyl-1,2-dihydro-2-methyl-2,1-borazanaphthalene (152) (Found: M, 291.2152. $C_{20}H_{26}NB$ requires M, 291.2158). ν_{max} 3250 cm^{-1}. P.m.r: δ 7.30-6.49, m, 10H, ArH; 5.91, d, J 6Hz, ArH_3; 4.23, m, 3H; $NHCH_2$; 1.61-0.87, m, $CH_2CH_2CH_3$; 0.22, br s, 5H, CH_2BCH_3. The high Rf compound (0.014 g) was isolated as an oil and identified as 1-benzyl-2-methyl-2,1-borazanaphthalene (152) (Found: M, 233. $C_{16}H_{16}BN$ requires M, 233). P.m.r: δ 7.71, d, J 11Hz; ArH_4; 7.45-6.79, m, 9H, ArH; 6.65, d, J 11Hz, ArH_3; 5.31, s, $ArCH_2$; 0.77, s, BCH_3.

3-(2'-Ethenylphenylamino)-isobenzofuran-1(3H)-one (154)

A solution of o-aminostyrene (1.0 g, 9.2 mmol) and phthalaldehydic acid (1.4 g, 9.2 mmol) in acetone (40 ml) with a catalytic quantity of p-toluenesulfonic acid was heated at reflux for 1h. The solvent was removed *in vacuo* to give (154) which was recrystallised from ethanol (2.0 g, 87%), m.p. 126-128° (Found: C, 76.5; H, 5.2; N, 5.6. $C_{16}H_{13}NO_2$ requires C, 76.4; H, 5.4; N, 5.5%). ν_{max} 3360, 1760 cm^{-1}. P.m.r: δ 7.87-6.51,m,ArHCH; $CH=CH_2$; 5.72-5.13, m, $CH=CH_2$; 4.71, br, NH.

Reaction of (154) with Boron trichloride

Boron trichloride (2.0 mmol) in benzene (1.0 ml) was added to a stirred solution of (154) (0.5 g, 2.0 mmol) in benzene (20 ml) at room temperature under an atmosphere of nitrogen. During the addition a bright orange precipitate resulted. The mixture was stirred at room temperature for 36h, after which time methanol (10 ml) was added and stirred for an additional 10 min. The solvent was removed *in vacuo* to yield a black oil which consisted of at least 8 compounds by t.l.c. Examination of the p.m.r. spectrum of the crude product suggested the presence of 3-methoxyphthalide.

A similar reaction using Phenylboron dichloride in chloroform afforded 3-ethoxyphthalide (67%) and boronic acid (14%) as evidenced by the p.m.r. spectrum of the crude product. 3-Ethoxyphthalide was formed due to the work up procedure involving ethanol. The alkoxy phthalides were formed by the reaction of the alcohol with 3-chlorophthalide (145).

3-(2-Bromobenzylidene)-isobenzofuran-1(3H)-one (157)

This was prepared using a method identical to that of Howe[69].

A solution of (36) (7.0 g, 15.8 mmol), o-bromobenzaldehyde (2.93 g, 15.8 mmol) and triethylamine (1.6 g, 15.8 mmol) in dichloromethane (150 ml) was stirred at room temperature under nitrogen for 4h. The reaction mixture was diluted with dichloromethane (100 ml), washed with water (2 x 50 ml) and dried. The dichloromethane was removed *in vacuo* to yield a white solid. This was recrystallised from acetone to give (157) (35 g, 74%), m.p. 159-161° (Found: C, 59.9; H, 3.1. $C_{15}H_9BrO_2$ requires C, 59.8; H, 3.0%). ν_{max} 1775, 1660 cm^{-1}. P.m.r: δ 7.96-7.08, m, ArH; 6.73, s, ArCH.

4-[(2-Bromophenyl)methyl]-2-methylphthazin-1(2H)-one (158)

Methyl hydrazine (1.8 g, 19.0 mmol) in ethanol (30 ml) was added dropwise over 10 min. to a stirred refluxing suspension of (157) (6.0 g, 19.0 mmol) in ethanol (100 ml). The reaction mixture was stirred at reflux temperature for 14h, cooled and the solvent removed *in vacuo* to yield (158) as a white solid which was recrystallised from ethanol (6.2 g, 98%), m.p. 160-162° (Found: C, 58.5; H, 4.1; N, 8.6. $C_{16}H_{13}BrN_2O$ requires C, 58.4; H, 4.0; N, 8.5%). ν_{max} 1645 cm^{-1}. P.m.r: δ 8.33, m, ArH_8; 7.70-7.32, m, 4H, ArH; 7.21-6.93, m, 3H, ArH; 4.34, s, $ArCH_2$; 3.80, s, NCH_3.

