# THE SYNTHESIS OF PERLOLINE

AND

# SOME REACTIONS OF α,β UNSATURATED ISOCYANATES WITH ACTIVATED OLEFINS

A THESIS

PRESENTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

THE UNIVERSITY OF ADELAIDE

BY

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CONTENTS

## SUMMARY

Chapter 1 of this thesis describes the first total synthesis of perloline (1), an alkaloid found in New Zealand rye grass. The key step of the synthesis is the final ring closure of the amide (32) which was achieved using strong base or copper catalysed conditions, both in good yield (86% and 73% respectively). The amide (32) was prepared from 2-bromoacetophenone in four steps in 65% overall yield. Several methods of forming the chloro amide (31) are also described as well as the ring closure of (31).

Chapter 2 describes some reactions of $\alpha,\beta$ unsaturated isocyanates with activated olefins. The aim of this work was to find a method of annelating a 2-pyridone ring onto a preformed ring system. Although no method of achieving this aim was found some interesting reactions of isocyanates are described.

## 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.

STEPHEN T. WERE

## ACKNOWLEDGEMENTS

I wish to express my sincere thanks to Dr. R.H. Prager for his encouragement, enthusiasm, and guidance during the supervision of this work. In addition I wish to thank Dr. A.D. Ward for many helpful discussions and my laboratory colleagues for their help. I am indebted to Miss L. Schrippa for preparing compound (58).

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## PUBLICATIONS

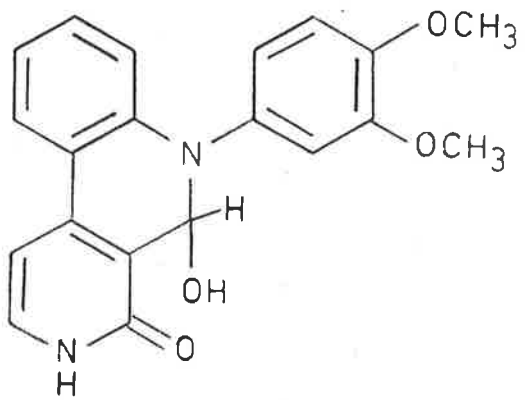
1. A 'Biogenetic Like' Synthesis of Perloline, 6-(3,4-Dimethoxyphenyl)-5-hydroxy-5,6-dihydrobenzo[C][2,7]naphthyridin-4(3H)-one.
Duong, T., Prager, R.H., and Were, S.T.,
*Aust.J.Chem.*, 1983, *36*, 1431.

2. The Synthesis of Perloline, 6-(3,4-Dimethoxyphenyl)-5-hydroxy-5,6-dihydrobenzo[C][2,7]naphthyridin-4(3H)-one.
Prager, R.H., and Were, S.T.,
*Aust.J.Chem.*, 1983, *36*, 1441.

# CHAPTER 1

## 1.1 INTRODUCTION

Perloline (1) is a novel diazaphenanthrene alkaloid which occurs in several pasture grasses throughout the world, including New Zealand rye grass* (Lolium perenne)[1] and tall fescue (Festuca arundinacea).[2] The concentrations of the alkaloid in these grasses have been shown to vary with several factors including the weather and the season.[3] The peaks of the levels of perloline correspond with the peaks in susceptibility of sheep and cattle grazing on the grass to a disabling but temporary disease of the central nervous system called "rye grass staggers".[3]




(1)

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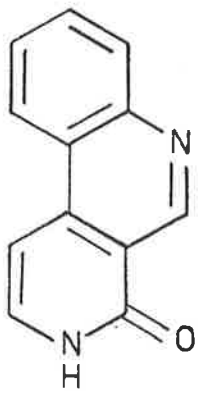
* Listed in *Chem.Abstr.* under "English Rye Grass".

The implication that perloline (1) was involved in the cause of rye grass staggers has prompted several studies of perloline (1).[4,5] Recent work at the C.S.I.R.O. has shown that a similar disease in annual rye grass (L. multiflorum) is caused by a nematode and bacterial infection.[6,7]

Perlolidine (2) has been found accompanying perloline (1) and is another alkaloid with the diazaphenanthrene skeleton. Studies have shown that perloline (1) can be chemically converted to perlolidine (2), dehydroperloline (3), and reversibly to deoxyperloline (4).[5] Four syntheses of perlolidine (2) have been reported,[8-10] and one synthesis of dehydroperloline (3) has been reported.[11] This thesis details the first reported synthesis of perloline (1).[12]

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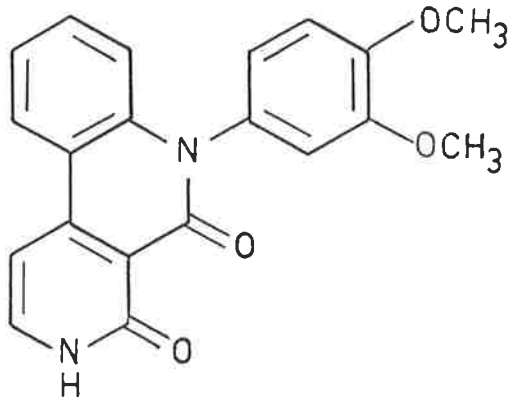


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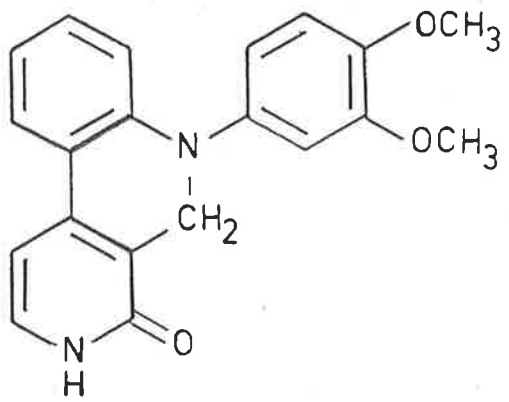
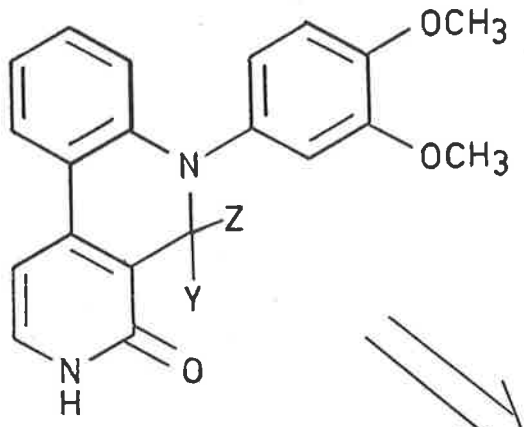



(4)

The design of a synthetic approach to perloline (1) was simplified because deoxyperloline (4) could be readily converted to perloline (1),[5,13] and it was considered that dehydroperloline (3) could be reduced to perloline (1) or deoxyperloline (4). The oxidation level at C-5 could therefore be readily adjusted after the skeleton was assembled.

The retrosynthetic analysis of the synthesis from the hypothetical perloline equivalent (5) (see scheme 1) the bond dissection between the nitrogen and aromatic ring would give the precursor (6). The reaction to form the N-aryl bond was envisaged as being a benzyne cyclization. A compound represented by (6) could be formed from dimethoxyaniline (7) and an appropriately functionalised pyridone such as (8). Accordingly the first major target was the formation of the 2-pyridone ring.

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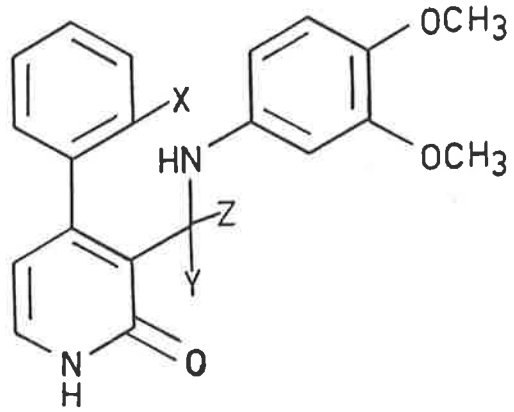


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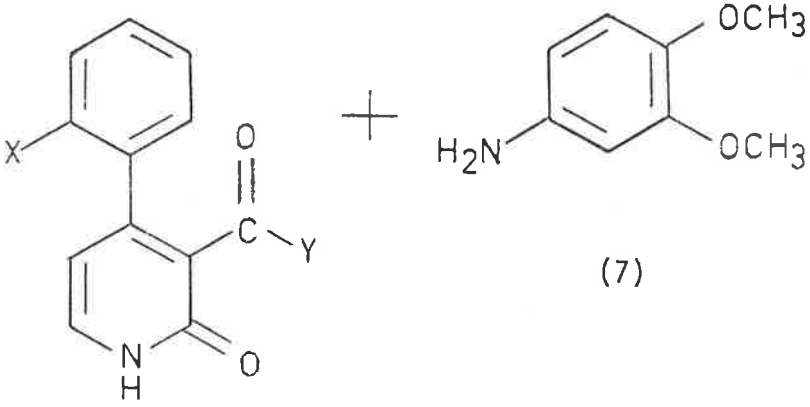
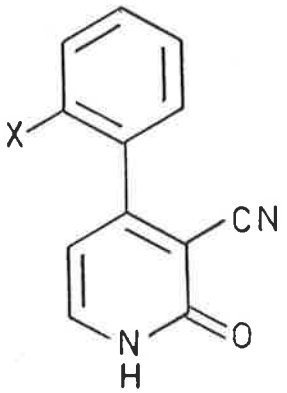



(8) (7)

SCHEME 1

## RESULTS AND DISCUSSION

None of the classical 2-pyridone syntheses were designed to produce the required substitution pattern.[14,15] The 2-pyridone (9) could be formed by the method used by Powers and Ponticello[9] to form the 2-pyridone (10), but their yield of (10) was unacceptably low, and another approach was sought. The method of Saito[16] works well to produce 3,4,6-trisubstituted 2-pyridones - particularly 6-aryl, but its adaptation to a 2-pyridone unsubstituted at C-6 is somewhat circuitous. The application of this method involved forming a 2-pyridone substituted at C-6 by a carboxyl group which could be decarboxylated to give the 2-pyridone (9).

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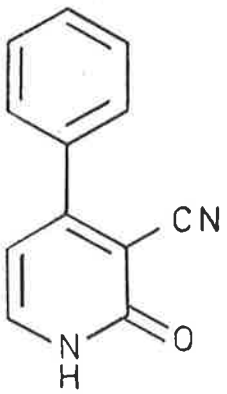
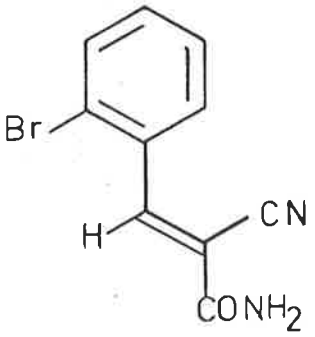



(10)

The Knoevenagel reaction between 2-bromobenzaldehyde and cyanoacetamide gave the propenamide (11) in good yield.[17] The 2-pyridone formation, using ethyl pyruvate to add the two carbon unit

to the propenamide, was first tried in benzene with ammonium acetate catalyst; but there was no reaction of the propenamide, presumably due to the lack of solubility of the amide and the catalyst. The reaction was attempted in dimethylsufoxide but only traces of the desired 2-pyridone (12) formed.

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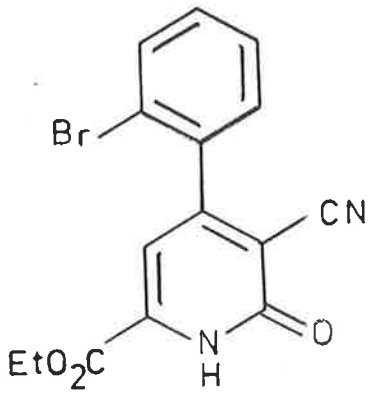


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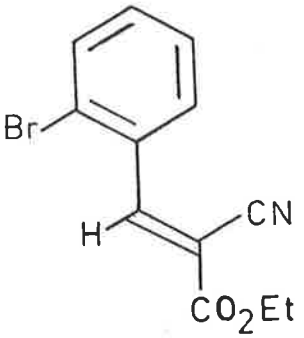
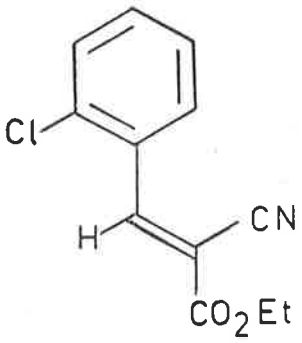



(13)

The solubility problems, due to the amide functionality, were overcome using the ester (13)[18] which was prepared by the method of Popp.[19] The reaction with ethyl pyruvate and ammonium acetate could be carried out in either ethanol or benzene and the 2-pyridone (12) crystallized from solution, but the yield was very low. The bulk of the bromo substituent might have been inhibiting the reaction so the less bulky chloro analogue was used. The chloro ester (14)[19] reacted with ethyl pyruvate and ammonium acetate and the required 2-pyridone (15) was obtained in 20% yield. Hydrolysis of the ester (15) to the acid (16) proceeded smoothly (90% yield).

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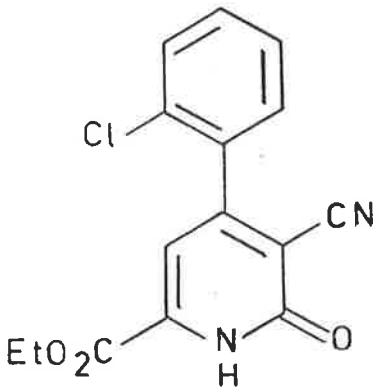
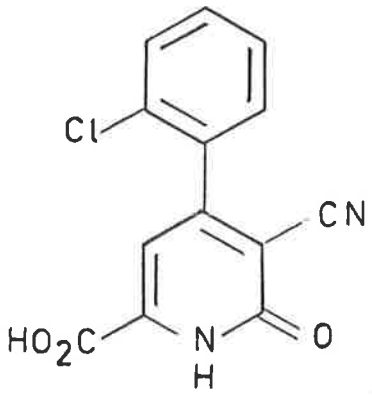



(15)

Thermolysis of the acid (16) in the presence of copper bronze surprisingly gave only a 40% yield of decarboxylated material (17). Copper bronze in quinoline failed to produce any (17). Copper promoted decarboxylations are reported to give good yields in most cases;[20,21] although there are some cases where decarboxylation could not be effected,[22] Jackson and Bowlus[23] found that the copper/quinoline decarboxylation of 5-hydroxy-3-methylbenzo[b]thiophene-2 carboxylic acid was very low yielding, the low yield was attributed to the phenolic group. A similar inhibition could be acting in the present work. Other methods tried to effect decarboxylation also failed.

Owing to the low yields of two steps this approach was abandoned and an alternative method of adding a two carbon unit to the $\alpha,\beta$ unsaturated ester (14) leading to (17) was sought. The synthons required to convert (14) into (17) were acetaldehyde or acetic acid,

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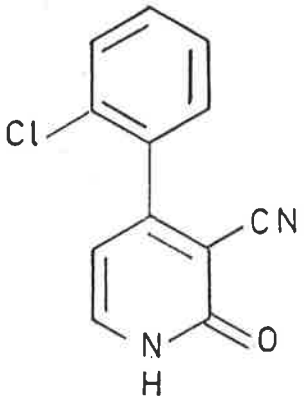
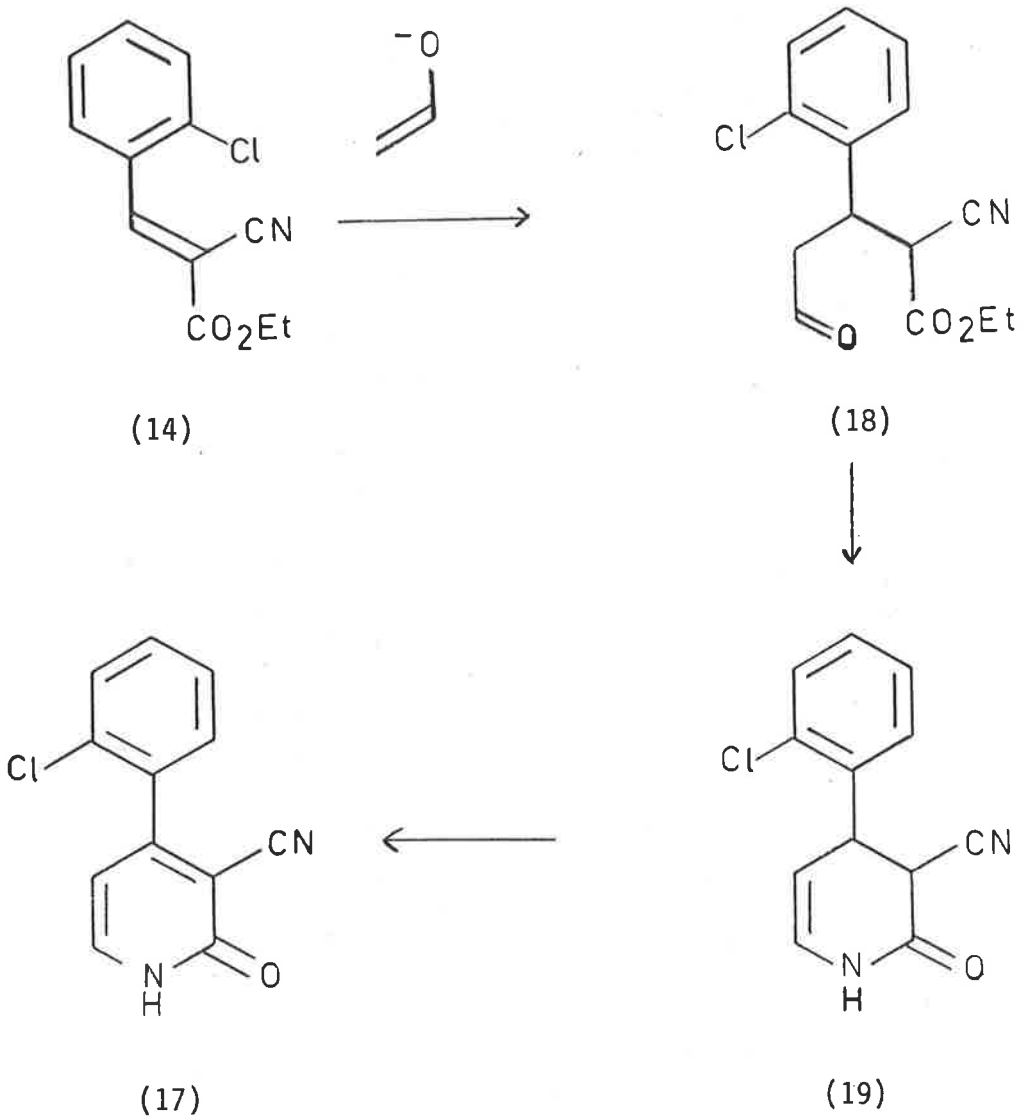



(17)

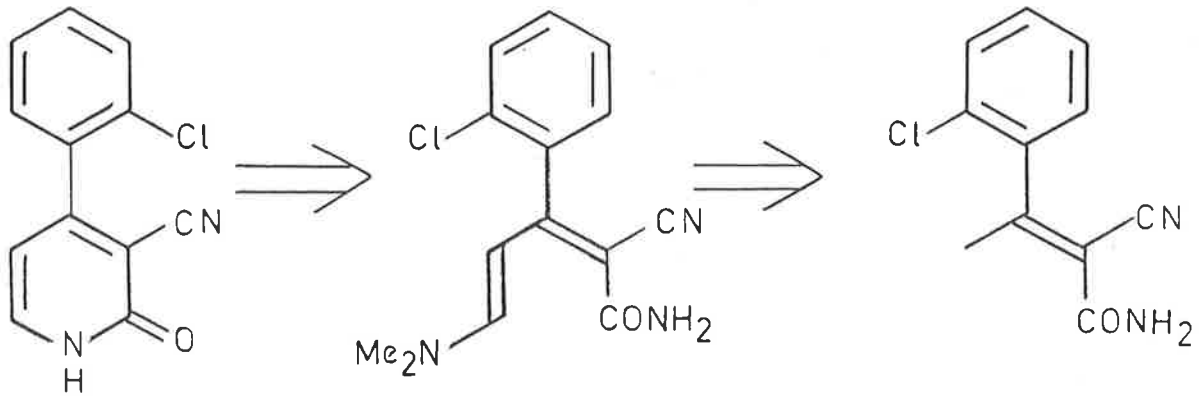
and ammonia. A Michael reaction between the lithium enolate of acetaldehyde and the $\alpha,\beta$ unsaturated ester (14) followed by the addition of ammonia and oxidation could give the 2-pyridone (17) (see scheme 2). Unfortunately the lithium enolate of acetaldehyde[24] gave only polymeric material when reacted with (14), no trace of either (18) or (19) could be detected.




(14) (18) (19) (17)

SCHEME 2

A different approach to the formation of the 2-pyridone ring was investigated. The concept involved the intramolecular cyclization of an appropriately substituted diene-amide (20), as shown in scheme 3, with a leaving group at the terminal carbon to maintain the required oxidation level of the ring. The diene (20) could be obtained from a conjugated butenamide (21).