4-[(2-Bromophenyl)hydroxymethyl]-2-methylphthalazin-1(2H)-one (164)

A solution of (158) (1.0 g, 3.2 mmol) and N-bromosuccinimide (0.55 g, 3.2 mmol) in carbon tetrachloride (50 ml) was heated at reflux temperature while irradiating with a 100 Watt globe. After all the N-bromosuccinimide had been consumed, the mixture was filtered and the filtrate concentrated *in vacuo* to leave an oil (1.2 g, 95%) which was identified as 4-[(2-bromophenyl)bromomethyl]-2-methylphthalazin-1(2H)-one (162). P.m.r: δ 8.37, m, ArH_8; 7.91-7.02, m, 7H, ArH; 6.95, s, CHBr; 3.73, s, NCH_3.

Treatment of (162) with sodium hydroxide and methanol afforded a complex mixture as indicated by t.l.c. and p.m.r. spectroscopy.

The oil (162) (1.2 g, 3.04 mmol) was dissolved in dimethylformamide (10 ml) and sodium acetate (1.0 g) added and the mixture stirred at 55° for 48h. The reaction mixture was poured into ether (100 ml), washed with water (5 x 40 ml), dried and the ether removed *in vacuo* to yield 4-[(2-bromophenyl)acetoxymethyl]-2-methylphthalazin-1(2H)-one (163) (1.1 g, 95%). P.m.r: δ 8.32, m, ArH_8; 7.72-7.01, m, 7H, ArH, 7.45, s, ArCH; 3.68, s, NCH_3; 2.01, s, $COCH_3$.

(163) (1.0 g, 2.7 mmol) was dissolved in methanol (10 ml) and 5% sodium hydroxide (5 ml) and stirred at room temperature for 24h. The precipitated solid (164) was collected (0.58, 65%) and recrystallised from ethanol and water, m.p. 156-157° (Found: C, 55.5; H, 3.7; N, 7.9. $C_{16}H_{13}BrN_2O_2$ requires C, 55.7; H, 3.8; N, 8.1%). ν_{max} 3320, 1645 cm^{-1}. P.m.r: δ 8.32, m, ArH_8; 7.73-7.43, m, 4H, ArH; 7.30-7.06, m, 3H, ArH; 6.48, s, ArCH; 4.35, s, OH; 3.83, s, NCH_3.

Attempted Preparation of (159)

A solution of (158) (0.48 g, 1.52 mmol) in dry tetrahydrofuran (10 ml) under a blanket of nitrogen at -78°, was treated with butyl lithium (1.52 mmol) in hexane (1.2 ml). Tributyl borate (0.35 g, 1.52 mmol) was added after 5 min. and the mixture kept at -78° for 18h and then at ambient temperature for 18h. The mixture was poured into 10% hydrochloric acid (15 ml) and extracted with dichloromethane (3 x 30 ml). The combined extracts were dried and concentrated *in vacuo* to yield an oil (0.45 g), and an attempt to separate by preparative t.l.c. (ethyl acetate/dichloromethane, 1:1) gave a variety of compounds, none of which could be identified. The p.m.r. spectrum suggested that the amide carbonyl had taken part in the reaction. Alkaline and neutral extracts did not yield any recognisable products.

Attempted Preparation of (161)

To a solution of (164) (0.05 g, 0.15 mmol) in dry tetrahydrofuran (5 ml) under an atmosphere of nitrogen at -78°, was added butyl lithium (0.3 mmol) in hexane (0.22 ml) to produce a deep orange coloured solution. Tributyl borate (0.04 g, 0.17 mmol) in dry tetrahydrofuran (5 ml) was added producing a yellow solution. Stirring was continued at -78° for 2h, then at room temperature for 0.5h. 15% Sodium hydroxide (5 ml) was

then added and stirred for 3h at 25°, extracted with ether (2 x 10 ml), acidified with concentrated hydrochloric acid and extracted with dichloromethane (3 x 20 ml). The combined dichloromethane extracts were dried and evaporated to dryness to yield a complex mixture of compounds as evidence by t.l.c. and p.m.r. spectroscopy. The p.m.r. spectrum suggested the presence of a small amount of (168).

o-Tolyl Boronic Acid (169)

This was prepared according to the method of Bean[59] m.p. 164-167° (lit.[123] 168°) in 62% yield.

o-Tolyl-2,5-dioxaborolane (170)

A mixture of o-tolylboronic acid (1.0 g, 7.4 mmol) and ethylene glycol (0.46 g, 7.4 mmol) in benzene (15 ml) with a crystal of p-toluenesulfonic acid was stirred at reflux, in a Dean Stark apparatus, for 12h. The benzene was removed *in vacuo* to yield (170) as a colourless oil (1.2 g, 100%), b.p. 105-110° (block)/15 mm (Found: C, 66.9; H, 6.8. $C_9H_{11}BO_2$ requires C, 66.7; H, 6.8%). ν_{max} 1600 cm^{-1}. P.m.r: δ 7.69, m, 1H, ArH; 7.30-7.00, m, ArH; 4.28, s, CH_2CH_2; 2.51, s, $ArCH_3$.

Benzyltriphenyl-2-(2,5-dioxaborolan-1-yl)-phosphosphonium bromide (172)

A solution containing (170) (1.0 g, 6.2 mmol) and N-bromosuccinimide (1.1 g, 6.2 mmol) and benzoylperoxide (0.11 g, 0.8 mmol) in carbon tetrachloride (40 ml) was refluxed for 2.5 h, irradiating with a 100 Watt globe. The mixture was filtered and the filtrate evaporated to yield (171) as an oil (1.3 g, 97%). P.m.r: δ 7.73-6.99, m, ArH; 4.78, s, $ArCH_2$; 4.33, s, CH_2CH_2. This oil was identified as 1-(2-bromomethylphenyl)-2,5-dioxaborolane (171) which was used directly in the next step.

Triphenylphosphine (1.7 g, 6.3 mmol) and (171) (1.5 g, 6.2 mmol) in benzene (30 ml) were stirred at reflux temperature under nitrogen for 36h. The mixture was cooled and filtered to yield (172) (2.6 g, 84%) m.p. 253-255° (Found: M, 429. $C_{27}H_{23}BBrO_2P$,-C_2H_2 requires M, 429.) ν_{max} 1600, 1590 cm^{-1}. P.m.r: δ 7.31-7.12, m, ArH; 5.39, d, J 15Hz, $ArCH_2$; 4.00, s,CH_2CH_2. Attempts to recrystallise this compound led to its decomposition.

Attempted Preparation of (173)

(i) Sodium hydride (0.06 g, 1.25 mmol) was added to a stirred suspension of (0.5 g, 1 mmol) and phthalic anhydride (0.15 g, 1 mmol) in dry tetrahydrofuran (60 ml) and stirred under nitrogen for 72h. A white solid was collected but could not be identified, but is probably some type of boron hydride complex.

(ii) A suspension of phthalic anhydride (0.05 g, 0.3 mmol),(172) (0.15 g, 0.3 mmol) and potassium t-butoxide (0.044g, 0.3 mmol) in dry tetrahydrofuran (20 ml) was stirred under nitrogen for 4 days. P.m.r. and t.l.c. analysis showed only starting materials to be present. The mixture was washed with water (2 x 5 ml), and the aqueous washings extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried and evaporated to dryness. Examination of the p.m.r. spectrum showed the presence of triphenylphosphine oxide, o-tolylboronic acid and ethylene glycol.

WORK DESCRIBED IN PART III

[(3,4-Dimethoxyphenyl)methyl]-N,N-dimethylamine (12)

This was prepared using the method of Borch *et al.*[33], in 25% yield. HCl m.p. 204-206° (lit.[33] 207-208°). P.m.r: δ 6.67-6.50, m, 3H, ArH; 3.70, 3.68, two s, 6H, OCH_3; 3.23, s, 2H, CH_2N; 2.10, s, 6H, $N(CH_3)_2$.