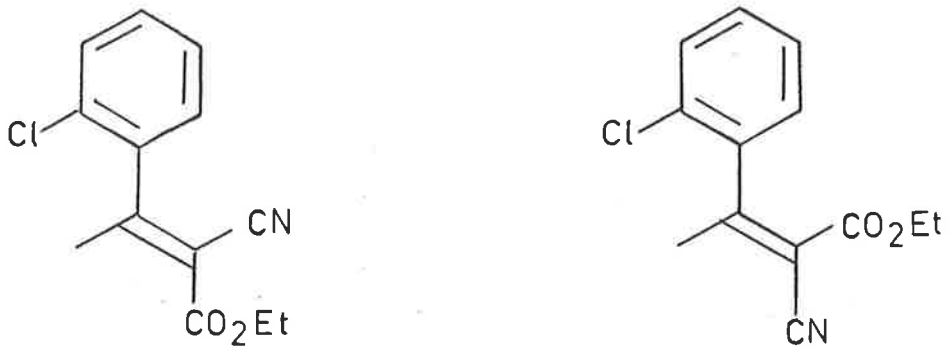



(17) (20) (21)

SCHEME 3

The condensation of 2-chloroacetophenone with cyanoacetamide did not proceed to give any of the butenamide (21); but the Knoevenagel condensation of 2-chloroacetophenone with ethyl cyanoacetate in benzene with ammonium acetate catalyst[25] gave the α,β unsaturated ester (22), as a mixture of E and Z double bond isomers, in about 65% yield. The reaction was accompanied by some decomposition and was very slow. A study by Hein, Astle, and Shelton,[26] of the catalytic effect of a range of amine/acid catalysts on the Knoevenagel condensation of acetophenones with ethyl cyanoacetate showed that primary amines, such as pentylamine, with acetic acid were among the more effective catalysts for the condensation.[27] When pentylammonium acetate was used as the catalyst the Knoevenagel condensation reaction between 2-chloroacetophenone and ethyl cyanoacetate was complete after 24h and the

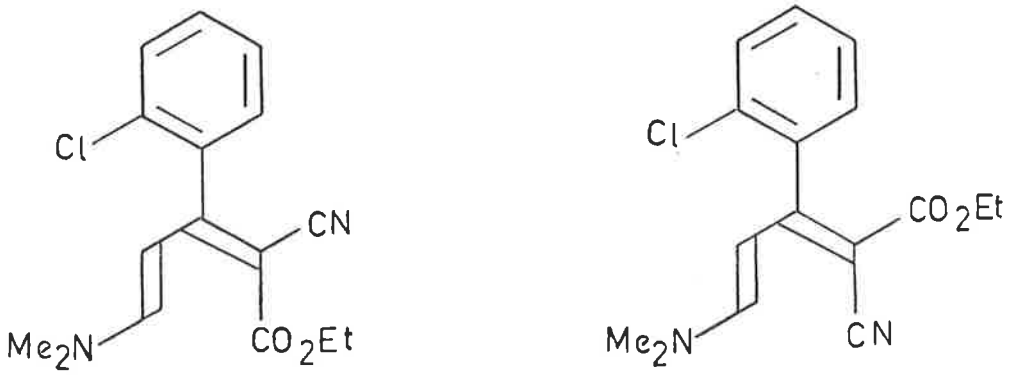
α,β unsaturated ester (22) was isolated in 84% yield. The two double bond isomers of (22) were obtained as a 1:1 mixture but separation of the isomers was not necessary.




(22)

To form the 2-pyridone ring what was required was the addition of a one carbon unit so functionalized to allow subsequent ring closure by the ester or nitrile groups and at the formic acid oxidation level. Formamide acetals are powerful formylating agents, able to add a one carbon unit, in the form of a aminomethylene group, to an activated methyl or methylene group.[28,29] Addition of N,N-dimethylformamide dimethyl acetal to the α,β unsaturated ester (22) gave the diene-ester (23) in quantitative yield. The newly formed double bond had E stereochemistry so (23) was obtained as a mixture of E,E and Z,E isomers.

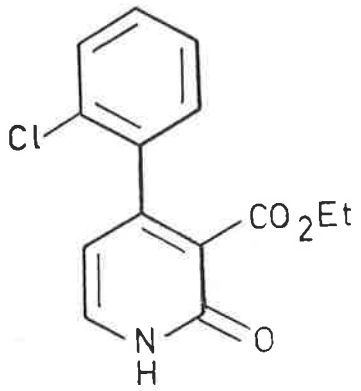
The initial plan was to convert the ester to the amide,[29] but the amide could not be formed readily. The apparent inertness of the




(23)

ester (23) to nucleophilic substitution could be due to the extensive donor-acceptor conjugation inherent in the system and the high electron density near the ester. The ester of (23) could not be converted to an amide, but the cyano group could be converted to an amide under acidic conditions. When the ester (23) was heated with 80% acetic acid the ester (24) was formed in good yield. This method of forming 2-pyridones has been reported in a few isolated cases.[30-33]

The conditions used to effect cyclization were considerably milder than are usually required to hydrolyse a nitrile to an amide, hence it may be presumed that intramolecular attack of the nitrile by the enamine facilitated the hydrolysis. Evidence for this mechanism was provided by the observation that the malononitrile derivatives (35) and (36) cyclized to yield cyano containing products.[33]

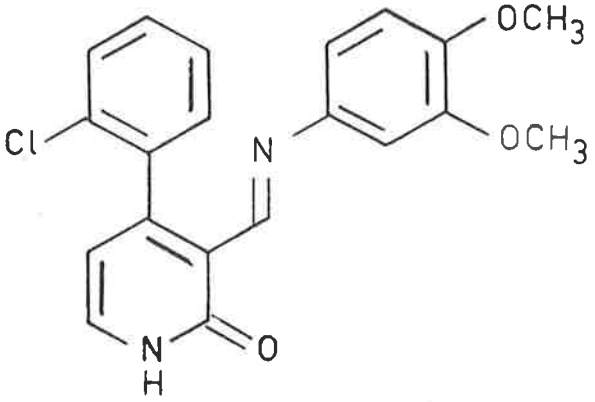



(24)

Conversion of the ester (24) into perloline (1) requires essentially three operations; the adjustment of the oxidation level of the carbon attached to C-3 of the 2-pyridone ring, and formation of the two N-aryl bonds. Several combinations of these three operations were considered as feasible approaches.

The original concept was to set up the benzyne cyclization using the imine (6; X=H) which on cyclization would give perloline (1) directly. The imine (25) should be readily obtained from the aldehyde (26). There are many methods documented for the selective formation of aldehydes from esters, directly[34,35] or via the corresponding primary alcohol.[34,35] Accordingly the adjustment of the oxidation level was tackled first.

The standard conditions used to reduce an ester an aldehyde using diisobutylaluminium hydride[36] failed to effect any change to the



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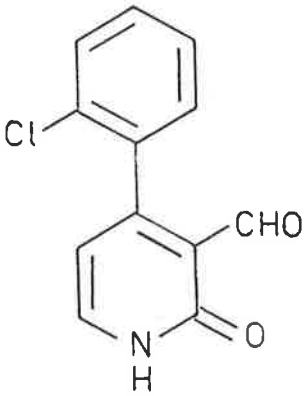
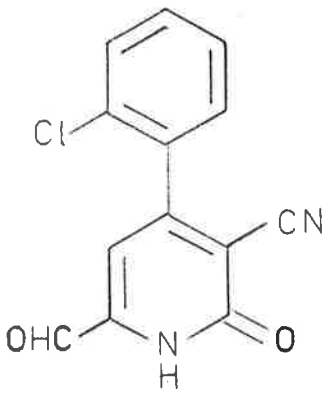


(26)

ester (24). The ester (15) was selectively reduced to the corresponding aldehyde (27) by diisobutylaluminium hydride at -60° in good yield as determined by $^{1}H$ n.m.r. spectroscopy. At -30° the ester (15) was reduced using an excess of reducing agent to a mixture of the aldehyde (27) and the alcohol (28).



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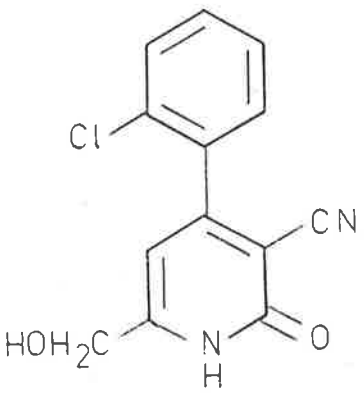
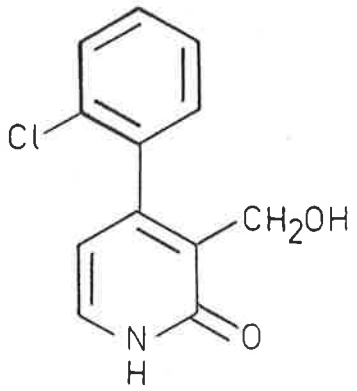


(28)

The ester (24) remained inert to excess diisobutylaluminium hydride in tetrahydrofuran at -30°. Diisobutylaluminium hydride is reported to have greater reducing strength in toluene than in tetrahydrofuran,[36] but none of the conditions examined, from stirring at 25° for 6h to refluxing toluene, produced any trace of aldehyde (26), only some over reduction to the primary alcohol (29) was observed.




(29)

The inability of diisobutylaluminium hydride to effect the required reduction could be a result of steric congestion and chelation of the metal to the 2-pyridone. A complex metal hydride with only two hydride ions available per complex, such as sodium bis(methoxyethoxy)aluminium hydride (Red Al), could react with the acidic hydrogen to form a complex with the 2-pyridone moiety through oxygen and then have only one hydride available to deliver to the ester carbon. The reduction was attempted with one equivalent of Red Al, but the product mixture obtained was a 1:1 mixture of the ester (24)

and the alcohol (29).

Since the selective reduction of the ester (24) to the aldehyde (26) was unsuccessful attention was directed towards obtaining the aldehyde through oxidation of the primary alcohol (29). Reduction of the ester was first attempted using lithium aluminium hydride in ether; the ester (24) proved to be insoluble in ether so it was silylated using bis(trimethylsilyl)acetamide.[37] Subsequent work showed that silylation was not necessary and reduction of the ester (24) proceeded to give the alcohol (29) in 94% yield using sodium bis(methoxyethoxy)aluminium hydride.

The $^{1}H$ n.m.r. spectrum of the alcohol (29) exhibited an AB quartet pattern for the methylene protons. The contributing factors are firstly the two aromatic rings adopted a preferred conformation with each ring in a different plane,[38] and secondly the strong intramolecular hydrogen bonding between the hydroxyl group and the oxygen of the 2-pyridone, as shown in fig. 1.

The oxidation of the alcohol (29) was attempted using pyridinium chlorochromate,[39] and manganese dioxide,[40] the pyridone appeared to chelate with the transition metal,[15] but no aldehyde (26) was obtained. Accordingly an oxidizing agent was sought which did not utilize a transition metal, such as an activated dimethylsulfoxide reagent.[34] Several methods for preparing activated dimethylsulfoxide reagents were tried,[41,42] but only that using oxalylchloride at -60° gave any of the desired aldehyde, and even then only 5% was observed.

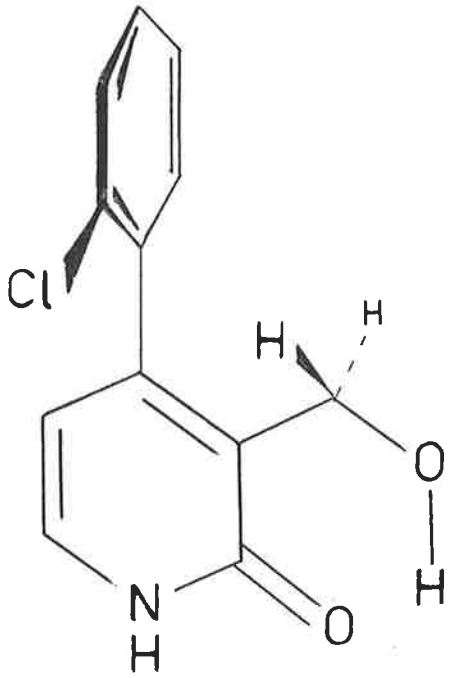


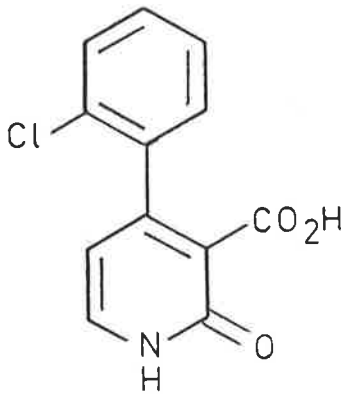

FIGURE 1

Owing to the difficulties encountered in forming the aldehyde (26) an alternate route was sought, one in which the adjustment of the oxidation level of the ester carbon was carried out later. Two options available for the next step of the synthesis were formation of the *N*-aryl bond or the amide bond.

There have been some reports of the direct conversion of esters to amides;[34] notably the use of 2-hydroxypyridine to catalyse the formation of amides from amines and esters[43] which introduced the possibility of internal catalysis. In no case was any amide formed, even when the amide anion was formed.[44]

The carboxylic acid (30) was obtained by hydrolysis of the ester (24) in 90% yield. Several attempts to form the amide (31) using

ethyl polyphosphate (PPE) were tried.[45] Eventually, heating at 150° for 24h did produce some of the required amide (31), but its formation was accompanied by large amounts of dark intractable material.



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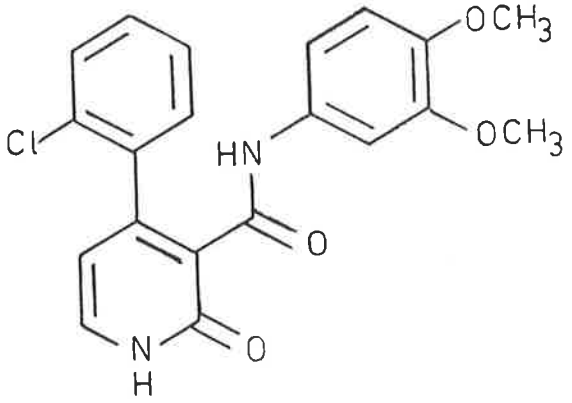


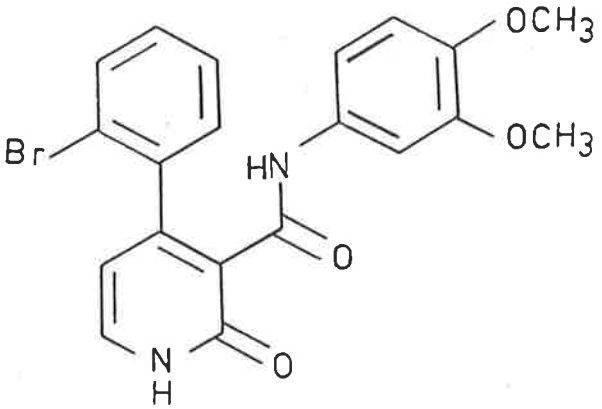
(31)

The amide was formed from 3,4-dimethoxyaniline (7) and the acyl chloride, which was formed from the acid (30) and either thionyl chloride[46] or oxalyl chloride[47] - the yields of amide (31) were 44% and 73% respectively. Dicyclohexylcarbodiimide proved to be the best and easiest reagent for coupling the acid (30) with 3,4-dimethoxyaniline (7), the amide (31) being readily isolated in 83% yield.[48,49]

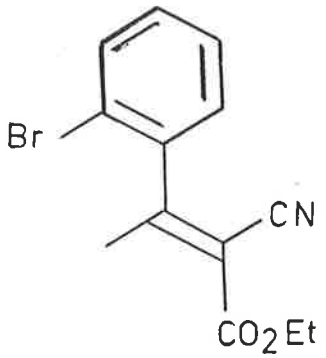
The synthesis of the corresponding bromo analogues leading to the amide (32) was attempted using the methods described to form the amide (31), as it was considered that the proposed benzyne cyclization would proceed more readily with bromine as the leaving group.[50]

The reaction of 2-bromoacetophenone with ethyl cyanoacetate using

pentylammonium acetate catalyst produced only a trace of the required product (33) after one day and there was also some tar formed; the reaction appeared to be considerably slower than that of the corresponding chloro compound. The decrease in reactivity presumably was due to the greater steric bulk of the bromine compared with the chlorine.

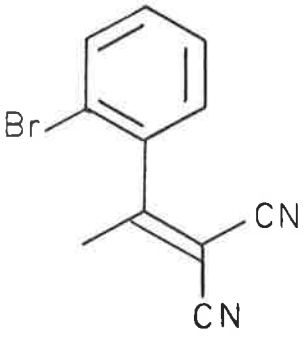



(32)

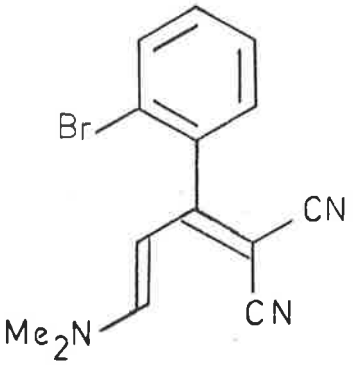



(33)

Hein, Aston, and Shelton[26] showed that malononitrile was more reactive than ethyl cyanoacetate for condensation reactions with various acetophenones, particularly with the more hindered *ortho* substituted acetophenones. This was confirmed when the malononitrile derivative (34) was obtained, after purification, in 87% yield. The dimethylaminomethylene group was added to (34) as before by reaction with dimethylformamide dimethyl acetal, the reaction proceeding rapidly to give (35) in 95% yield.

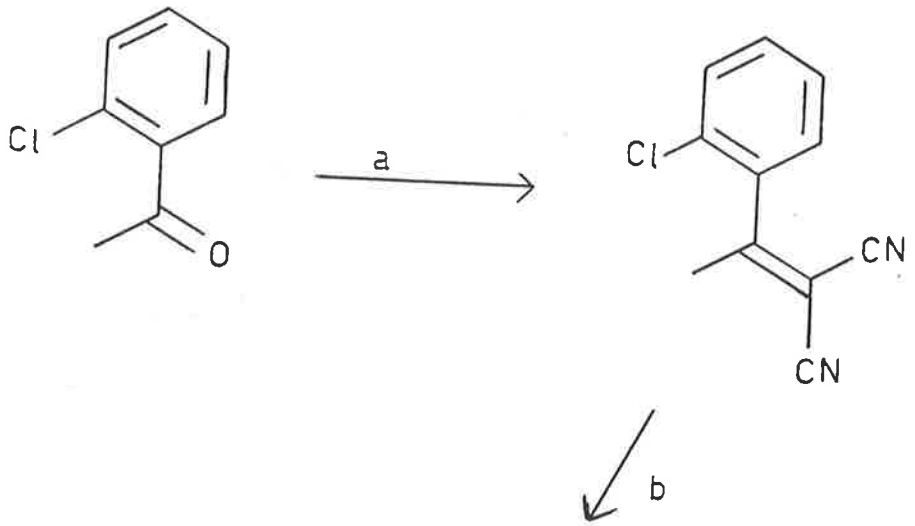



(34)




(35)

The malononitrile derivative (35) was heated in 80% acetic acid - conditions which cyclized the cyano ester (23) to (24) - but the cyclization was slow and remained incomplete after four hours. The chloro substituted malononitrile derivative (36), prepared in a similar manner to (34) (see scheme 4), was slow to cyclize with 80% acetic acid so stronger acid was used. Acetic acid with concentrated hydrochloric acid cyclized the chlorophenylmanononitrile derivative (36) to the nitrile (17) in 80% yield. Identical conditions cyclized the bromophenylmalononitrile derivative (35) to a mixture of the nitrile (37) (43%) and the chloropyridinenitrile (38) (24%).