Carboxylation of [(3,4-Dimethoxyphenyl)methyl]-N,N-dimethylamine

(i) A solution of (12) (0.3 g, 1.6 mmol) in freshly distilled tetrahydrofuran (8 ml) was treated at 20° under nitrogen with butyl lithium (1.6 mmol) in hexane (0.8 ml). After stirring for 1.2h, solid carbon dioxide was added, stirred for a further 4h, acidified with 10% hydrochloric acid (4 ml), brought back to neutrality with 10% sodium hydroxide and extracted with dichloromethane (5 x 15 ml). The combined extracts were concentrated *in vacuo* to yield 2,3-dimethoxy-6-(dimethylamino)methylbenzoic acid (15) (0.025 g, 7.1%). P.m.r: δ 7.33, br s, $CO_2\underline{H}$; 6.76, m, 2H, ArH; 4.05, s, CH_2N; 3.90, s, OCH_3; 3.84, s, 3H, OCH_3; 2.70, s, 6H, $N(\underline{C}H_3)_2$. Repeated extraction using dichloromethane failed to give any additional material which suggests that the amino acid is very water soluble. Due to the isolation difficulties no further work in this carboxylation procedure was undertaken.

(ii) A solution of (12) (0.3 g, 1.6 mmol) in tetrahydrofuran (8 ml) was treated at 20° under nitrogen with butyl lithium (1.6 mmol) in hexane (0.8 ml). After stirring for 1.5h, ethyl chloroformate (3 ml) was added and the resultant yellow solution stirred at 20° for 24h. At regular intervals, a small aliquot was removed and evaporated to dryness and the p.m.r. spectrum recorded. Because of the complex nature of the p.m.r. spectrum, only the ratio of the two diagnostic signals which suggested the formation of the intermediate carbamate are recorded. These signals were ascribed on the basis of similar results observed when (12) was stirred with ethyl chloroformate. After 0.5h a small aliquot was removed and the p.m.r. spectrum recorded. The ratio of $N(\underline{C}H_3)_2$, δ1.95, to $N\underline{C}H_3CO_2Et$, δ 2.80 was 1.59.

After 1h, $N(CH_3)_2$:$NC\underline{H}_3CO_2Et$ was 0.7. The i.r. showed absorptions at 1775, 1740, 1710 cm^{-1} which confirmed the presence of the compounds (12), (13) and (14). The only compound present after 20h was (13). After 20h, the reaction mixture was poured into brine (10 ml), extracted with ether (3 x 20 ml), and the combined etheral extracts dried and concentrated to yield an oil (0.33 g), which was purified by preparative t.l.c. (developing with light petroleum-ether; 9:1) to give (13) (0.28 g, 73%) which had an identical p.m.r. spectrum to that recorded in the literature[30]. (Found: M, 261, 259, $C_{12}H_{15}ClO_4$ requires M, 261, 259).

Dealkylation of [(3,4-Dimethoxyphenyl)methyl]-N,N-dimethylamine

A solution of (12) (0.5 g, 2.6 mmol) and ethyl chloroformate (1 g, 10 mmol) in dry tetrahydrofuran (10 ml) was stirred at room temperature under nitrogen. Small aliquots were removed at various intervals, evaporated to dryness and the p.m.r. spectrum recorded. After 0.5h, the dimethylamine group signal at δ2.1 had disappeared to be replaced by a signal at δ2.83, $N\underline{C}H_3CO_2Et$. Thus, the N-methyl bond had cleaved rapidly. The ratio of $N\underline{C}H_3CO_2Et$:Ar$\underline{H}$ was then calculated. After 12h, NCH_3CO_2Et: Ar$\underline{H}$; 0.71; after 36h, 0.38; and after 72h, 0.3. Thus, the benzylic cleavage appears to be very slow.

Preparation of 6,7-Dimethoxyisobenzofuran-1(3H)-one. (Meconine, (9)).

A solution of 3,4-dimethoxybenzyl alcohol (0.15 g, 0.9 mmol) in dry tetrahydrofuran (5 ml) under an atmosphere of nitrogen, was treated at 20° with butyl lithium (1.8 mmol) in hexane (1.3 ml). After stirring for 2h, dry carbon dioxide was bubbled into the white suspension for 1h, with the occasional addition of more dry tetrahydrofuran. 10% Hydrochloric acid (5 ml) was then added and the reaction mixture stirred for 0.5h. The mixture was extracted with dichloromethane (4 x 10 ml) and evaporated

to yield an oil. This was purified by preparative t.l.c. (ether) to yield meconine (0.1 g, 59%) m.p. 97-100° (lit.[28] 101-102°). The reaction has been repeated on a 5 gm scale and the yield of recrystallised meconine was 65%. The other reactions which failed to yield meconine and gave only starting material are recorded in Table 1. In each experiment there was at least 95% of meconine recovered.