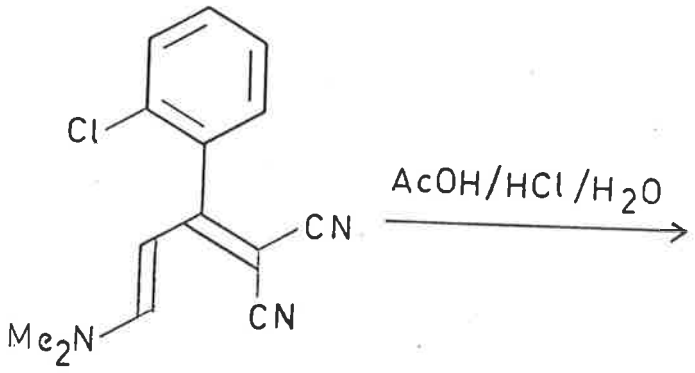



(36)

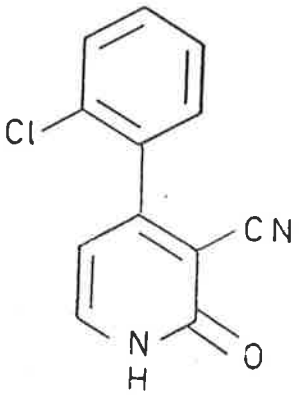
a $CH_2(CN)_2$, $nC_5H_{11}NH_2$, AcOH, PhH

b $(CH_3O)_2CH\ N(CH_3)_2$

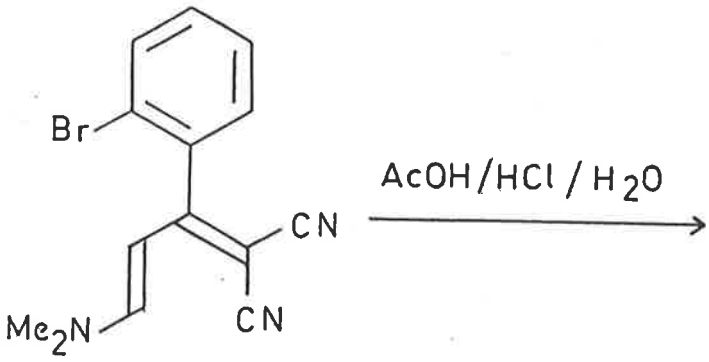
SCHEME 4


Cl
CN
CN
$Me_2N$
AcOH/HCl /$H_2O$

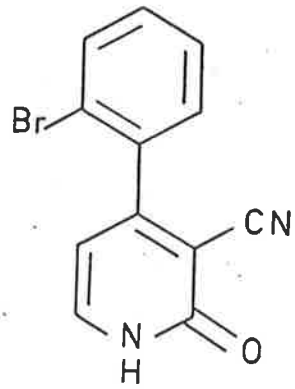
(36)


Cl
CN
N
H
O

(17)

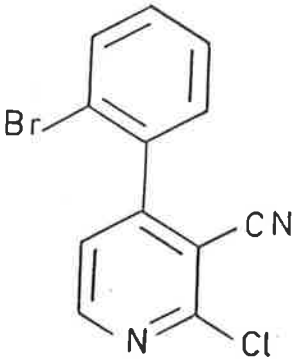

Br
CN
CN
$Me_2N$
AcOH/HCl / $H_2O$

(35)


Br
CN
N
H
O

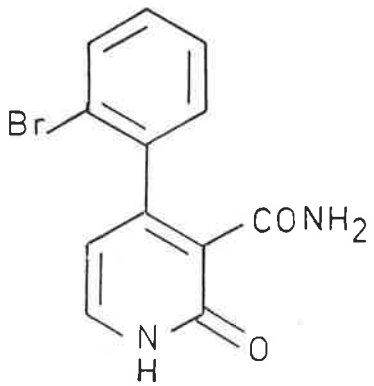
(37)

+


Br
CN
N
Cl

(38)

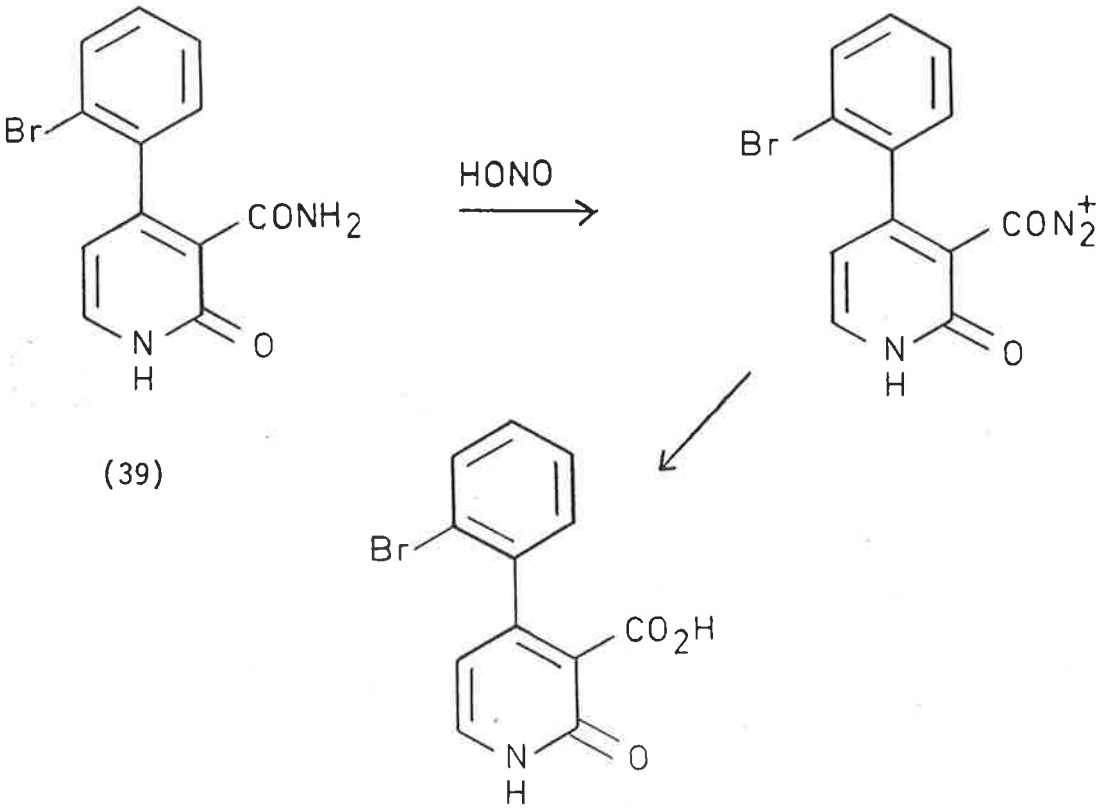
The chloropyridine (38) was formed as a result of chloride ion addition to the nitrile followed by ring closure. This reaction is similar to the formation of a 2-bromopyridine by Bryson.[31] In order to circumvent this problem a non-nucleophilic acid was used. A mixture of acetic acid, sulfuric acid, and water (5:1:4) did cyclize the malononitrile derivative (35); but gave a mixture of the nitrile (37) and the amide (39). Acetic acid, sulfuric acid, and water (10:2:3) cyclized (35) to the nitrile (37) cleanly in 87% yield.




(39)

The usual methods for the hydrolysis of a nitrile to an acid are alkaline conditions;[51] but in the present work the nitriles (17) and (37) proved to be inert to alkaline hydrolysis. Alkaline hydrogen peroxide hydrolysis conditions[52] produced only a trace of the amide (39). The inertness of the nitrile (37) to alkaline hydrolysis was a result of the close proximity of the pyridonate anion which electrostatically hindered the approach of a nucleophile to the nitrile.

The amide was readily formed under strongly acidic conditions; the nitrile (37) was hydrolysed by 70% sulfuric acid to the amide (39) in 93% yield.[53] The amide (39) was also inert to alkaline hydrolysis conditions, but nitrous acid did hydrolyse the amide (39) to the carboxylic acid (40) in 78% yield.[54,55] The reaction proceeds by the pathway shown in scheme 5.[55]



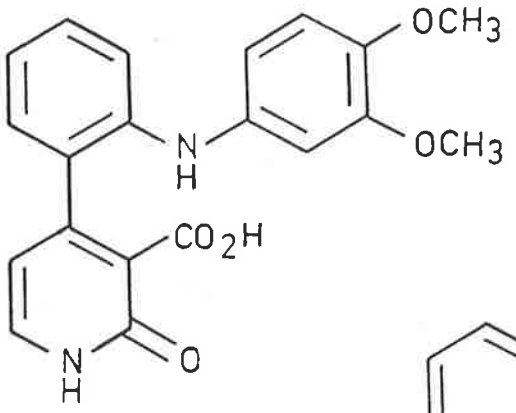

SCHEME 5

The hydrolysis steps (35) → (37) → (39) → (40) each required acidic conditions so attempts were made to combine several steps. Accordingly the nitrile (37) was readily hydrolysed to the carboxylic acid (40) in 76% yield after sequential reaction with 75% sulfuric acid and then sodium nitrite addition. The malononitrile derivative (35) was cyclized and hydrolysed to the amide (39) in 92% yield by 75% sulfuric acid, and all three steps were done in "one pot" in 91% overall yield.

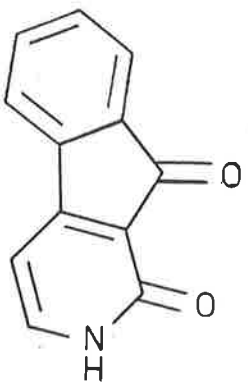
The formation of the amide (32) was achieved, using the same method used to prepare the chloro analogue (31), in 87% yield. The reaction took much longer to complete and required excess dicyclohexylcarbodiimide, possibly because of the greater steric hindrance of the bromine.

The alternate route, with initial formation of the *N*-aryl bond using a copper promoted coupling was tried, but the acids (30) or (40) did not couple with ~~veratrylamine~~ 3,4 dimethoxyaniline (7) under standard Jourdan, Ullmann reaction conditions,[56-58] giving instead a complex mixture of products, none of which corresponded with (41), isolated elsewhere.[59]

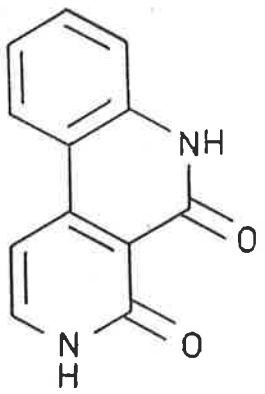
The nitrile (37) on treatment with cooper bronze did not produce any cyclized products such as (42)[9,11,60] or (43).




(41)



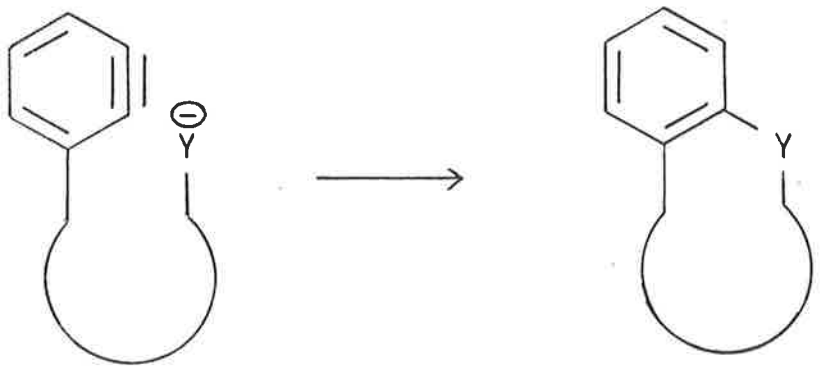

(42)




(43)

## 1.2 INTRODUCTION

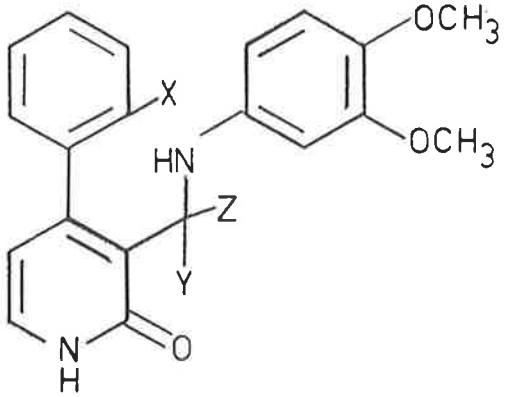
The original concept was to use an intramolecular nucleophilic attack onto a benzyne intermediate to effect the final cyclization. The intramolecular reaction between a good nucleophile, such as an anion centred on carbon, nitrogen, oxygen or sulfur, and an aryne intermediate (44) to form a fused heterocyclic system (45) has been shown to offer a useful entry into several heterocyclic systems: indoles,[61,62] benzoxazoles,[61,62,63] benzothiozoles,[61] phenothiazine[61] dihydroindoles,[64,65] tetrahydroquinolines,[64,66] dihydroisoquinolines,[67] and more recently some complex ring systems such as the aporphine alkaloid skeleton.[68,69]




(44) (45)

A common method of forming an aryne is by dehydrohalogenation of an arylhalide using a strong base, commonly potassium amide or a lithium alkylamide.[50] In the present work the nucleophile would be the nitrogen anion of an amine (6, Y =Z = H) or an amide (6, Y = Z = O),

and the aryne would be formed by dehydrohalogenation of the halide

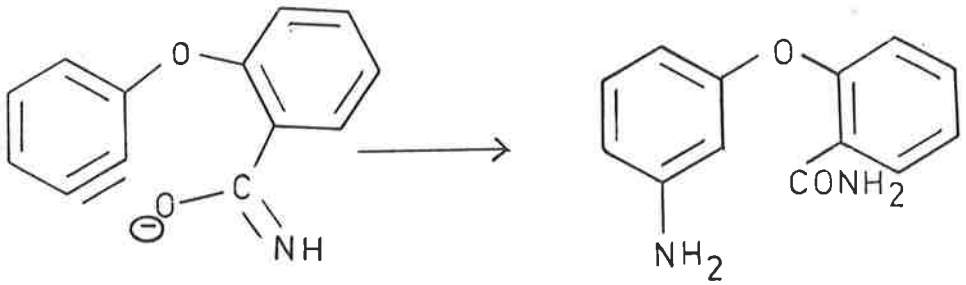



(6)

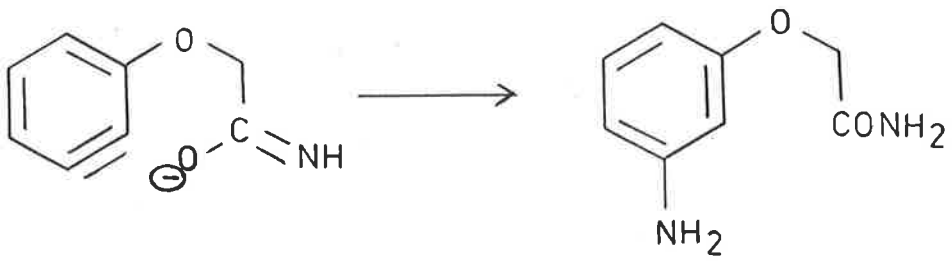
(6, X = Cl or X = Br). Some general observations of early work were that 5- and 6- membered rings were formed readily;[50] that oxygen was a poor nucleophile unless it was derived from a carboxamide anion;[61] and that the aryne derived from the corresponding arylbromide often gave higher yields than from the arylchloride.[50]

Benzyne is a soft acid and therefore hard nucleophiles do not react as easily as softer nucleophiles.[50] When oxygen is part of an ambident anion, which makes it a softer nucleophile, the intramolecular addition of oxygen can compete with intermolecular nitrogen addition.[61,62] Nitrogen anions are softer than oxygen anions which is shown by the observation that non conjugated nitrogen anions react with arynes in intramolecular reactions in ammonia but the corresponding oxygen compounds give only very low yields of cyclized product.[64,70]

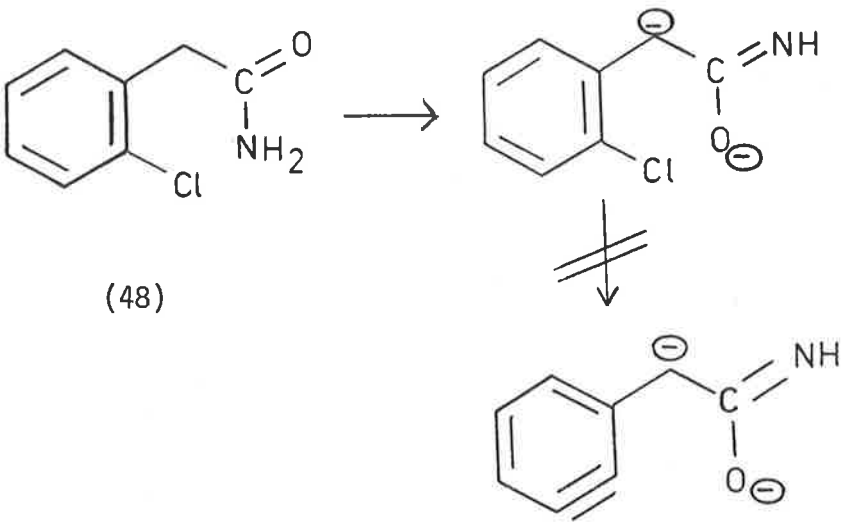
Studies of aryne cyclizations involving carboxamide anions can be classified into two groups, firstly those reactions which formed oxazoles, where only the oxygen could be the nucleophile,[61,62] or secondly the reactions where either oxygen or nitrogen could act as the nucleophile.[62] The second category is of interest for the cyclization of (31) or (32); unfortunately none of the attempts described in the literature produced any cyclized products.[7,61,62] In each case one or more factors operated to inhibit the cyclization reaction: the arynes (46)[62] and (47)[62] each had an oxygen adjacent to the aryne which has been shown to have a strong directing effect on nucleophilic addition to arynes,[71] and the aryne from (48) was never formed.[61,17]




(46)




(47)

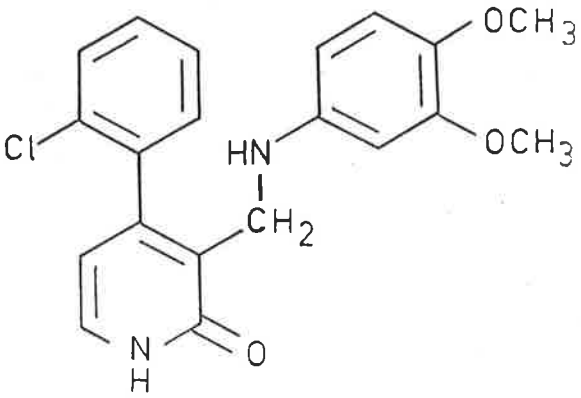


(48)

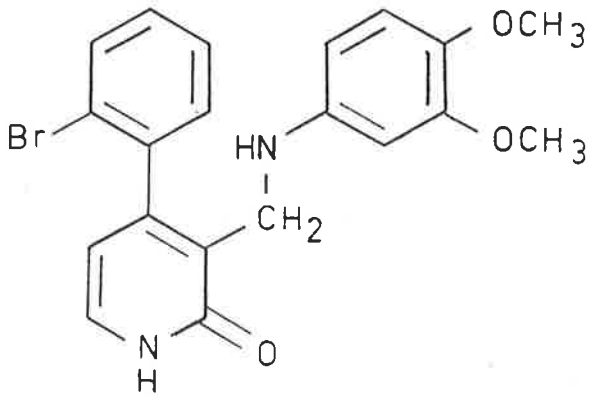
The direct competition between an oxygen anion and a nitrogen anion for an aryne intramolecular reaction has not been studied, although two reports do propose such a direct competition as possible alternate mechanism.[5,61,69] Direct competition between oxygen and nitrogen for addition to benzyne in an intermolecular reaction has been proposed, in that case the O-substituted product was isolated.[72]

## RESULTS AND DISCUSSION

Since there was more literature precedence for aryne cyclizations involving amide anion than carboxamide anion,[50] and also the product of an aryne cyclization of the amines (49) or (50) would be deoxyperloline which has been converted to perloline,[5] several attempts were made to obtain the amides (49) and (50). The amide (31) was inert to lithium aluminium hydride or Red Al. The conditions described by Brown *et al*[73,74] using borane reagents also failed to yield any of the amines (49) or (50).




(49)

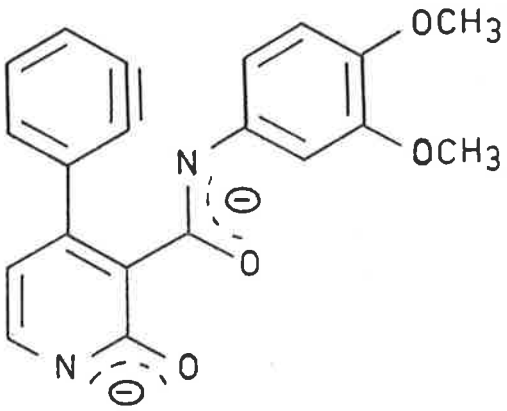



(50)

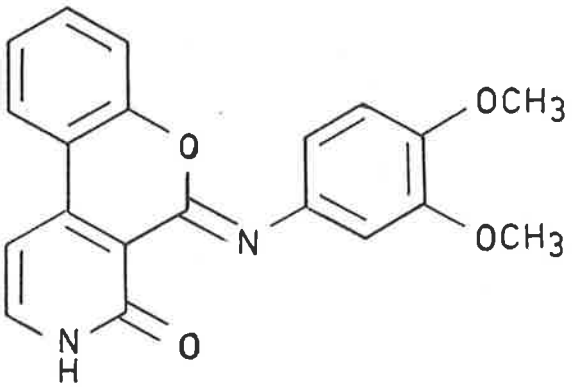
The reaction of the chloro amide (31) with potassium amide gave starting amide (31) accompanied by numerous other compounds; no dehydroperloline (3) was observed. The reaction of (31) with lithium diisopropylamide required refluxing for several days before most of the starting amide (31) had reacted; the crude material did show the presence of some dehydroperloline (3) by mass spectrometry, but none

was isolated. The reaction was attempted with n-butyllithium but no dehydroperloline was formed and butylated compounds were observed. Since arylbromides often form arynes more readily than the corresponding arylchlorides[50] the bromosubstituted amide (32) was treated with diisopropylamide. On work-up the basic fraction contained veratrylamine (7) (15%) and the neutral extract contained dehydroperloline (3) (18%).