TABLE I Attempted Metallation and Carboxylation of 3,4-Dimethoxybenzyl alcohol.

Solvent	Metallation time [a] (h)	Result
Ether	2	starting material
THF/HMPA [b]	2	starting material
THF/HMPA	14	starting material
THF	16	starting material

a: This is the time allowed for the metallation to occur between two equivalents of butyl lithium and 3,4-dimethoxybenzyl alcohol.

b: HMPA refers to hexamethylphosphoric triamide.

6,7-Methylenedioxyisobenzofuran-1(3H)-one (24)

A solution of 3,4-methylenedioxybenzyl alcohol (0.3 g, 2.0 mmol) in dry tetrahydrofuran (10 ml) under an atmosphere of nitrogen at 0° was treated with butyl lithium (4.0 mmol) in hexane (2.8 ml). After 1h dry carbon dioxide was bubbled into the yellow solution for 0.5h, 10% hydrochloric acid (5 ml) added and the reaction mixture stirred at room temperature overnight. The mixture was extracted with dichloromethane

(3 x 20 ml), dried and concentrated to yield (24) which was recrystallised from methanol (0.17 g, 48%) m.p. 236-238° (lit.[50] 226°). P.m.r:(d_6DMSO): δ 7.10, d, J 8Hz, ArH; 6.93, d, J 8Hz, ArH; 6.10, s, OCH_2O; 5.22, s, $ArCH_2$.

6,7-Dimethoxyisobenzofuran-1(3H)-one-3-carboxylic acid (26)

6,7-Dimethoxyphthalide (0.2 g, 1.1 mmol) in dry tetrahydrofuran (5 ml) was added to a solution of lithium diisopropylamide [prepared from diisopropylamine (0.11 g, 1.1 mmol) and butyl lithium (1.1 mmol) in hexane (0.78 ml) at 0° in tetrahydrofuran (10 ml)] at -78° under an atmosphere of nitrogen, to produce a yellow coloured solution. After 2 min, dry carbon dioxide was bubbled into the stirred reaction mixture for 5 min, allowed to warm to room temperature over 10 min. and then 10% hydrochloric acid (5 ml) was added. The mixture was extracted with dichloromethane (3 x 15 ml) and the organic extracts dried, filtered, and evaporated to dryness to yield (26) (0.23 g, 94%). A small sample was recrystallised from dichloromethane/light petroleum m.p. 157-159° (Found: M, 238.0474, $C_{11}H_{10}O_6$ requires M, 238.0477). ν_{max} 3100–2900, 1760 cm^{-1}. P.m.r: δ 8.44, br s, CO_2H; 7.20, s, 2H, ArH; 5.70, s, $CHCO_2H$; 4.03, s, OCH_3, 3.87, s, OCH_3.

6-Methoxyisobenzofuran-1(3H)-one-3-carboxylic acid (29)

6-Methoxyphthalide was prepared as described in the experimental section of Part II.

6-Methoxyphthalide (0.2 g, 1.2 mmol) in dry tetrahydrofuran (5 ml) was added to a solution of lithium diisopropylamide [prepared from diisopropylamine (0.12 g, 1.2 mmol) and butyl lithium (1.2 mmol) in hexane (0.8 ml) at 0° in tetrahydrofuran (10 ml)] at -78° under nitrogen, to produce a yellow coloured solution. After 2 min. ethyl chloroformate (1 ml) was added and the stirred reaction mixture allowed to warm to room temperature over 25 min. The reaction mixture was then poured into saturated ammonium chloride (10 ml), extracted with dichloromethane (3 x 15 ml), extracts dried and evaporated to give an oil (0.36 g), which was a mixture

of mono- and di- carboxylates, as evidenced by the p.m.r. spectrum. The oil was hydrolysed with 20% potassium hydroxide (5 ml) until a solution was achieved. After cooling, the mixture was extracted with ether (10 ml), acidified with hydrochloric acid and immediately extracted with ether (4 x 15 ml), extracts dried and evaporated to yield a solid as colourless plates from dichloromethane / light petroleum (0.21 g, 84%) m.p. and mixed m.p. with an authentic sample 170-172° (lit.[52] 169-170°).

Deutration of 3-methoxybenzyl alcohol.