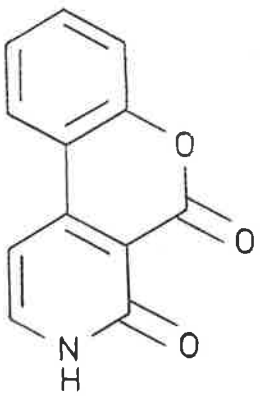
The veratrylamine (7) must have been cleaved from either the starting amide (32) or an undesired product. If some water was present in the reaction then the conditions would be very similar to those reported by Gassman, Hodgson, and Balchunis,[75] for the hydrolysis of tertiary amides, but primary and secondary amides are reported to be hydrolysed in only very low conversions and thus (32) should be largely unaffected by such hydrolysis. The dianion could cyclize either through nitrogen or oxygen; cyclization through oxygen would lead to the imino ether (52) which on work-up could hydrolyse to liberate veratrylamine (7) and the benzopyranopyridone (53) or the carboxylic acid (54) or the amide (55). Only veratrylamine (7) was isolated but some of the other possible products could have been too polar to be isolated by the chromatographic methods used. A trace of the reduced amide (56) was observed by mass spectrometry. The reduction of arynes by secondary amines has been reported as a common side reaction, as has the reduction of aryl halides.[50,76]



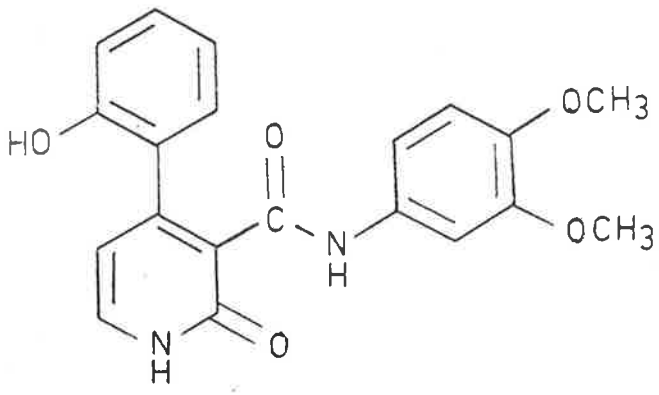

(51)



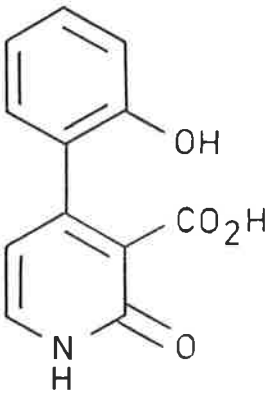

(52)




(53)




(55)

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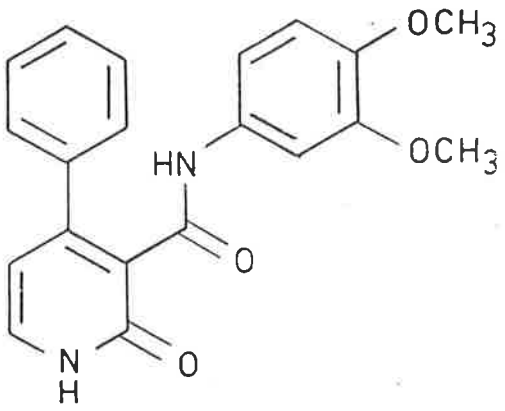
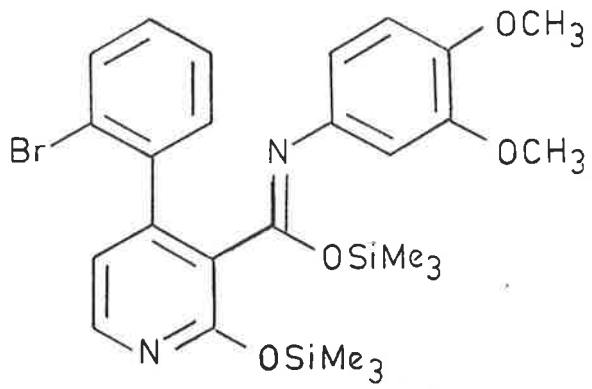



(56)

To overcome the problem of reduction the base was changed to lithium hexamethyldisilazide.[77,78] The cyclization of the bromo amide (32) using lithium hexamethyldisilazide in tetrahydrofuran was very slow and required four days. Simple work-up gave dehydroperloline in 86% yield. No evidence of O-cyclization was found (absence of veratrylamine (7)) and only a trace of the starting amide (32) remained. Hexamethyldisilazane is a silylating agent [79-82] capable of silylating pyridones[81] and amides.[82] Accordingly the benzyne could be formed from the disilylated amide (57) which could be cyclized only through nitrogen. The amide (32) was treated with hexamethyldisilazane and was monosilylated. The position of silylation was not determined but presumably the silicon was attached to the pyridone oxygen.[81] The more forcing conditions of the cyclization reaction may have been sufficient to form a disilylated species but that was not confirmed.

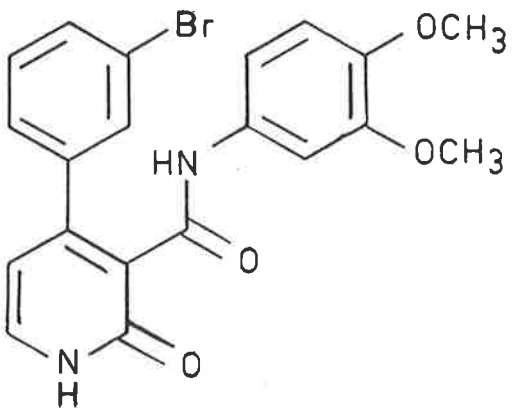



(57)

The chloro amide (31) also cyclized on treatment with lithium hexamethyldisilazide and afforded dehydroperloline (3) in 50% yield.

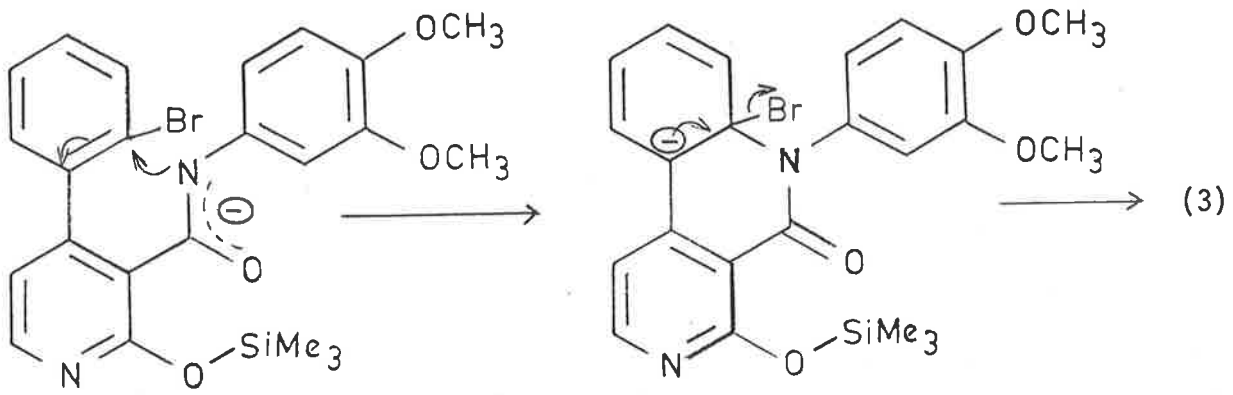
To confirm if a benzyne intermediate was involved in the cyclization to produce dehydroperloline (3) the isomeric bromo amide (58)[12,83] was reacted under identical conditions as (32). After careful chromatography no dehydroperloline (3)could be observed and the intermediacy of a benzyne must remain in doubt.

An alternate mechanism could be direct nucleophilic addition followed by elimination,[84,85] which would explain why only the




(58)

2-haloamides (31) and (32) could be cyclized but not (58) (see fig. 2).




(3)

FIGURE 2

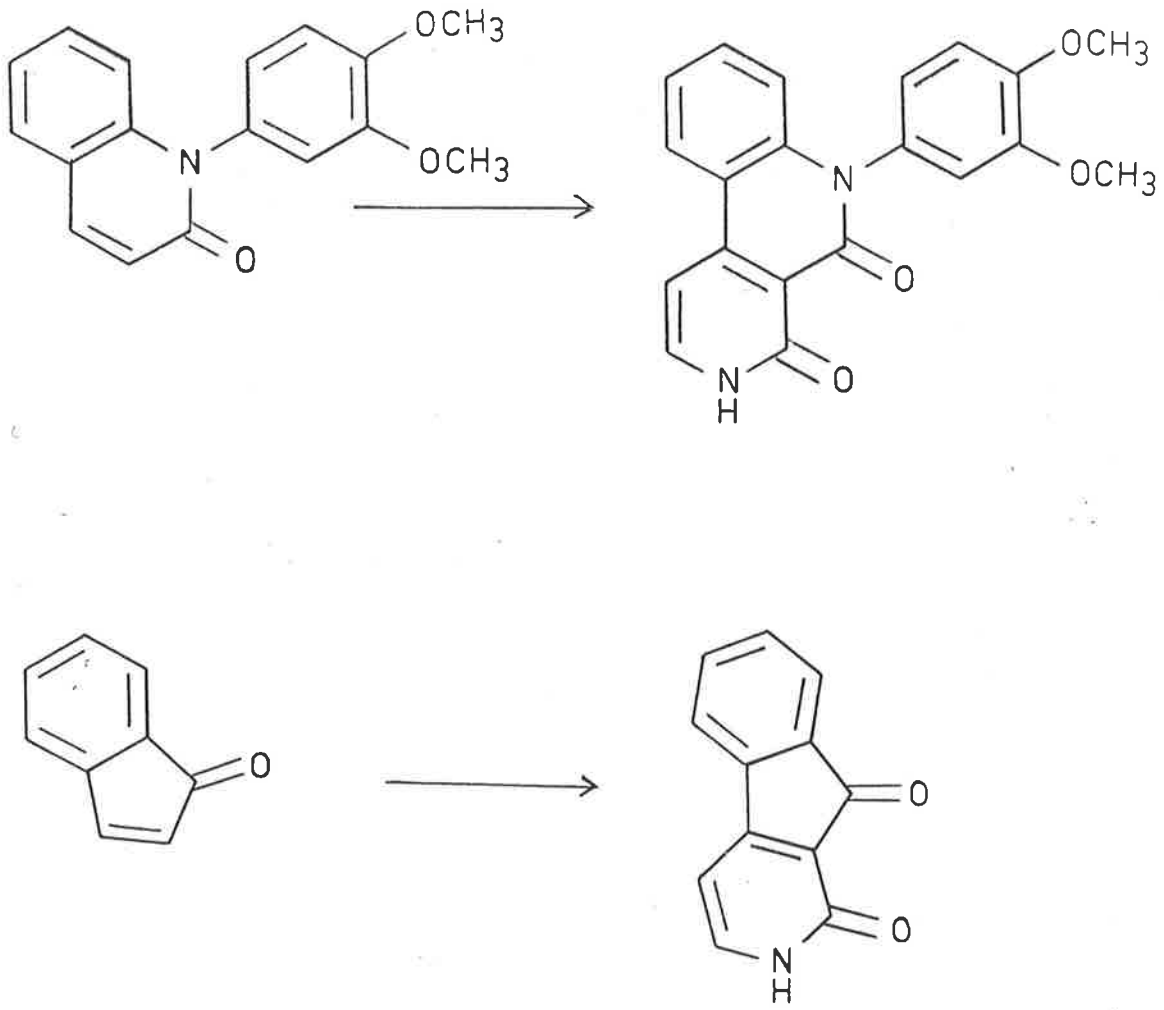
The Ullmann reaction has long been known to couple aromatic halides with aromatic amines,[56,86,87] so Ullmann reaction conditions were investigated as a means of cyclizing the amides (31) and (32). There have been very few examples of an Ullmann reaction succeeding with an N-aryl amide,[88] and Ullmann reactions often proceed in poor yield and form considerable undesired material, but in the present work the reaction would be intramolecular which may minimise the amount of by-products. The amide (32) when treated under standard Ullmann conditions[56] afforded dehydroperloline (3) in 73% yield. The chloro amide (31) was inert under these conditions.

The reduction of dehydroperloline (3) has not been previously reported, although perloline (1) has been reduced.[5] It was considered that similar conditions would reduce dehydroperloline (3) either to perloline (1) or to deoxyperloline (4). Dehydroperloline (3) when briefly reacted with sodium bis(methoxyethoxy)aluminium hydride was reduced selectively to perloline (1) in 70% yield which was identical with an authentic sample extracted from L. perenne.

# CHAPTER 2

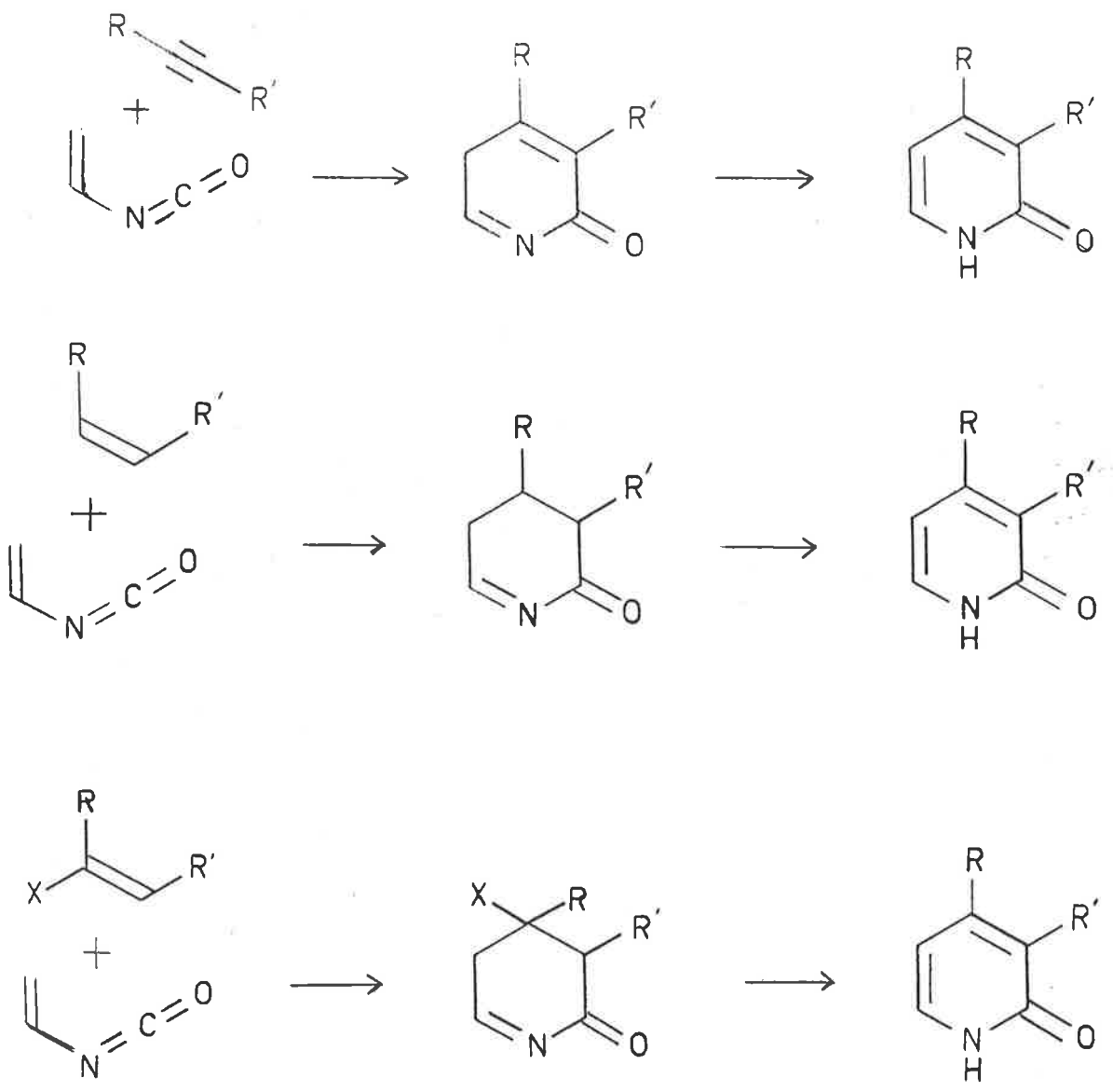
## INTRODUCTION

An alternate approach to the synthesis of perloline (1) which was considered involved the annelation of a 2-pyridone ring onto a performed indenone or quinoline (see scheme 6). The required ring




SCHEME 6

formation could be considered as a [4 + 2] cycloaddition of an alkyne or olefin with vinylisocyanate or its synthetic equivalent (see scheme 7). An olefin activated with an appropriate leaving group could form a ring system at the required oxidation level.



SCHEME 7

Isocyanates adjacent to a carbonyl have been shown to behave as a diene in [4 + 2] cycloaddition reactions.[89] Phenylisocyanate has been used as a diene in [4 + 2] cycloaddition reactions with ynamines to produce 2-quinolines.[89-93] Similarly styrylisocyanates have been reacted with ynamines to produce 4-amino-2-pyridinones.[94] Phenylisocyanate has been reported to undergo cyclization with benzyne to form a phenanthridone ring system.[72] An isocyanate adjacent to an olefin has been reacted with an activated olefin (an enamine) to form a 2-pyridinone ring,[95] but no other cases have been reported.

The reactions between an isocyanate and an enamine have been studied by several groups[96-98] which have shown that the reaction proceeds by initial [2 + 2] cycloaddition followed by ring opening if the enamine possesses a β hydrogen.[89,98] The outcome of the reaction between phenylisocyanate and an ynamine has been shown to be solvent dependent; in toluene initial [2 + 2] cycloaddition followed by rearrangement to a 6 membered ring predominates; in acetonitrile [4 + 2]cycloaddition predominates.[90]

## RESULTS AND DISCUSSION

The reaction between vinyl isocyanate (59) and 1-pyrrolid-1-ylcyclopentene (60) gave a mixture of the 1:1 adduct (61) and the trimer, 1,3,5-trivinylisocyanurate (62) (see table 1 and scheme 8). When the

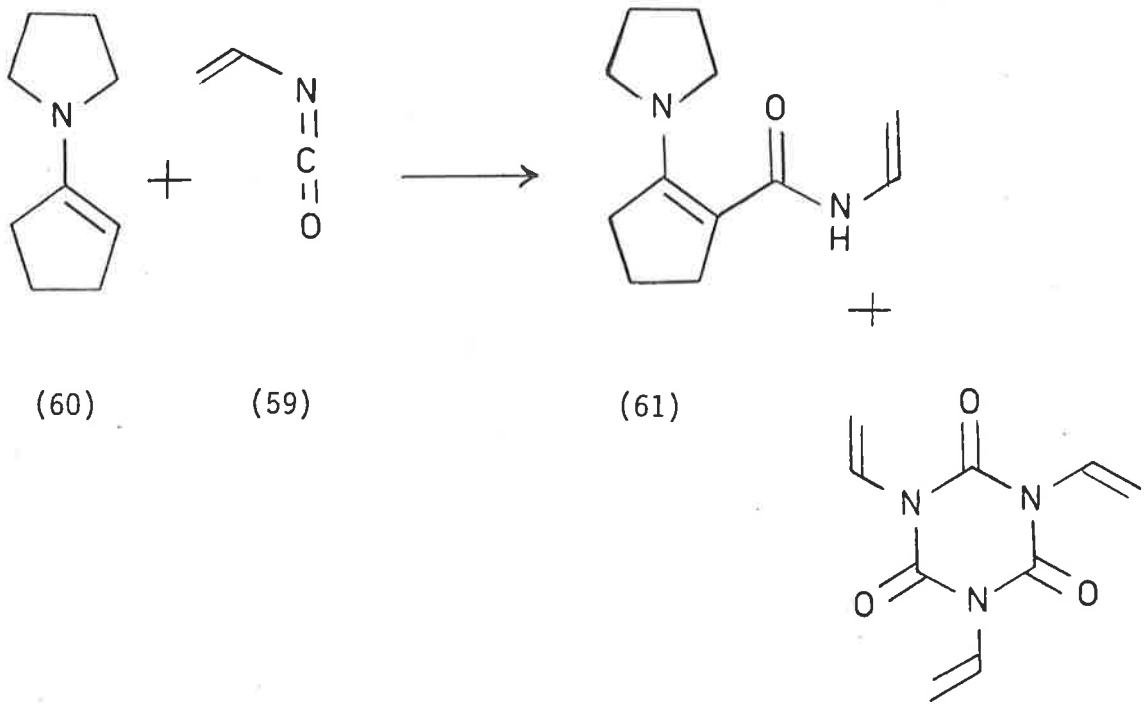
Table 1

Temperature dependence of the reaction between vinylisocyanate (59) and (60) in acetonitrile.

| Temperature | Yield (%) | |
|---|---|---|
| °C | (61) | (62) |
| -30 | 7 | 8 |
| 0 | 15 | 6 |
| 20 | 42 | 3 |
| 25 | 47 | trace[a] |
| 35 | 38 | trace[a] |

[a] although some (62) was observed by $^1$H n.m.r. spectroscopy none was isolated.

reaction was attempted at lower temperature in other solvents, -40° in tetrahydrofuran and -60° in toluene, larger amounts of the trimer (62) were formed, 10% and 19% respectively, and reduced amounts of (61) were formed, 6% and a trace respectively. Apparently the two reactions, [2 + 2] cycloaddition and trimerisation of (59) were competing and at low temperature the enamine behaved as a base only which catalysed the formation of the trimer (62)[99] At higher

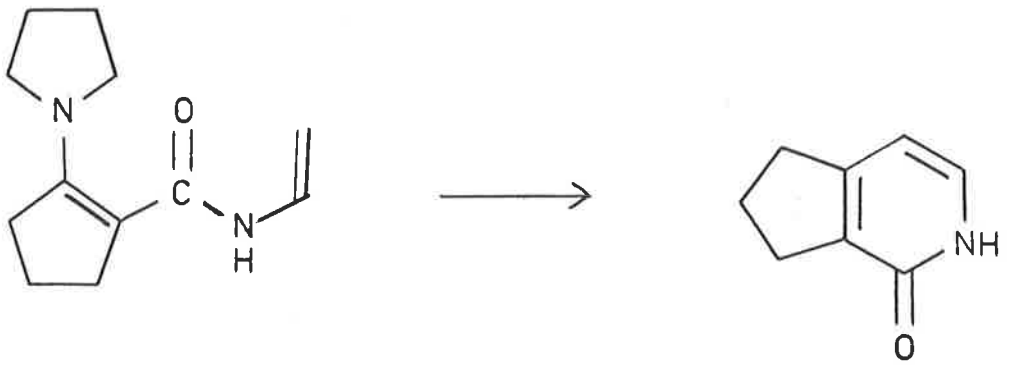


(60) (59) (61) (62)

SCHEME 8

temperature the [2 + 2] cycloaddition was more competitive and became the prediminant reaction pathway. Unfortunately, temperatures above 25° reduced the yield, due to the high volatility and low boiling point of vinylisocyanate.[100] Sealed tube reactions did not improve the yield at all because the reaction was complete before tubes could be sealed and heated.

In principle the amide (61) could be cyclized to give the required 2-pyridone annelation product (63), so a means of effecting the cyclization was sought. A tautomer of the amide would be a 1,3,5 hexatriene system which could undergo electrocyclic ring closure to give, after elimination, (63) (see fig. 3). Heating the amide (61) failed to effect any cyclization. The product from silylation of the amide (61) could be a conjugated triene system, but heating of the product failed to produce any cyclization. The anion of the amide (61)




(61) (63)

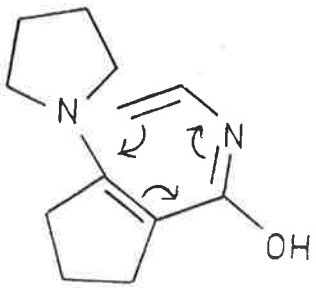



FIGURE 3

could undergo electrocyclic ring closure (see fig. 4). Alternatively the anion of (61) could undergo a nonconcerted cyclization reaction

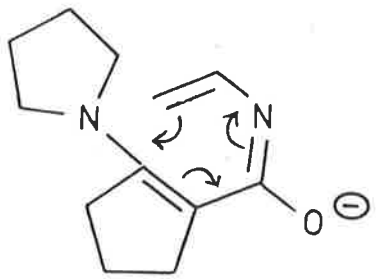
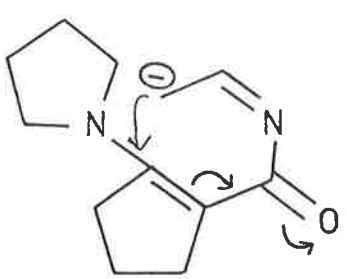


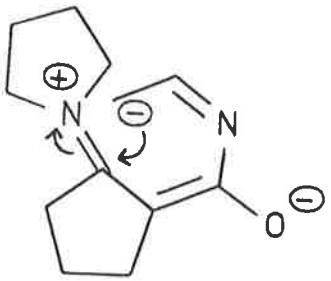

FIGURE 4

which could be described as a 6 Endo-Trigonal process or a 6-Exo-Trigonal ring closure, both of which are allowed under Baldwins "Rules for ring closure"[101] (see fig. 5). Similar reactions have been described but with more stable anions.[102-105] The anion of (61) was formed using sodium hydride, but heating of the anion in tetrahydrofuran failed to produce any cyclized product (63).

The cyclization of the adduct (61) could not be effected under any conditions, which could be a result of the low nucleophilicity of the terminal carbon. The nucleophilicity of that terminal carbon could be increased by adding an activating group to it. A carbomethoxyl group



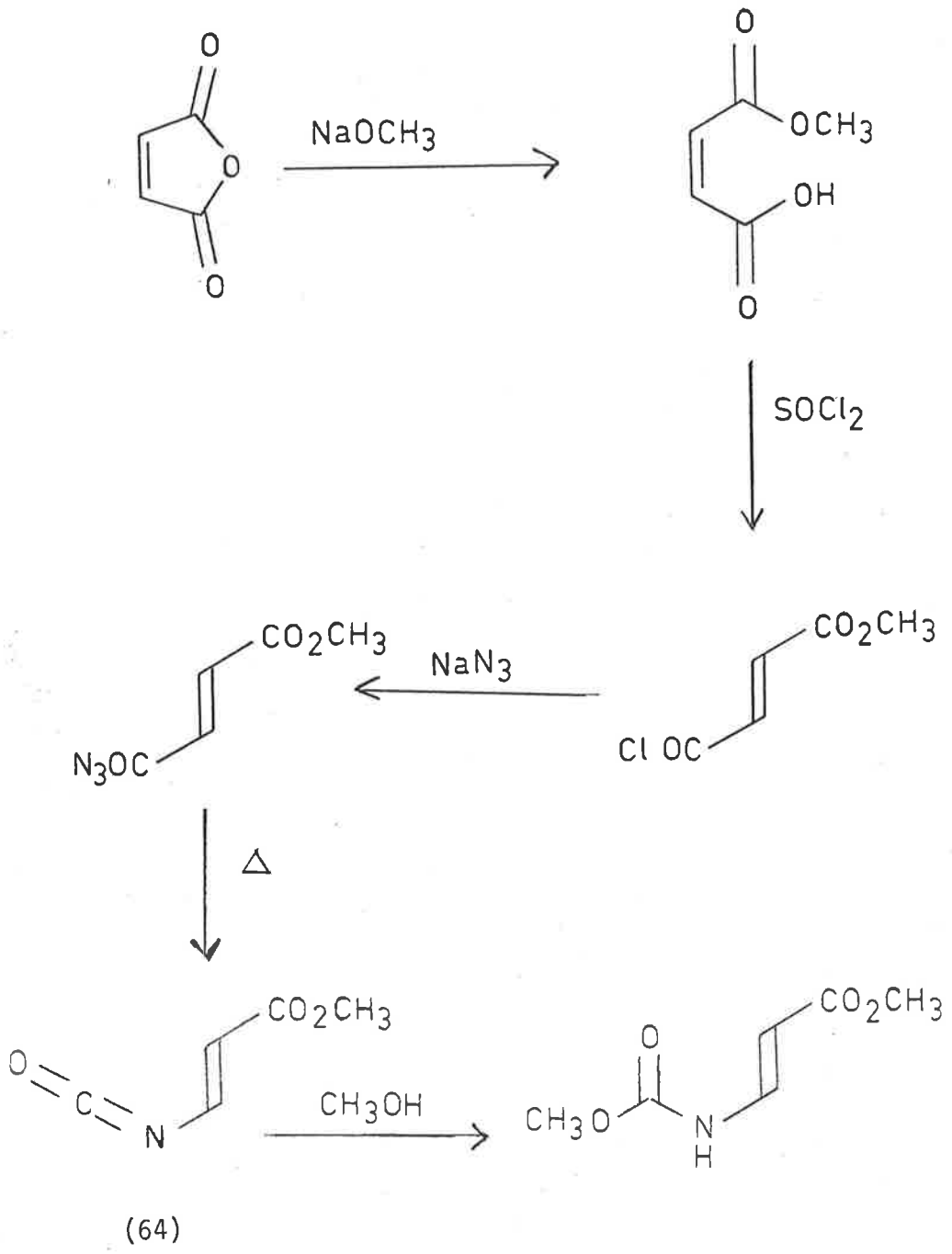
6-Endo-Trig



6-Exo-Trig

FIGURE 5

was considered, which would make the system very similar to the cyclizations described by Danishefsky,[103,105] and by Berchtole.[104] (see fig. 6) The isocyanatoester (64) was synthesised by the method


O
O
O
NaOCH3
O
OCH3
OH
O
SOCl2
CO2CH3
Cl OC
NaN3
CO2CH3
N3OC
Δ
CO2CH3
O
C
N
CH3OH
O
CH3O
N
H
CO2CH3

(64)

SCHEME 9

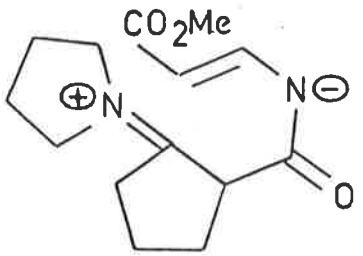
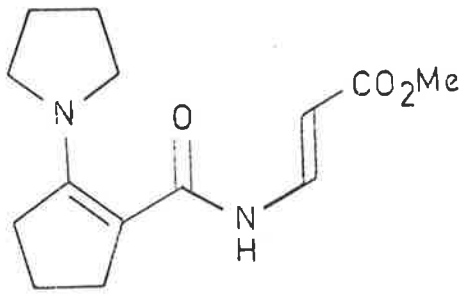



FIGURE 6

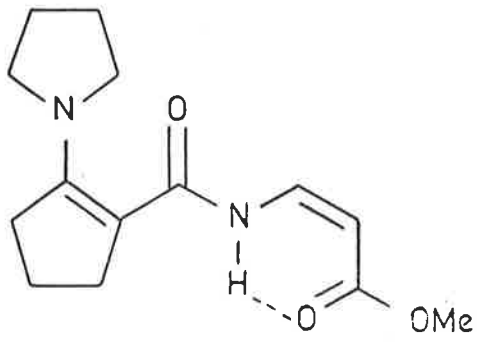
outlined in scheme 9.

The isocyanatoester (64) reacted with the enamine (60) to give the adduct (65) in 17% yield. The $^{1}H$ n.m.r. spectrum showed the




(65)

olefinic protons as an AB quartet with a coupling constant consistent with that expected of an (E) olefin. No trace of any cyclized product was evident. Attempts to cyclize (65) included heating, treatment with trifluoroacetic acid, and formation of the anion using sodium hydride followed by heating. All the above failed to yield any cyclized product; in each case the stereochemistry of the olefin was changed from (E) to (Z). The change in stereochemistry was observed by a change in the $^{1}H$ n.m.r. spectrum, the coupling constant of the olefinic protons changing from 13 Hz to 9 Hz. The formation of (Z) (66) was a




(66)

result of the intramolecular hydrogen bonding of (66) which made the (Z) isomer (66) more stable than the (E) isomer (65). The anion formed from (65) would be delocalized throughout the amide/ester system (see fig. 7), and on acidification the (Z) isomer (66) formed.

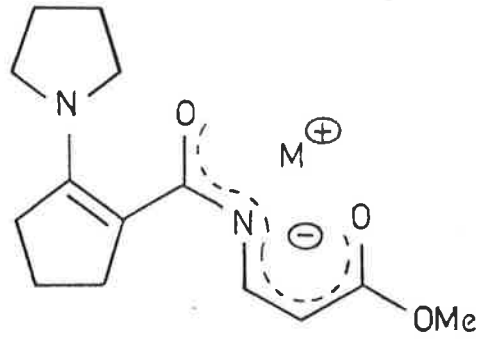
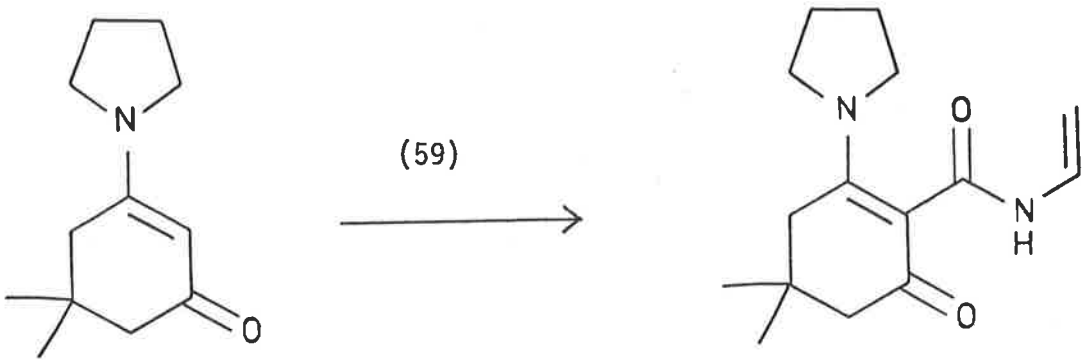



FIGURE 7

The isomerisation of the double bond of (65) meant that the electrons were delocalized, which was required for cyclization, but still no cyclization occurred and the approach was abandoned.

Quaternisation of the pyrrolidine nitrogen should aid cyclization by making the enamine more electrophilic and creating a better leaving group, but alkylation of the enamine system of (65) could not be made regiospecific and a complex mixture was obtained.[106]

The enaminoketone (67)[106] was prepared as it was hoped that the isocyanate adduct (68) would be more readily cyclized, the side




(67) (68)

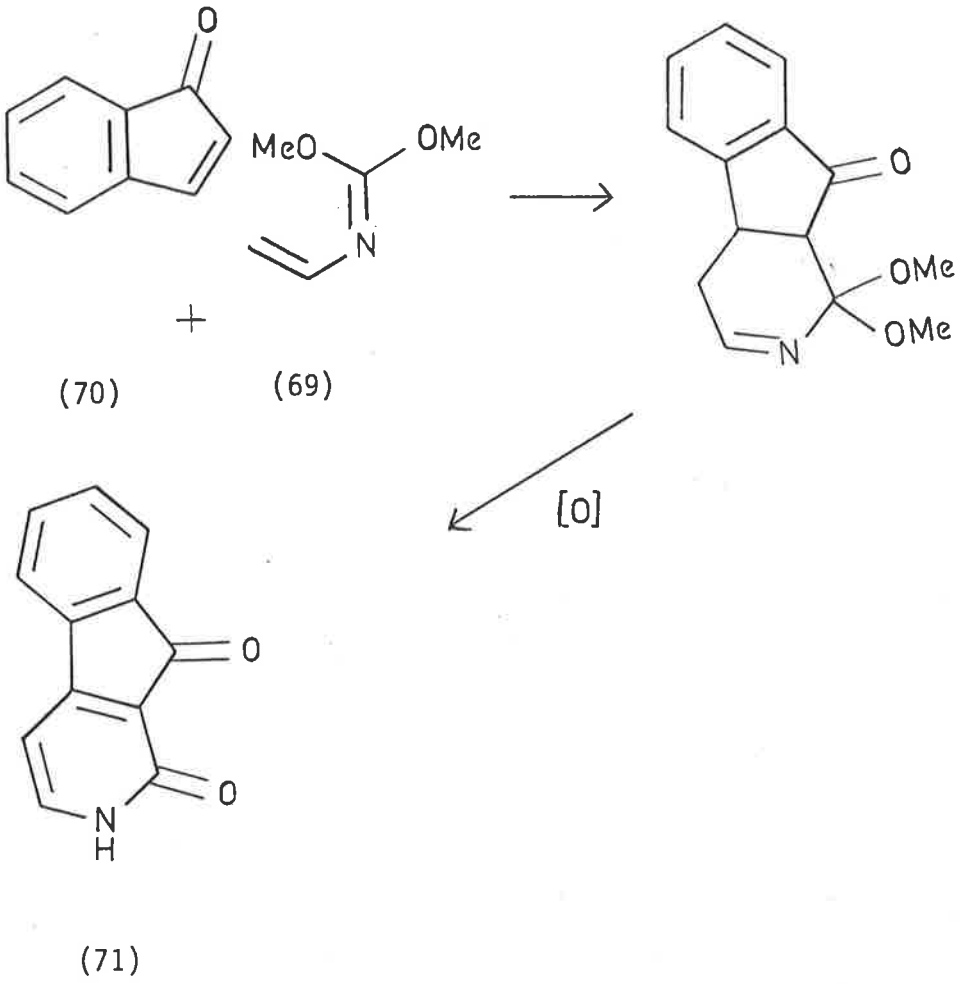
chain could add in a Michael type reaction to the conjugated ketone, or in a 1,2 addition reaction to the ketone (see fig. 8). The reaction


1,4 addition 1,2 addition

FIGURE 8

between the enaminoketone (67) and vinylisocyanate (59) produced an excellent yield of the trimer (62) and the enaminoketone (67) was recovered quantitatively. Apparently the conjugation of the enamine with the ketone reduced the reactivity of the enamine double bond towards [2 + 2] cycloaddition with the isocyanate and the basic character of the pyrrolidine moiety catalysed the trimerisation of vinyl isocyanate.[99,107] The isocyanato ester (64) also failed to react with the enamino ketone (67), even on heating. The next idea was to mask the carbonyl in (67) for the initial isocyanate addition and then reveal the carbonyl for the cyclization step. Attempts to mask the carbonyl of (67) as a thioacetal or an alcohol failed, leading only to decomposition of the enamine.

The use of 2-azabutadiene systems in [4 + 2] cycloaddition reactions, including Diels Alder reactions, has recently been reviewed.[108-110] The review[108] included the [4 + 2] cycloaddition reactions of isocyanates adjacent to a double bond; but in the present work vinylisocyanate failed to show any tendency to act as a diene.[95] Boger[108] explains that the best 2-azabutadienes for [4 + 2] cycloaddition reactions have strong electron-donating groups, this enhances the reactivity of the 2-azabutadiene system towards electron deficient dienophiles. The 2-azabutadiene (69) which could be derived from vinylisocyanate (59) could react with indenone (70)[111] to give, after oxidation the indenopyridine dione (71).[11] Indenone has been shown to

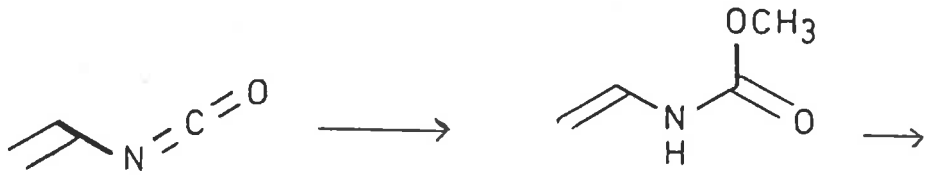



(70) (69)

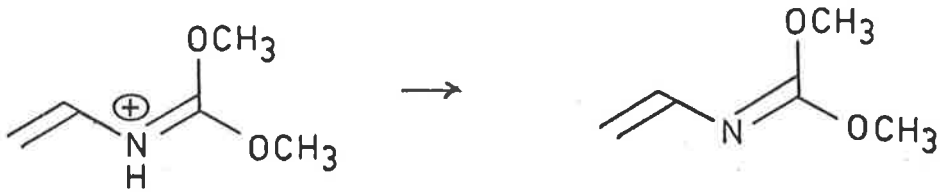
(71)

be a good dienophile in Diels Alder reactions.[112,113] The attempted synthesis of (69) from (59)is shown in scheme 10 but no 2-azabutadiene was isolated.