Butyl lithium (2.2 mmol) in hexane (1 ml) was added to a stirred solution of 3-methoxybenzyl alcohol (0.15 g, 1.1 mmol) in dry tetrahydrofuran (15 ml) under an atmosphere of nitrogen and the reaction mixture stirred at 20°. The reaction mixture was initially a pale yellow but on prolonged stirring a colourless solution resulted. Deuterium oxide (1 ml) was added at various time intervals to an aliquot, to give a white precipitate and the mixture was then poured into ammonium chloride (5 ml), and the product isolated by extraction as usual. The deuterium incorporation was calculated from the p.m.r. spectrum. The results are tabulated below (Table II).

TABLE II Deuterium incorporation studies of lithiated 3-methoxybenzyl alcohol.

Time allowed for metallation (h)	Amount of Aromatic Deuterium incorporation (%)
0.25	0
1.5	10
3	60
16	60; 40 [a]

a: this is the amount of deuterium incorporated at the benzylic position.

2.2

1-(2-Bromo-4,5-dimethoxybenzyl)6,7-dimethoxyisoquinoline (36)

Papaverine (35) was brominated using a method of Kametani[51]. (36) was obtained in 70% yield. m.p. 142-144°. (lit.[46] 143-143.5°).

Carboxylation of 1-(2-Bromo-4,5-dimethoxybenzyl,6,7-dimethoxyisoquinoline

To a solution of 2'-bromopapaverine (36) (0.2 g, 0.48 mmol) in dry tetrahydrofuran (20 ml) under an atmosphere of nitrogen at -78°, was added butyl lithium (0.48 mmol) in hexane (0.44 ml) to produce a blood red coloured solution. After 6 min, dry carbon dioxide was bubbled into the reaction mixture to produce almost immediately a pale yellow solution. The reaction mixture was then extracted with 10% sodium hydroxide (2 x 3 ml) and the alkaline extracts were washed with ether, neutralised with 10% hydrochloric acid, extracted with dichloromethane (4 x 15 ml) and the organic extracts dried and evaporated to yield 4,5-dimethoxy-2[(6,7-dimethoxyisoquinolin-1-yl)methyl]-benzoic acid (40) which was recrystallised from dichloromethane (0.1 g, 56%) m.p. 260-262° (Found: C, 65.4; H, 5.8; N, 3.7. $C_{21}H_{21}NO_6$ requires C, 65.8; H, 5.5; N, 3.7%). ν_{max} 3300, 1700 cm^{-1}. P.m.r: δ 12.7, br, 1H, CO_2H; 8.11,d,J 6Hz, ArH_3; 7.67, s, ArH; 7.43, d, J 6Hz, ArH_4; 7.40, s, ArH; 7.07, s, ArH; 6.61, s, ArH; 4.73, s, $ArCH_2$; 4.10, 4.03, 3.83, 3.71, four s, 4 x OCH_3.

A sample of this acid was reduced with borane-methyl sulfide to give 2'-hydroxymethylpapaverine as confirmed by p.m.r. and t.l.c. analysis with an authentic sample which was prepared according to the method of Shamma[49] m.p. 170-172° (lit.[49] 172-174°).

Lithiation and alkylation of (36)

(i) To a solution of (36) (0.1 g, 0.24 mmol) in dry tetrahydrofuran (10 ml) under a blanket of nitrogen at -78° was added butyl lithium (0.24 mmol) in hexane (0.2 ml). After 6 min. deuterium oxide was added to the

blood red solution and instantly the colour was removed to produce a light yellow coloured solution. 10% Hydrochloric acid (5 ml) was added and the solution became colourless. The reaction mixture was basified with 10% sodium hydroxide and extracted with dichloromethane (4 x 20 ml). The extracts were dried and evaporated to yield papaverine (0.076 g, 94%) which consisted of 90% of 2'-deuteropapaverine (39) by examination of the p.m.r. spectrum.