The reaction of a β-diketone such as 1,3-indanedione (72) with vinylisocyanate (59) could give the adduct (73) which on cyclization could lead to (71). The first step is similar to work reported by



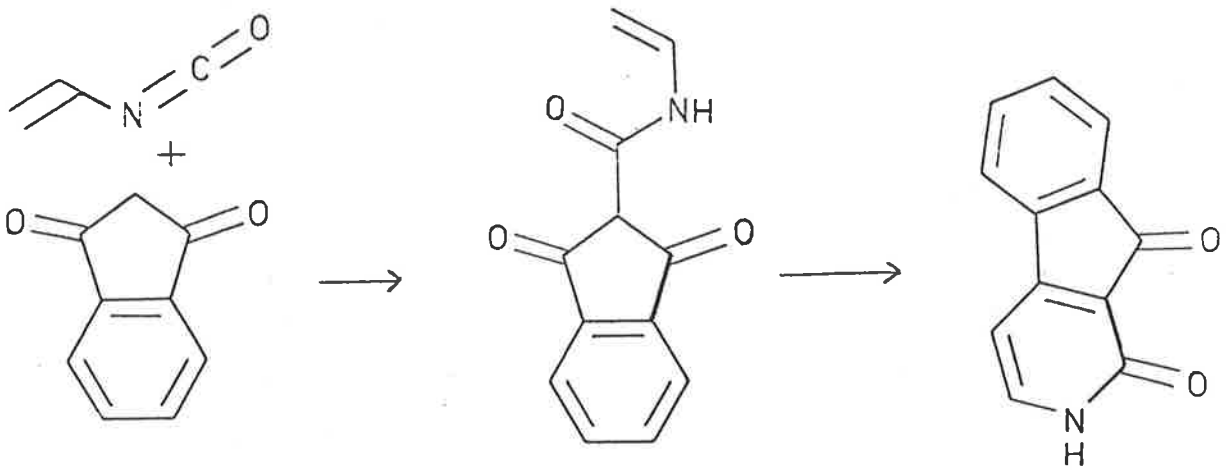
(59)



(69)

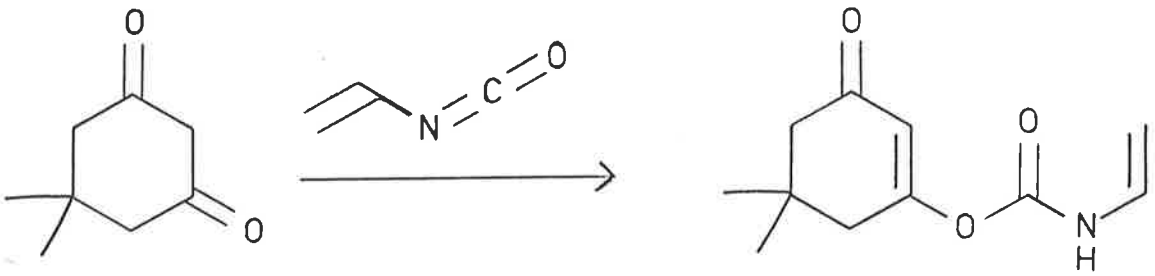
SCHEME 10

Dieckman, Hoppe, and Stein[114] and more recently by Muxfeldt, Grethe, and Rogalski,[115] the cyclization step is the addition of an enamine to a carbonyl.[103-105]



(72) (73) (71)

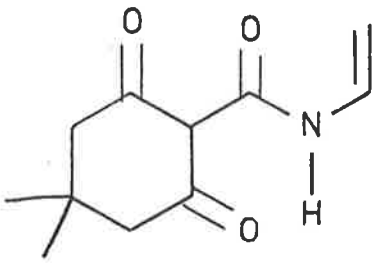
The reaction between dimedone and vinylisocyanate (59) in dichloromethane proceeded rapidly and in high yield to give the O-acylated product (74). The carbamate (74) was unstable and decomposed on standing at ambient temperature over several hours or more rapidly on heating. Recrystallisation of (74) from dichloromethane caused some decomposition to dimedone and vinylisocyanate.



(74)

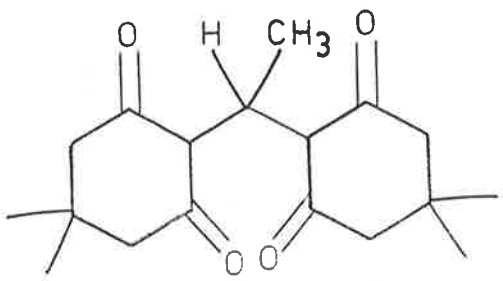
Rapid decomposition of a melting point sample occurred at 65-67°, the sample then melted at 147-149°.

The carbamate (74) was heated in the presence of a base (triethylamine or sodium acetate) at 120° but no C-acylated product (75) was obtained. The products were trivinylisocyanurate (62), the dimeric species (76) and (77), and tar materials derived from dimedone which could not be identified. The compounds (76) and (77) were identified by comparison with authentic samples. Both (76) and

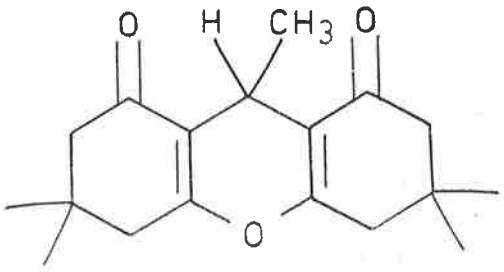


(75)

(77) were formed as a result of the N-vinyl group behaving as an aldehyde equivalent.[116]

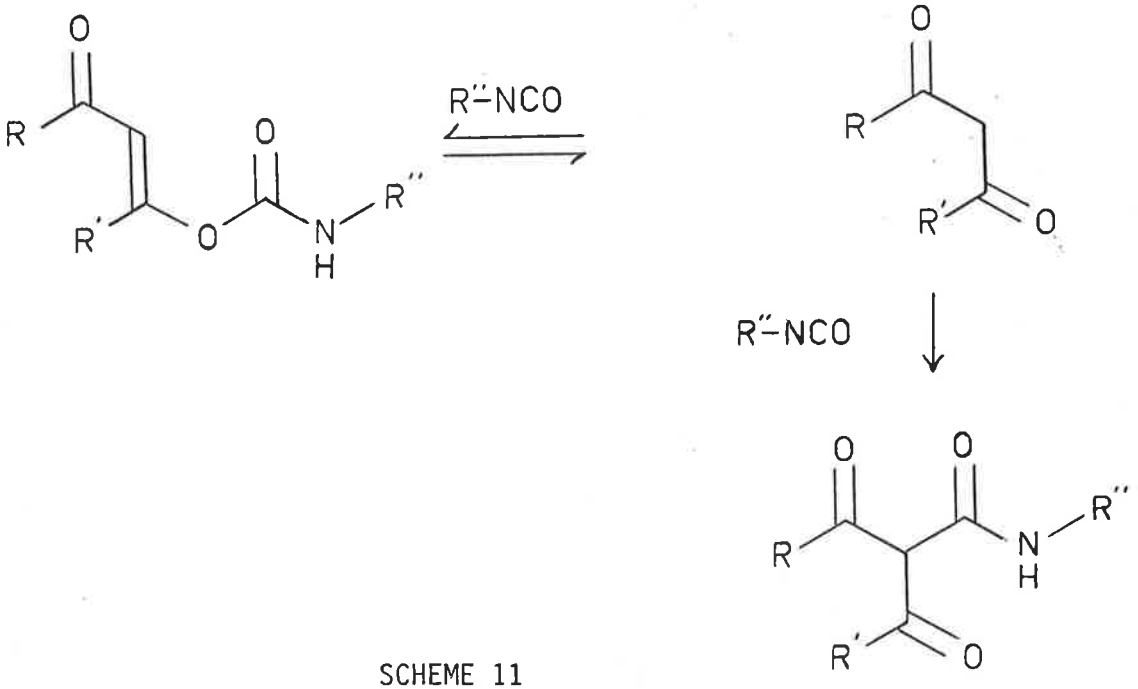


(76)



(77)

Dimedone was found to be unstable to heat in the presence of a base and produced a similar tar like material. Under the less vigorous conditions described by Muxfeldt et al.[115] the carbamate (74) produced a mixture of (77), dimedone and trivinylisocyanurate (62). Previous work on the O-C acyl rearrangement did not use isocyanates which were as liable to trimerisation as vinylisocyanate.[99,114,117] Presumably the reaction normally forms the O-acyl product first which under the conditions reverts to an isocyanate and a β-diketone but any C-acyl compound formed is more stable to the conditions (see scheme 11).



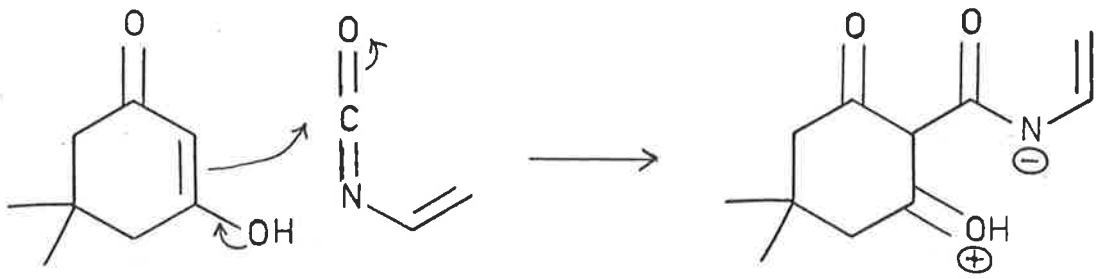

SCHEME 11

The anion of dimedone caused rapid trimerisation of vinylisocyanate (59) and no additional product was observed. Vinylisocyanate was inert to the enol methyl ether and enol acetate of dimedone.

The addition of vinylisocyanate to dimedone in acetonitrile solvent gave some interesting but inconsistent results. The product

identified was as the O-acyl adduct (74), or the C-acyl adduct (75), or a mixture of both. The C-acyl product (75) was identified by $^{1}H$ n.m.r. spectroscopy and infrared spectroscopy. Like the O-acyl product the C-acyl product was unstable and could not be characterised by mass spectrometry, nor would it survive long enough for combustion analysis. Decomposition was so rapid that no cyclization conditions could be found.

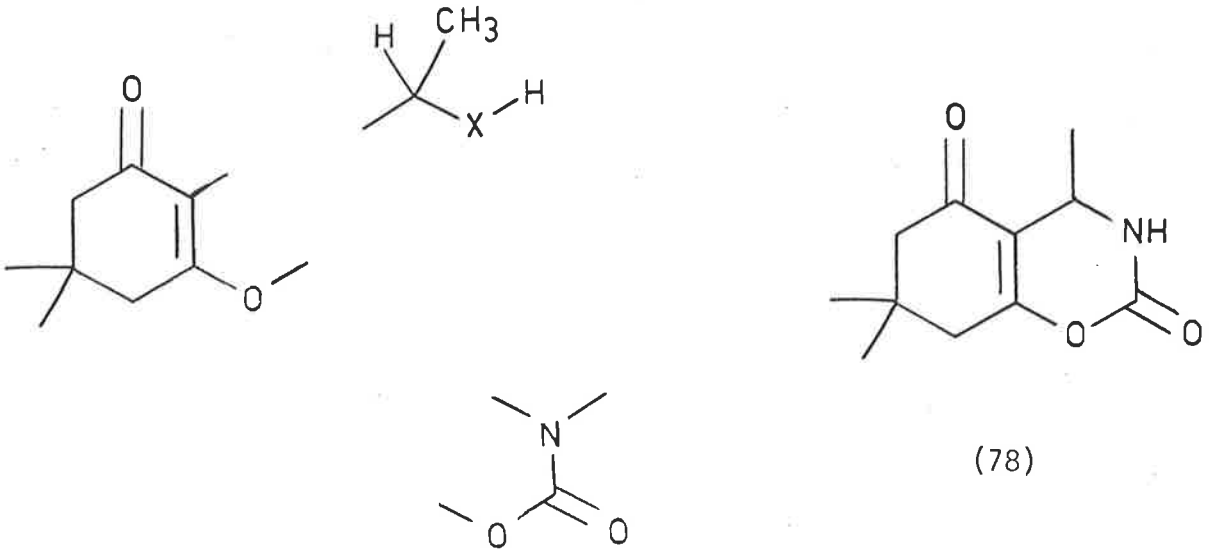
The addition of an isocyanate to a 1,3-diketone to give the C-acyl compound is similar to the Prins reaction (see scheme 12).[118-120]




SCHEME 12

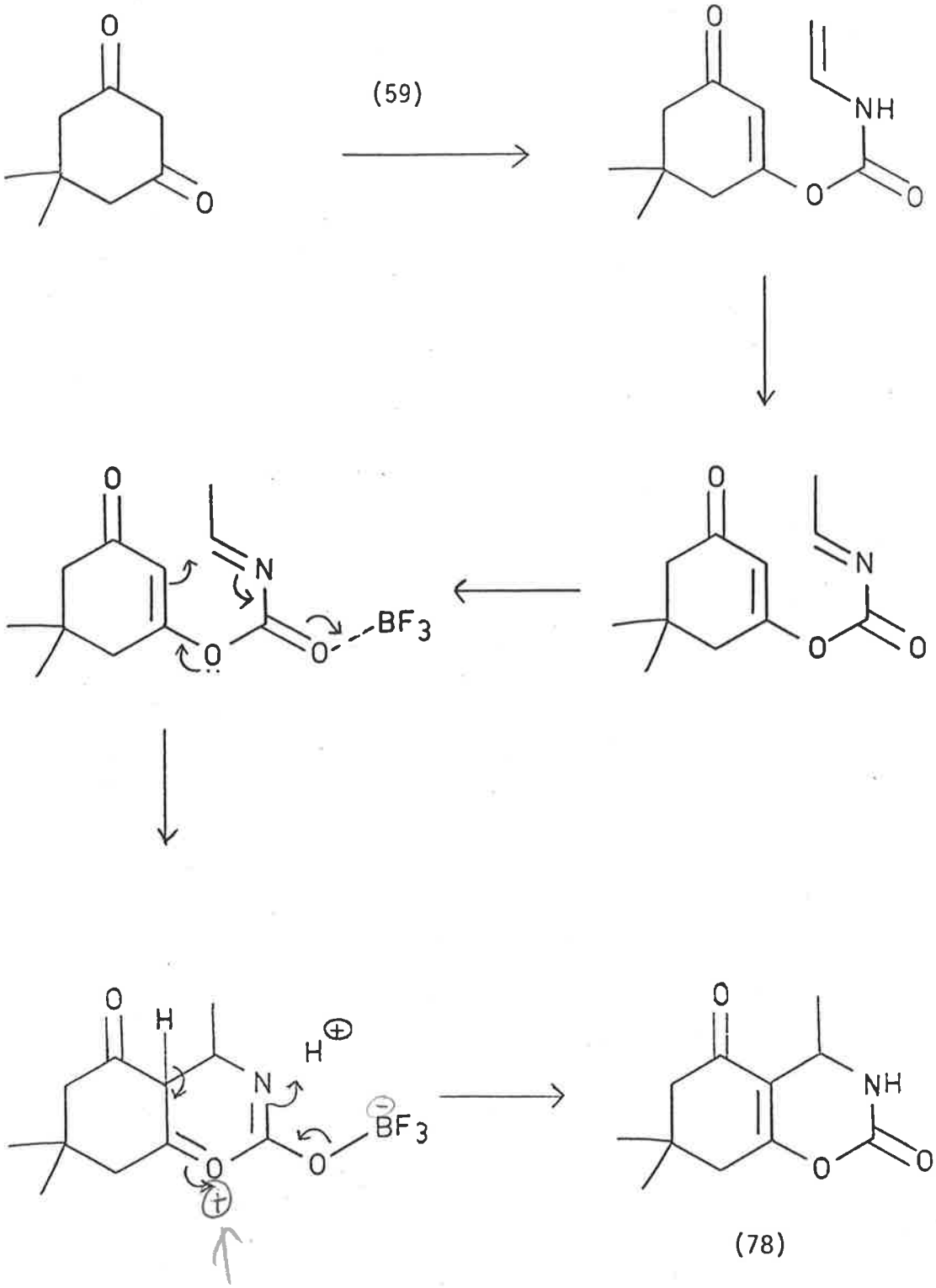
Lewis acids have been shown to catalyse the Prins reaction.[120,121] In addition, dimedone has been used as the olefin for a Prins reaction.[117] Accordingly boron trifluoride etherate was used to catalyse a reaction between vinylisocyanate (59)and dimedone. Several products were isolated from the reaction.

The first compound was a one to one addition compound. The $^1$H n.m.r. spectrum had a doublet at δ 1.34 which was coupled to a doublet of quartets at δ 4.32. In addition the doublet of quartets was coupled to an exchangeable proton at δ 7.17 suggesting the structural sub-unit $CH_3$-C(H)-XH. Also observed in the $^1$H n.m.r. spectrum were resonances consistent with dimedone in the enol form and substituted at the 2-position. The infrared spectrum had an absorption at 1765 $cm^{-1}$ which was consistent with a carbamate. The compound was identified as 4,7,7-trimethyl-3,4,7,8-tetrahydrobenz[1,3]-oxazine-2,5(6H)-dione (78).




(78)

The proposed mechanism (see scheme 13) involves initial formation of (74) followed by proton rearrangement and ring closure catalysed by boron trifluoride. The ring closure is analogous to the reaction of dimedone with an aldehyde catalysed by boron trifluoride.[120] The reaction of the O-acylated compound (74) with boron trifluoride also gave the cyclized product (78).




(78)

SCHEME 13

Another compound isolated had a $^{1}H$ n.m.r. spectrum which included the dimedone skeleton as the dione but the protons attached to C-2 were observed as a quartet there was also a doublet at $\delta$ 1.47, suggesting the structure (76). The dehydrated form (77) was isolated when the reaction was repeated. The two compounds (76) and (77) are normally formed in a reaction between dimedone and acetaldehyde.[116]

3-Chloro-5,5-dimethyl-2-cyclohexenone (79) has been used as a regenerable $\alpha,\beta$ unsaturated ketone system for 1,4 addition reactions.[122,123] In principle the anion of methyl vinylcarbamate could react with 3-chloro-5,5-dimethyl-2-cyclohexenone (79) in a Michael type reaction followed by ring closure to give an annelated 2-pyridone (80) (see scheme 14). The anion of methyl vinylcarbamate could be delocalised over five atoms (see fig. 9), but the desired reaction requires the addition proceeds with the terminus of the vinyl group adding in a 1,4 manner to the enone (79), but addition through nitrogen or oxygen also are possible.

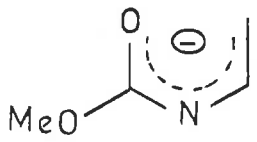
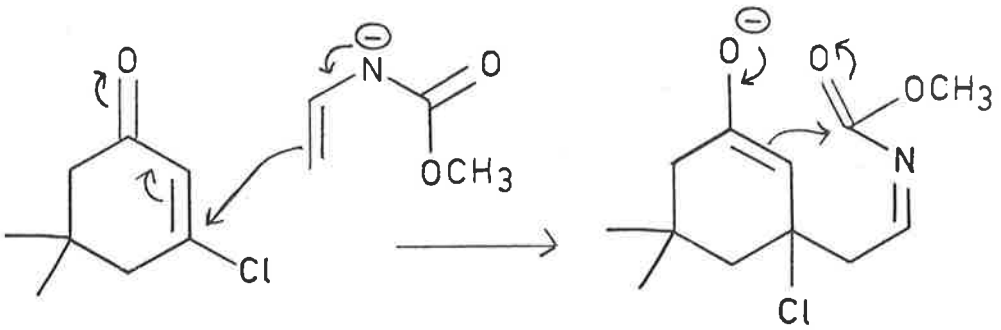
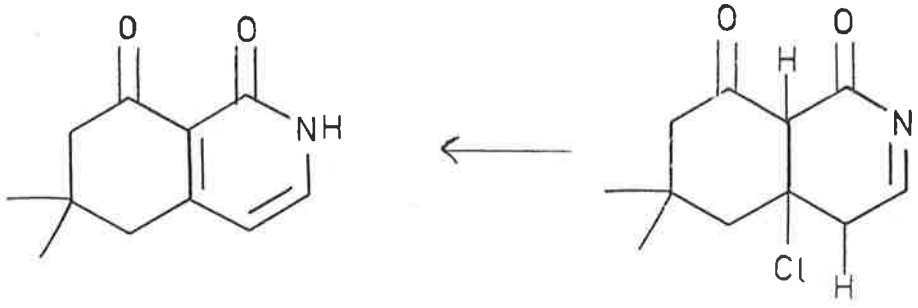



FIGURE 9



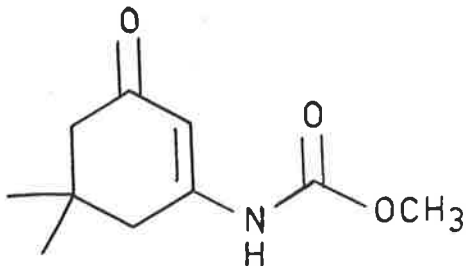
(79)



(80)

SCHEME 14

The anion of methyl vinylcarbamate was added to the enone (79) at low temperature, the reaction yielded two main products. The first component (81) was identified as resulting from 1,4 addition through nitrogen followed by hydrolysis during work up of the vinyl group. The compound was not fully characterised as it decomposed on attempted purification. Identification of the second component was more complex.