1-[2-(3,4-Methylenedioxyphenyl-hydroxymethyl)-4,5-dimethoxybenzyl]-6,7-dimethoxyisoquinoline (41)

(ii) To a solution of (36) (0.21 g, 0.5 mmol) in dry tetrahydrofuran (20 ml) under an atmosphere of nitrogen at -78°, was added butyl lithium (0.5 mmol) in hexane (0.4 ml). After 6 min. piperonal (0.075 g, 0.5 mmol) in dry tetrahydrofuran (2 ml) was added, and after stirring at -78° for 30 min. 10% hydrochloric acid (3 ml) was added and then basified with 10% sodium hydroxide. The reaction mixture was extracted with dichloromethane (3 x 25 ml), extracts dried, evaporated and the product isolated by preparative t.l.c. (developing twice with ethyl acetate) to give (41) (0.08 g, 34%) m.p. 153-155° (Found: M, 489.1770. $C_{28}H_{27}NO_6$ requires M, 489.1787). ν_{max} 3180, 1610 cm^{-1}. P.m.r: δ 8.10, d, J 6Hz, ArH_3; 7.33-6.50, m, 8H, ArH; 5.97, s, CHOH; 5.83, s, OCH_2O; 4.43, s, $ArCH_2$; 4.00-3.67, five s, OCH_3, OH. No other material could be characterised.

Attempted preparation of (42)

(iii) Butyl lithium (0.5 mmol) in hexane (0.4 ml) was added to a solution of (36) (0.21 g, 0.5 mmol) in dry tetrahydrofuran (20 ml) which was under an atmosphere of nitrogen at -78°. Tributyl borate (0.13 g, 0.5 mmol) in dry tetrahydrofuran (2 ml) was added after 6 min, however, the red coloured solution persisted. A second quantity of tributyl borate (0.4 g, 1.5 mmol) was added and the reaction mixture kept at -78° for 2h,

and then at room temperature for 1h during which time the solution became yellow. 10% Hydrochloric acid (5 ml) was added and stirred for 10 min, basified to pH14 and extracted with dichloromethane (3 x 25 ml). The extracts were dried and concentrated to yield an oil (0.19 g, 95%) which was identified as papaverine and c.6% of (36).

A similar reaction was attempted substituting boron trifluro etherate for tributylborate, but again only papaverine (96%) was isolated.

Attempted preparation of (50)

(iv) To a solution of (36) (0.1 g, 0.24 mmol) and ethyl chloroformate (0.03 g, 0.24 mmol) in dry tetrahydrofuran (10 ml) under a blanket of nitrogen at -78°, was added butyl lithium (0.24 mmol) in hexane (0.2 ml) to produce a transient red colour. The mixture was kept at -78° for 30 min, poured into saturated ammonium chloride (5 ml) and extracted with dichloromethane (3 x 15 ml). The combined extracts were dried (Mg_2SO_4), filtered and concentrated *in vacuo* to afford an oil (0.14 g) which was stirred with 20% sodium hydroxide (5 ml) and ethanol (5 ml) at 50° for 2h. The reaction mixture was cooled, brought back to neutrality with 10% hydrochloric acid and extracted as above to give (36) (0.95 g.)

An identical reaction was attempted except two equivalents of butyl lithium and ethyl chloroformate were used. After hydrolysis and work up, (36) was recovered, as well as pentanoic acid as evidenced by p.m.r. spectroscopy.

Attempted carboxylation of (36)

Butyl lithium (0.3 mmol) in hexane (0.24 ml) was added to a solution of papaverine (0.1 g, 0.3 mmol) in dry tetrahydrofuran (15 ml) at -78° under nitrogen. After 10 min. dry carbon dioxide was bubbled into the red coloured solution to produce a pale yellow solution. The reaction mixture was extracted with sodium hydroxide (2 x 10 ml) and the aqueous

phase was acidified with 10% hydrochloric acid and extracted with dichloromethane (3 x 15 ml). The combined extracts were dried and concentrated *in vacuo* to give (35) (0.97 g).

Reaction of (51) with boron-dimethyl sulfide

2'-Hydroxypapaverine (0.1 g,0.03 mmol) and boron-dimethyl sulfide (1 ml) in tetrahydrofuran (10 ml) were stirred at 20° for 1h. Water (6 ml) was added and the mixture extracted with dichloromethane (3 x 10 ml). The organic extracts were dried and concentrated *in vacuo* to yield a solid, identified as (52). P.m.r: δ 8.31, d, J 7Hz, ArH; 7.38, d, J 7Hz, ArH; 7.17, s, 2H, ArH; 6.92, s, ArH, 6.72, s, ArH, 5.89, s, ArCH; 4.85, s, $ArCH_2$; 4.71, s, BOH, 3.88, s, OCH_3; 3.70, s, 6H, OCH_3, 3.34, s, OCH_3. This was identical to the intermediate obtained on the reduction of (40). Treatment of (52) with acid yielded (51).

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