(81)

The mass spectrum revealed that the compound was a 1:1 addition product, formula $C_{12}H_{18}ClNO_3$. The infrared spectrum had absorptions correspondng to a carbamate at 1720 $cm^{-1}$ and an $\alpha,\beta$ unsaturated carbonyl at 1665 and and 1610 $cm^{-1}$. The $^1H$ n.m.r. spectrum had resonances which were very similar to those of the starting enone (79), but the vinyl proton was absent; an O-$CH_3$ group was evident and there was a pattern corresponding to a sub-unit $CH_3$-C(H)-NH- similar to that of (78). The sub-units of the structure (see fig.10) were assembled to give the

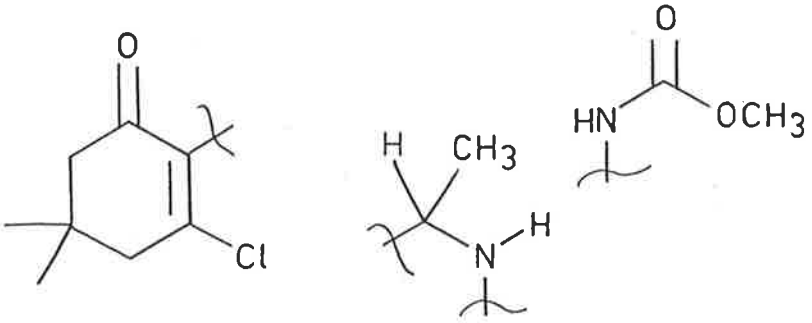
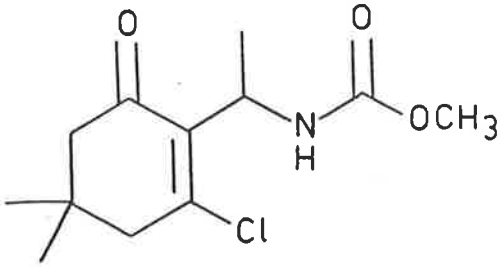
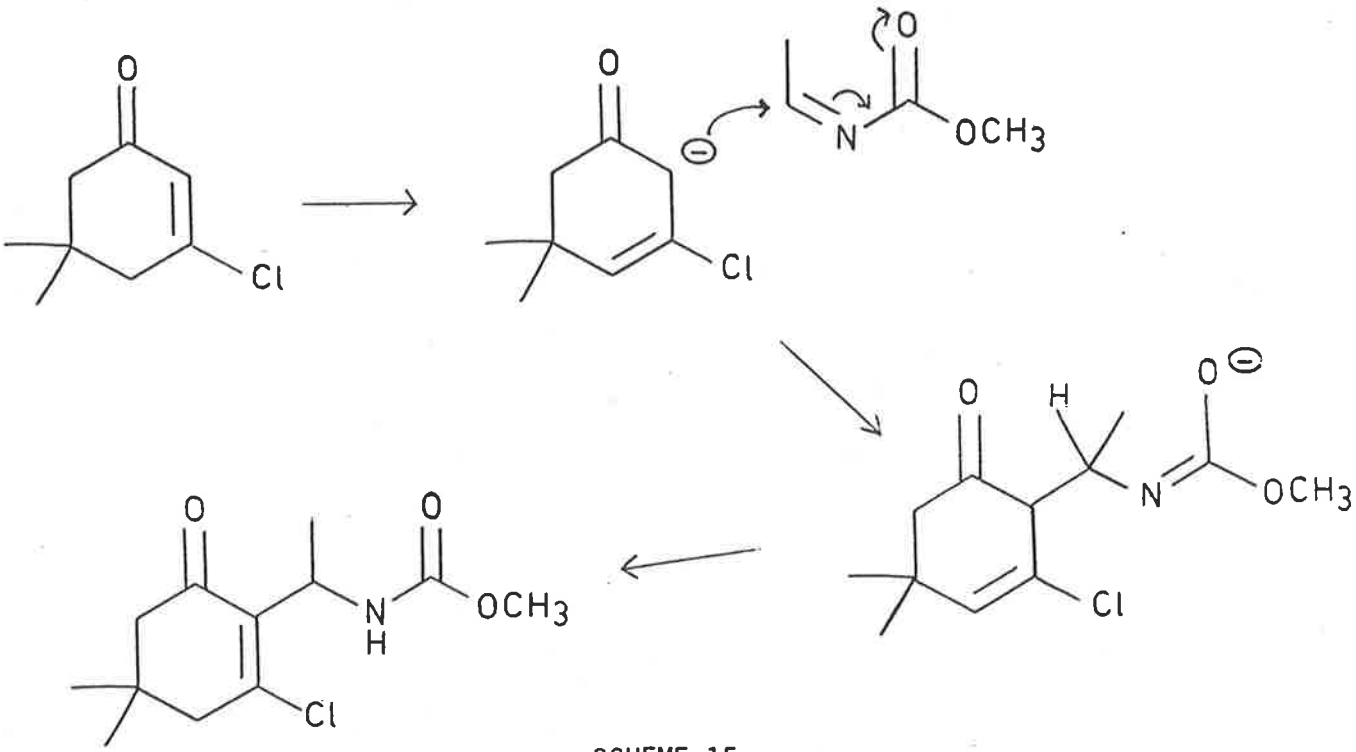


FIGURE 10



(82)

compound (82). The proposed mechanism for the formation of (82) is shown in scheme 15 and involves initial proton obstraction from the enone (79) by the anion of methyl vinyl carbamate followed by addition.



SCHEME 15

(82)

# CHAPTER 3

# EXPERIMENTAL

## GENERAL

Melting points (m.p.) were measured on a Reichert hot stage microscope. Melting points and boiling points (b.p.) are uncorrected.

Microanalyses were performed by the Australian Microanalytical Service, Melbourne.

Infrared spectra were recorded on either a Perkin-Elmer 397 infrared spectrophotometer or a Jasco IRA-1 grating infrared spectrophotometer using the 1603 $cm^{-1}$ bond of polystyrene as a reference. Samples were prepared as nujol mulls unless otherwise stated. Solution spectra were determined in chloroform ($CHCl_3$) with 0.2 mm cells. Only significant bands are quoted.

Proton nuclear magnetic resonance ($^1H$ n.m.r.) spectra were recorded on a Varian T60 spectrometer or a Jeol JNM-PMX60 spectrometer both operating at 60 MHz or a Bruker WP80 pulse Fourier Transform spectrometer operating at 80 MHz. Samples were dissolved in deuteriochloroform ($CDCl_3$) and spectra were calibrated using tetramethylsilane as an internal standard unless otherwise stated. Samples dissolved in hexadeuterioacetone ($CD_3COCD_3$) or hexadeuteriodimethylsulfoxide ($CD_3SOCD_3$) were calibrated using the proton impurity in the solvent at 2.05 p.p.m. ($CD_3COCD_3$) or 2.50 ($CD_3SOCD_3$). Samples dissolved in deuteriotrifluoroacetic acid ($CF_3CO_2D$) or trifluoroacetic acid ($CF_3CO_2H$) were calibrated externally using TMS dissolved in hexadeuteriobenzene. Data are presented as chemical shift ($\delta$) in parts per million (p.p.m.); multiplicity, signlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), doublet of quartets (dq), AB quartet (ABq), complex multiplet (m); coupling constants (J) and width at half height ($W_{h/2}$) are expressed in Hz;

relative intensities of resonances are expressed in whole proton units.

Carbon-13 nuclear magnetic resonance ($^{13}C$ n.m.r.) spectra were determined using a Bruker WP80 spectrometer operating at 20.1 MHz. Samples were dissolved in $CDCl_3$ and calibrated using TMS as an internal reference or using the $\delta$ 77.0 p.p.m. resonance of $^{13}CDCl_3$ unless otherwise stated. Samples dissolved in $CD_3COCD_3$ or $CD_3SOCD_3$ were calibrated using the central $^{13}C$ resonance of the solvent, at $\delta$ 29.8 p.p.m. ($^{13}CD_3COCD_3$) or at $\delta$ 39.5 p.p.m. ($^{13}CD_3SOCD_3$). Spectra are quoted as $\delta$ chemical shift downfield from TMS, multiplicity, assignment. Signals of carbons with long relaxation times were observed by acquiring spectra using a 4 second interval between pulses.

Mass spectra were recorded on a Hitachi Perkin-Elmer RMV-7D double focusing spectrometer or an AEI MS3074 spectrometer both operating at 70 eV. Only the molecular ion and/or significant fragment ions are quoted.

All solvents for chromatography, extractions or recrystallisations were redistilled. All purified solvents and reagents were purified by standard methods.[124-128] Dry ether and dry tetrahydrofuran were distilled from sodium/benzophenone under nitrogen immediately prior to use. Light petroleum refers to the fraction boiling between 63-67°.

All organic extracts were dried using anhydrous magnesium sulfate.

Analytical thin layer chromatography (t.l.c.) was performed using Merck Kieselgel 60 F254 aluminium foil backed plates or Merck Aluminium oxide 150 $F_{254}$ neutral (Type T) aluminium foil backed plates. Preparative t.l.c. was done using Merck Kieselgel 1:1 G and HF 254, coated on glass plates 200 mm x 200 mm to a thickness of 2.5 mm.

Column chromatography was carried out using Sorbsil silica gel or Spence neutral alumina or Woelm neutral alumina. Flash chromatography was carried out using Merck Kieselgel 60 (230-400 mesh).[129]

3.1 3-(2-Bromophenyl)-2-cyanoprop-2-enamide (11)

Cyanoacetamide (2.4 g, 30 mmol) and 2-bromobenzaldehyde (5.55 g, 30 mmol) were refluxed in ethanol (200 ml) with 2 M sodium hydroxide (0.2 ml) for 15 h, the resulting mixture was cooled and the solid collected by filtration (yield 4.65 g, 62%). Recrystallization from ethanol gave 3-(2-bromophenyl)-2-cyanoprop-2-enamide (11) as white needles, m.p. 193-194°.

(Found: $M^{+\cdot}$ 251.97194. $C_{10}H_7{}^{81}BrN_2O$ requires 251.972254).

$\nu_{max}$ 3375, 1710, 1600 $cm^{-1}$. $^1H$ n.m.r. $\delta$ 6.82, br s, $W_{h/2}$ 16 Hz, 2H, $NH_2$; 7.3-7.9, m, 3H; 7.9-8.3, m, 1H; 8.55, s, 1H. Mass spectrum m/e 252,250 (M).

Ethyl 4-(2-Bromophenyl)-5-cyano-6-oxo-1,6-dihydropyridine-2-carboxylate (12)

(i) 3-(2-Bromophenyl)-2-cyanoprop-2-enamide (11) (251 mg, 1.0 mmol) was dissolved in dimethylsulfoxide (5 ml), ethyl pyruvate (116 mg, 1.0 mmol) and ammonium acetate (0.2 g) were added and the solution was stirred at 20° for 16 h. The solution was diluted with water (20 ml) and extracted with dichloromethane (5 x 10 ml). The combined organic extracts were dried and evaporated to dryness leaving a red oil which could not be purified.

(ii) Ethyl 3-(2-bromophenyl)-2-cyanoprop-2-enoate[18,19] (2.8 g, 10 mmol) and ethyl pyruvate (1.16 g, 10 mmol) were dissolved in ethanol (20 ml) with ammonium acetate (1 g), the mixture was refluxed for 36 h. The solvent was removed and the residue was chromatographed on silica with dichloromethane/ethanol (95:5), the fraction containing the ester was concentrated then taken up in ethanol, ethyl 4-(bromophenyl)-5-cyano-

6-oxo-1,6-dihydropyridine-2-carboxylate (12) crystallized as a yellow powder, further recrystallization from ethanol and then dichloromethane/light petroleum furnished clear needles 67 mg (2%) m.p. 215-217° (Found $M^{+\cdot}$ 347.99475. $C_{15}H_{11}{}^{81}BrN_2O_3$ requires $M^{+\cdot}$ 347.993805). $\nu_{max}$ 1740, 1650 $cm^{-1}$. $^1H$ n.m.r. ($CDCl_3/CD_3SOCD_3$) $\delta$ 1.40, t, J 7Hz, 3H; 4.43, q, J 7Hz, 2H; 6.93, s, 1H (H3); 7.2-7.8, m, 4H. Mass spectrum m/e 348, 346 (M), 320, 318, 303, 301.

Ethyl 4-(2-Chlorophenyl)-5-cyano-6-oxo-1,6-dihydropyridine-2-carboxylate (15).

Ethyl 3-(2-chlorophenyl)-2-cyanoprop-2-enoate (14)[17,18] (2.3 g, 10 mmol), ethyl pyruvate (1.09 ml, 10 mmol) and ammonium acetate (1g) were dissolved in ethanol at 70-80° and kept at that temperature for 24 h. The solution was concentrated and the solid was collected, yielding ethyl 4-(2-chlorophenyl)-5-cyano-6-oxo-1,6-dihydropyridine-2-carboxylate (15) (0.62 g, 20%). Recrystallization from dichloromethane/light petroluem gave almost white crystals, m.p. 234-235.5°. (Found: C, 59.5; H, 3.7; N, 9.3. $C_{15}H_{11}ClN_2O_3$ requires C, 59.5; H, 3.7; N, 9.3%).
$\nu_{max}$ 2225, 1730, 1645 $cm^{-1}$. $^1H$ n.m.r. $\delta$ 1.36, t, J 7 Hz, $CH_3$; 4.48, q, J 7Hz, $CH_2$; 7.12, s, H 3; 7.5-7.9, m, 4H. Mass spectrum m/e 304, 302 (M).

4-(2-Chlorophenyl)-5-cyano-6-oxo-1,6-dihydropyridine-2-carboxylic Acid (16).

Ethyl 4-(2-chlorophenyl)-5-cyano-6-oxo-1,6-dihydropyridine-2-carboxylate (15) (100 mg, 0.33 mmol) was refluxed in methanol (20 ml)

containing water (5 ml) and sodium hydroxide (0.1 g) for 2 h. The resulting solution was cooled, acidified and concentrated, giving 4-(2-chlorophenyl)-5-cyano-6-oxo-1,6-dihydropyridine-2-carboxylic acid (16) as a white powder (82 mg, 90%), m.p. 282-287° (dec.) (Found: C, 56.7; H, 2.6, N, 9.9. $C_{13}H_7ClN_2O_3$ requires C, 56.9; H, 2.6; N, 10.2%).

$\nu_{max}$ 3300-3200, 3125, 2230, 1900, 1705, 1620 $cm^{-1}$. $^1H$ n.m.r. $\delta$ 6.95, s, H3; 7.3-7.5, m, 4H. Mass spectrum m/e 276, 274 (M).

4-(2-Chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (17).

(i) 4-(2-Chlorophenyl)-5-cyano-6-oxo-1,6-dihydropyridine-2-carboxylic acid (16) (443 mg, 1.61 mmol) was mixed with copper bronze (2.6 g) in a sublimator and then heated to 320-340° under vacuum (0.1 mm Hg). After heating for 30 min the pressure returned to 0.01 mm, and heating was then terminated. The material which had sublimed was dissolved in dichloromethane (20 ml) and combined with the extracts of the residue. The solution was chromatographed on silica using dichloromethane/methanol (95:5). The nitrile (17) was recrystallized from dichloromethane/light petroleum and was recovered in 41% yield (152 mg, 0.66 mmol) m.p. 214-218°, and was identical in all respects with that obtained below.

(ii) 2-[-1-(2-Chlorophenyl)-3-dimethylaminoprop-2-enylidene]malononitrile (36) (223 mg, 0.87 mmol) was dissolved in a solution of acetic acid and 11 M hydrochloric acid (1:1) (10 ml) at reflux, forming a green solution. After 2 h at reflux the colourless solution was neutralized with solid sodium hydrogen carbonate and water. The aqueous solution was then extracted with dichloromethane (3 x 20 ml), the combined organic extracts were dried and the solvent was removed.

The residue was purified by preparative t.l.c. on silica using dichloromethane/methanol (95:5). The band at $R_F$ 0.25-0.40 was isolated and afforded 4-(2-chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (17) in 80% yield (160 mg, 0.69 mmol). Recrystallization from dichloromethane/light petroleum gave colourless prisms, m.p. 218-222° (Found: C, 62.4; H,3.3; N, 12.0. $C_{12}H_7ClN_2O$ requires C, 62.5; H, 3.1; N, 12.1%). $\nu_{max}$ 2240, 1600, 1605, 770 $cm^{-1}$. $^1H$ n.m.r. ($CD_3SOCD_3$) (80 MHz) δ 6.33, d, J 6.6Hz, H5; 7.4-7.7, m, 4H; 7.84, d, J 6.6Hz, H6. Mass spectrum m/e 232, 230 (100%) M.

Attempted Reaction of Ethyl 3-(2-Chlorophenyl)-2-cyanoprop-2-enoate (14) with the Lithium Enolate of Acetaldehyde.

Ethyl 3-(2-chlorophenyl)-2-cyanoprop-2-enoate (14)[19] (203 mg, 0.86 mmol) was dissolved in dichloromethane (10 ml) and was added to a solution of lithium acetylate (0.9 mmol) hexane (50 ml)[24] at -78°. The mixture was warmed to 20° and acidified with dilute hydrochloric acid, then extracted with ether (3 x 15 ml). The combined organic extracts were dried and concentrated leaving an intractable brown oil.

Ethyl 3-(2-Chlorophenyl)-2-cyanobut-2-enoate (22)

A solution of 2-chloroacetophenone (3.93 g, 25.4 mmol), ethyl cyanoacetate (2.97 ml, 28 mmol), pentylamine (0.32 ml, 2.8 mmol), and acetic acid (0.16 ml, 2.8 mmol) in benzene (20 ml) was refluxed, and the water formed was collected in a Dean-Stark water separator until the theoretical amount of water (0.5 ml) had been collected. The solvent was removed under reduced pressure and the residue distilled. Ethyl 3-(2-chlorophenyl)-2-cyanobut-2-enoate (22) (5.3 g, 84%) boiled

at 118°/0.01 mm (Found: C, 62.2; H, 5.1; N, 5.8. $C_{13}H_{12}ClNO_2$ requires C, 62.5; H, 4.8; N, 5.6%). $\nu_{max}$ (liquid film) 2230, 1730, 1615 $cm^{-1}$. $^1H$ n.m.r. δ 1.12, t, J 7Hz, 1.35, t, J 7Hz, 3H; 2.43, s, 2.57, s, 3H; 3.96, q, J 7Hz, 4.30, q, J 7Hz, 2H; 6.7-7.4, m, 4H. Mass spectrum m/e 251, 249 (M), 214 (M-Cl).

Ethyl 3-(2-Chlorophenyl)-2-cyano-5-dimethylaminopenta-2,4-dienoate (23).

Dimethylformamide dimethyl acetal (1.0 ml, 1.2 equiv.) was added to ethyl 3-(2-chlorophenyl)-2-cyanobut-2-enoate (22) (2.5 g, 10 mmol) under nitrogen. The mixture rapidly coloured and solidified after 30 min. The residue was dried under vacuum and then chromatographed on alumina with dichloromethane: the product (3.0 g, 98%) was eluted rapidly. Recrystallization from dichloromethane/light petroleum gave yellow prisms of ethyl 3-(2-chlorophenyl)-2-cyano-5-dimethylaminopenta-2,4-dienoate (23), m.p. 193.5-194.5° (Found: C, 63.1; H, 5.6; N, 9.1. $C_{16}H_{17}ClN_2O_3$ requires C, 63.1; H, 5.6; N, 9.2%). $\nu_{max}$ 2200, 1680, 1610 $cm^{-1}$. $^1H$ n.m.r. δ 1.12, t, J 7Hz, 1.32, t, J 7Hz, 3H; 2.97, s, $(CH_3)_2N$; 3.78, q, J 7Hz, 4.20, q, J 7Hz, 2H; 5.78, d, J 12Hz, 6.27, d, J 12Hz, 1H, (N-C=CH); 6.8-7.4, m, 5H. Mass spectrum m/e 306,304 (M).

Attempted Formation of 4-(2-Chlorophenyl)-2-oxo-1,4-dihydropyridine-3-carbonitrile (17) from Ethyl 3-(2-Chlorophenyl)-2-cyano-5-dimethylaminopenta-2,4-dienoate (23).

Ethyl 3-(2-chlorophenyl)-2-cyano-5-dimethylaminopenta-2,4-dienoate (23) (134 mg, 0.4 mmol) was dissolved in ethanol (10 ml) and ammonia solution (5 ml) was added, the solution was then refluxed for 16h.

The solvent was removed, the residue was acidified and extracted with dichloromethane (3 x 20 ml), the combined organic extracts were dried and evaporated to dryness leaving the starting material (23).

The process was repeated using ammonium acetate but only (23) was recovered.

Ethyl 4-(2-Chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (24).

Ethyl 3-(2-chlorophenyl)-2-cyano-5-dimethylaminopenta-2,4-dienoate (23) (615 mg, 2.0 mmol) was dissolved in refluxing 80% acetic acid (50 ml) under nitrogen with stirring. The heating was stopped after the solution changed colour from green-yellow to tan. After removal of most of the solvent the solution was neutralized with sodium hydrogen carbonate and extracted with dichloromethane (4 x 20 ml). The combined organic extracts were dried and the solvent removed. Chromatography on Sorbsil, with 30% ethyl acetate in dichloromethane, gave 470 mg (85%) of a solid which was recrystallized from dichloromethane/light petroleum to give ethyl 4-(2-chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (24) as white crystals, m.p. 202.5-203° (Found: C, 60.4; H, 4.3; N, 4.9. $C_{14}H_{12}ClNO_3$ requires C, 60.6; H, 4.3; N, 5.0%). $\nu_{max}$ 1735, 1685, 1640 $cm^{-1}$. $^1H$ n.m.r. $\delta$ 0.87, t, J 7Hz, 3H; 3.98, q, J 7Hz, 2H; 6.18, d, J 6Hz, H5; 7.0-7.7, m, 5H (including 7.68, d, J 6Hz (H6)).
Mass spectrum m/e 242 (M-Cl), 234, 232 ($M-OC_2H_5$).

Reduction of Ethyl 4-(2-Chlorophenyl)-5-cyano-6-oxo-1,6-dihydropyridine-2-carboxylate (15).

The ester (15) (250 mg, 0.83 mmol) was dissolved in dry

tetrahydrofuran (30 ml) at -60°, diisobutylaluminium hydride (2.5 equiv.) was added and the solution was stirred at -60° for 22h. The reaction was then worked up by adding 3M hydrochloric acid (10 ml) and warming to 20°, then brine (10 ml) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 x 15 ml) and the combined organic extracts were dried and evaporated to dryness.

$\nu_{max}$ 1705, 1660 $cm^{-1}$. $^1H$ n.m.r. $\delta$ 6.53, s, H5; 6.7-7.6, m, ArH; 7.90, br s, NH; 9.55, s, CHO.

Attempted Reduction of Ethyl 4-(2-Chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (24) to 4-(2-Chlorophenyl-2-oxo-1,2-dihydropyridine-3-carbaldehyde (26).

The ester (24) was partially dissolved in the solvent (20 ml) and diisobutylaluminium hydride was added under nitrogen. The reaction was worked up by pouring into 3M hydrochloric acid (10 ml) followed by brine (10 ml). The layers were separated and the aqueous layer was extracted with dichloromethane (4 x 20 ml). The combined organic extracts were dried and the solvent was removed under reduced pressure. The residue was examined by t.l.c. and by infrared and $^1H$ n.m.r. spectroscopy.

The results are summarized in Table 2.

Table 2

Attempted reduction of (24) with diisobutylaluminium hydride

| Amount of ester (mmol) | Solvent | DIBAL-H (equiv.) | Temp (°C) | Time (h) | Product |
|---|---|---|---|---|---|
| 0.54 mmol (silylated) | toluene | 2.4 | -60 | 1 | ester + alcohol |
| 0.38 | THF | 2.5 | 25 | 30 | ester |
| 0.52 | THF | 2.5 | 65 | 6 | ester + alcohol |
| 0.55 | toluene | 5 | 110 | 12 | ester + alcohol |

4-(2-Chlorophenyl)-3-hydroxymethyl)pyridin-2(1H)-one (29)

Ethyl 4-(2-chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (24) (1.06 g, 3.8 mmol) was suspended in dry tetrahydrofuran (20 ml) and sodium bis(methoxyethoxy)aluminium hydride (2.04M, 4 ml, 2.1 equiv.) was added. The solution was refluxed and the reaction was followed by t.l.c. When no further ester (24) remained (1.5h) the reaction mixture was cooled to 20° and hydrochloric acid (3M, 20 ml) was added. Brine (20 ml) was added to the solution, the layers separated, and the aqueous phase extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried and the solvent removed.

The residue was recrystallized from dichloromethane/light petroleum which gave 4-(2-chlorophenyl)-3-hydroxymethylpyridin-2(1H)-one (29) (840 mg, 94%). The analytical sample was prepared by flash chromatography in dichloromethane/methanol (95:5), followed by recrystallization from dichloromethane/light petroleum, and had

m.p. 203-205° (Found: C, 61.0; H, 4.4; N, 6.2. $C_{12}H_{10}ClNO_2$ requires C, 61.2; H, 4.3; N, 5.9%). $\nu_{max}$ 3250, 3100, 1660, 1590 $cm^{-1}$. $^1H$ n.m.r. δ 2.7-3.1, s (br), 1H, OH; 4.21, 4.52, ABq, J 12Hz, 2H, $CH_2O$; 6.18, d, J 7Hz, H5; 7.1-7.6, m, 5H. $^{13}C$ n.m.r. ($CD_3SOCD_3$) δ 56.63 ($CH_2O$), 107.64 (C5), 127.20, 128.90, 129.50, 130.11, 131.20, 133.51, 137.03, 149.06 (C6), 163.15 (C-O). Mass spectrum m/e 237,235 (M), 198, 182.

Attempted Oxidation of 4-(2-Chlorophenyl)-3-hydroxymethylpyridin-2(1H)-one (29) to 4-(2-Chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carbaldehyde (26).

(i) The alcohol (29) (412 mg, 1.7 mmol) was dissolved in purified dichloromethane (40 ml), then pyridinium chlorochromate[39] (0.4g, 1.1 equiv.) was added. After 3 h the mixture was passed through a short column of Florisil which was then washed with dichloromethane and ethyl acetate. The solvents were removed under vacuum but no products were eluted.

(ii) The alcohol (29) (31.6 mg, 0.13 mmol) was dissolved in dichloromethane (15 ml) and manganese dioxide[40] (0.2 g) was added. The mixture was stirred for 3 days, then filtered through Celite and Florisil and washed with ethyl acetate and acetone; this gave a white solid (3 mg) which was identified as the alcohol (29).

(iii) To a solution of oxalyl chloride (0.20 ml, 2.3 mmol) in dichloromethane (5 ml) at -60° was added dimethyl sulfoxide (0.4 ml, 5.6 mmol) in dichloromethane (5 ml). The alcohol (29) (496 mg, 2.10 mmol) in dichloromethane (20 ml) was added and the mixture was stirred at -60°, followed by the addition of triethylamine (1 ml). The reaction was

warmed to 20° and water (15 ml) was added. The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried and evaporated to dryness. $^1$H n.m.r. spectroscopy showed an aldehydic resonance at δ 10.13 p.p.m. which accounted for 5% of the pyridone-containing material.

Attempted Formation of 4-(2-Chlorophenyl)-N-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (31) from Ethyl 4-(2-Chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (24).

(i) The ester (24) (375 mg, 1.35 mmol) was dissolved in ethanol (20 ml) and 3,4-dimethoxyaniline (7) (227 mg, 1.1 equiv.) was added at reflux under nitrogen. The solution was refluxed for 24h, cooled and then examined by t.l.c. and $^1$H n.m.r. spectroscopy, only the starting materials were observed.

(ii) The ester (24) (171 mg, 0.62 mmol) was dissolved in ethanol (20 ml) and then 3,4-dimethoxyaniline (103 mg, 2.4 equiv.) was added. A solution of sodium ethoxide (2 equiv.) in ethanol (10 ml) was added and the solution was stirred at reflux for 2h, t.l.c. showed no change, only the starting materials were present.

4-(2-Chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic Acid (30)

(i) Ethyl 4-(2-chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (24) (194 mg, 0.70 mmol) was dissolved in methanol (30 ml) and aqueous sodium hydroxide (2M, 10 ml) and the solution was refluxed for 1h. The solution was acidified (3M HCl), the methanol was removed under reduced pressure and 4-(2-chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (30) (157 mg, 0.63 mmol; 90%) was collected.

Recrystallization of the product from acetone afforded tan feathery crystals, m.p. 250-255° (Found: C, 57.8; H, 3.3; N, 5.5. $C_{12}H_8ClNO_3$ requires C, 57.7; H, 3.2; N, 5.6%). $\nu_{max}$ 3200, 1720, 1620, 1595 $cm^{-1}$. $^1H$ n.m.r. ($CD_3SOCD_3$) δ 6.48, d, J 6Hz, H5; 7.1-7.7, m, 4H; 7.94, d, J 6Hz, H6. Mass spectrum m/e 234, 232 (M-OH); 214 (M-Cl).

(ii) 4-(2-Chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (17) (15.6 mg, 0.68 mmol) was dissolved in 75% sulfuric acid 20 ml) and heated to 100°-120° for 4h, then analytical t.l.c. confirmed that no nitrile remained. Sodium nitrite (200 mg, 4 equiv.) was added portion wise over 2 h, the resulting solution was poured into water (100 ml), cooled and then left for the acid (30) to crystallize. The acid (30) was collected (126 mg, 75%) m.p. 247-254 and was identical in all respects with that obtained above.

4-(2-Chlorophenyl)-N-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (31).

(i) 4-(2-Chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (30) (277 mg, 1.1 mmol) was heated in thionyl chloride (5 ml) at reflux for 2h, the residual thionyl chloride was removed under vacuum. A solution of 3,4-dimethoxyaniline (7) (194 mg, 1.3 mmol, 1.1 equiv.) in dry pyridine (10 ml) was added and the resulting mixture was refluxed for 4h, acidified (3M HCl) and extracted with dichloromethane (5 x 20 ml). The combined organic extracts were washed with 3M hydrochloric acid (20 ml), dried and the solvent was removed. The residue was chromatographed on Sorbsil with dichloromethane/methanol (95:5), 4-(2-chlorophenyl)-N-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

(31) was then recrystallized from dichloromethane/light petroleum as green needles (189 mg, 44%), m.p. 250-252° (Found: C, 62.6; H, 4.2; N, 7.4. $C_{20}H_{17}ClN_2O_4$ requires C, 62.4; H, 4.5; N, 7.3%).
$\nu_{max}$ 3200 br NH; 1675, 1615, 1590, 1240, 1215, 760 $cm^{-1}$. $^1H$ n.m.r. ($CD_3SOCD_3$) (80 MHz) δ 3.58, s, $OCH_3$; 3.66, s, $OCH_3$; 6.16, d, J 6Hz, H5; 6.6-6.8, m, 8H (including 7.62, d, J 6Hz, H6).
$^{13}C$ n.m.r. ($CD_3SOCD_3$) δ 55.8 ($OCH_3$), 56.0 ($OCH_3$), 105.2, 109.3, 112.1, 112.5, 124.6, 127.2, 129.5, 129.9, 130.8, 132.8, 136.5, 138.7, 140.8, 145.5, 149.1, 152.5, 161.9 (N-C=O), 162.4 (N-C=O).
Mass spectrum m/e 386, 384 (M).

(ii) The acid (30) (531 mg, 2.13 mmol) was mixed with 3,4-dimethoxyaniline (7) (432 mg, 2.8 mmol, 1.3 equiv.) and ethyl polyphosphate[45] (3 ml) and heated at 150° for 25 h. The mixture was mixed with water (40 ml) and heated to dissolve the ethyl polyphosphate. The aqueous solution was extracted with dichloromethane (5 x 20 ml), the combined extracts were dried and evaporated. The brown residue was examined by t.l.c. and was found to contain only a trace of the amide (31).

(iii) The acid (30) (612 mg, 2.45 mmol) was dissolved in oxalyl chloride and the solution was heated at reflux for 40 min, then the volatile material was removed under vacuum. The residue was dissolved in a solution of 3,4-dimethoxyaniline (7) (539 mg, 1.4 equiv., pyridine (20 ml) and the solution was heated to reflux for 2h, cooled and poured into 3M hydrochloric acid (100 ml). The solution was extracted with dichloromethane (4 x 30 ml), the combined organic extracts were dried and the solvent removed under vacuum. Chromatography of the residue on Sorbsil as above gave the amide (31) (689 mg, 73%), identical with that obtained above.

(iv) The acid (30) (390 mg, 1.6 mmol) and 3,4-dimethoxyaniline (7) (303 mg, 1.2 equiv.) were dissolved in dry tetrahydrofuran (20 ml) and the solution was cooled in ice. Dicyclohexylcarbodiimide (0.4 g, 1.2 eq.) was added and the solution was stirred under nitrogen at 15° for 14h. The solid dicyclohexylurea was removed by filtration and the solvent evaporated. The residue was recrystallized from dichloromethane/light petroleum which gave the amide (31) as green needles m.p. 248-250° (510 mg, 83%). Flash chromatography with dichloromethane/methanol (05:5) followed by recrystallization from dichloromethane/light petroleum afforded yellow amide (31) m.p. 250-252° identical with that obtained above.

2-[2-(2-Bromophenyl)ethylidene]malononitrile (34).

A solution of 2-bromoacetophenone (5.0 g, 25 mmol), malononitrile (2.49 g, 37.7 mmol, 1.5 equiv.), pentylamine (0.28 ml, 2.5 mmol, 0.1 equiv.), and acetic acid (0.14 ml, 2.5 mmol, 0.1 equiv.) in benzene (30 ml) was refluxed for 24h with a water separator. The reaction mixture was then cooled and the solvent was removed. The residual oil (5.3 g, 87%) was distilled and 2-[1-(2-bromophenyl)ethylidene]-malononitrile (34) had b.p. 102-104°/0.02 mm (Found: C, 53.3; H, 3.1; N, 11.6. $C_{11}H_7BrN_2$ requires C, 53.5; H, 2.9; N, 11.3%). $\nu_{max}$ (liquid film) 2230 (CN), 1600, 1580, 1465, 1420, 1025, 760 $cm^{-1}$. $^1H$ n.m.r. $\delta$ 2.53, s, CH ; 7.1-7.8, m, 4H. $^{13}C$ n.m.r. $\delta$ 24.2 (q), 89.1 (s), 111.1 (s), 118.8 (s), 127.5 (d), 127.8 (d), 131.4 (d), 133.1 (d), 137.4 (s), 176.7 (s). Mass spectrum m.e 248, 246 (M), 167, 140.

2-[1-(2-Chlorophenyl)ethylidene]malononitrile.

A solution of 2-chloroacetophenone (15.3 g, 99 mmol), malononitrile (6.6 g, 100 mmol), pentylamine (1.2 ml, 10 mmol) and acetic acid (0.57 ml, 10 mmol) in benzene (35 ml) was refluxed for 24h under nitrogen. The water produced was removed in a Dean-Stark apparatus. After the theoretical amount of water (1.8 ml) was collected the reaction mixture was cooled, the solvent was removed and 2-[1-(2-chlorophenyl)-ethylidene]malononitrile (19 g, 95%) was distilled at 102°/0.05 mm (Found: C, 65.4; H, 3.8; N, 13.9. $C_{11}H_7ClN_2$ requires C, 65.2; H, 3.5; N, 13.8%). $\nu_{max}$ (liquid film) 2240 (CN), 1600, 1585, 765 $cm^{-1}$. $^1H$ n.m.r. $\delta$ 2.53, s, $CH_3$; 7.0-7.5, m, 4H. $^{13}C$ n.m.r. $\delta$ 24.4 (q), 89.5 (s), 111.6 (s), 127.7 (d), 128.1 (d), 130.6 (d), 131.9 (d), 135.8 (s), 175.8 (s). Mass spectrum m/e 204,202 (M).

2-[1-(2-Chlorophenyl)-3-dimethylaminoprop-2-ethylidene]malononitrile (36).

Dimethylformamide dimethyl acetal (3.3 ml, 24.8 mmol, 1.2 equiv.) was added to 2-[1-(2-chlorophenyl)ethylidene]malononitrile (4.27 g, 21.1 mmol) under nitrogen with stirring at 20°. After the solid had formed (1h) the volatile materials were removed under vacuum at 50°. The residue was dissolved in dichloromethane and chromatographed on alumina with dichloromethane. 2-[1-(2-Chlorophenyl)-3-dimethylaminoprop-2-enylidene]malononitrile (36) (4.73 g, 18.3 mmol, 89%) was obtained pure after recrystallization from dichloromethane/light petroleum as yellow prisms, and had m.p. 185-186° (Found: C, 65.2; H, 4.6; N, 16.0. $C_{14}H_{12}ClN_3$ requires C, 65.3; H, 4.7; N, 16.3%). $\nu_{max}$ 2200, 1620, 1460, 1380 $cm^{-1}$. $^1H$ n.m.r. (80 MHz) $\delta$ 3.02, s($N(CH_3)_2$); 5.86, d, J 12.8 Hz, 1H (NCH-CH); 6.49, d, J 12.8Hz, 1H (NCH=CH); 7.1-7.7

m, 4H. $^{13}C$ n.m.r. δ 37.9, 46.0 (2 x $NCH_3$), 97.8, 116.0, 127.4, 130.5, 131.2, 132.6, 134.2, 155.5, 168.8. Mass spectrum m/e 259, 257 (M), 222 (M-Cl).

2-[1-(2-Bromophenyl)-3-dimethylaminoprop-2-enylidene]malononitrile (35).

To 2-[1-(2-bromophenyl)ethylidene]malononitrile (3.11 g, 12.6 mmol) was added, with stirring under nitrogen at 20°, dimethylformamide dimethyl acetal (2.5 ml, 1.5 equiv.). The reaction immediately turned yellow, then darkened to red and eventually purple. After about 1h the reaction mixture became solid. The reaction mixture was heated (50°) under vacuum to remove volatile material. The residue was dissolved in dichloromethane and chromatographed on alumina. 2-[1-(2-Bromophenyl)-3-dimethylaminoprop-2-enylidene]malononitrile (35) (3.60 g, 95%) was recrystallized from dichloromethane/light petroleum as yellow needles, m.p. 177-178° (Found: C, 55.4; H, 4.1; N, 13.8. $C_{14}H_{12}BrN_3$ requires C, 55.7; H, 4.0, N, 13.9%). $\nu_{max}$ 2200 (CN), 1610, 1265, 770 $cm^{-1}$. $^1H$ n.m.r. (80 MHz) δ 3.03, s, $N(CH_3)_2$; 5.84, 6.54 ABq, J 12.5Hz, HC=C(H)-N; 7.1-7.9, m, 4H, $^{13}C$ n.m.r. δ 37.9, 46.0 (2 x $NCH_3$); 97.5 (d), 116.2 (s), 122.1 (s), 128.0 (d), 130.5 (d), 131.3 (d), 132.0 (s), 133.7 (d), 136.3 (s), 145.2 (s), 155.8 (d), 170.2 (s). Mass spectrum m/e 303, 301 (M), 222 (M-Br).

4-(2-Bromophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (37).

(i) 2-[1-(2-Bromophenyl)-3-dimethylaminoprop-2-enylidene]malononitrile (35) (244 mg, 0.81 mmol) was dissolved in acetic acid (10.5 ml) containing 11M hydrochloric acid (3 ml) and water (1.5 ml) and the solution was refluxed for 2h. On cooling, the solution was basified

with 2M sodium hydroxide and extracted with dichloromethane (4 x 20 ml). The combined organic extracts were dried and the solvent was removed leaving 4-(2-bromophenyl)-2-chloropyridine-3-carbonitrile (38) (57 mg, 0.19 mmol, 24%) which was recrystallized from dichloromethane/light petroleum, m.p. 135-136° (Found: $M^{+\cdot}$, 291.9411. $C_{12}H_6{}^{79}Br^{35}ClN_2$ requires $M^{+\cdot}$, 291.9403). $\nu_{max}$ 2215 (CN), 1565, 1360, 750 $cm^{-1}$. $^1H$ n.m.r. δ 7.0-7.9, m, 5H; 8.53, d, J 5Hz, H6. Mass spectrum m/e 296, 294, 292 (M), 215, 213 (M-Br), 178, (M-Br-Cl), 177.

The aqueous solution was acidified (HCl) and neutralized to pH7 with sodium hydrogen carbonate and then extracted with dichloromethane (4 x 20 ml). The combined organic extracts were dried and the solvent was removed under vacuum. The residue (95 mg, 43%) was shown by $^1H$ n.m.r. spectroscopy and t.l.c. comparison to be 4-(2-bromophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (36), identical with that obtained below.

(ii) 2-[1-(2-Bromophenyl)-3-dimethylaminoprop-2-ethylidene]malononitrile (35) (966 mg, 3.2 mmol) was dissolved in acetic acid (10 ml) containing 98% sulfuric acid (2 ml) and water (3 ml). The solution was refluxed for 2h after which time the reaction was complete. The solution was then neutralized with sodium hydrogen carbonate and extracted with dichloromethane (4 x 15 ml). The combined organic extracts were dried and the solvent removed. The residue was recrystallized from dichloromethane/light petroleum giving the nitrile (37) as off-white crystals (723 mg, 87%).

The analytical sample was prepared by flash chromatography with dichloromethane/methanol (95:5). 4-(2-Bromophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (37) was then recrystallized from

dichloromethane/light petroleum, and had m.p. 228-229° (Found: C, 52.2; H, 2.5; N, 9.7. $C_{12}H_7BrN_2O$ requires C, 52.4; H, 2.6; N, 10.2%). $\nu_{max}$ 3240, 3110, 2230 (CN), 1700, 1628, 1603, 1210, 755 $cm^{-1}$. $^1H$ n.m.r. δ 6.14, d, J 7Hz, H5; 7.1-7.7, m, 5H. $^{13}C$ n.m.r. δ 103.5 (s), 107.4 (d), 115.3 (s), 120.3 (s), 128.2 (d), 129.8 (d), 131.5 (d), 133.0 (d), 137.3 (s), 140.9 (d), 160.4 (s), 160.7 (s). Mass spectrum m/e 276, 274 (M), 195 (M-Br).

4-(2-Bromophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (39).

(i) 4-(2-Bromophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (37) (237 mg, 0.86 mmol) was dissolved in hot 75% sulfuric acid (10 ml) at 100-120°. The solution was stirred at that temperature for 3h, then cooled and diluted with water (40 ml). The solution was neutralized with sodium hydrogen carbonate and extracted with dichloromethane (4 x 20 ml). The combined organic extracts were dried and the solvent removed. Recrystallization from dichloromethane/light petroleum afforded 4-(2-bromophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (39) (234 mg, 0.80 mmol, 93%) m.p. 230-232°. The analytical sample was purified by flash chromatography in dichloromethane/methanol (92:8) and had m.p. 233-234° (Found: C, 48.8; H, 2.9; N, 9.6. $C_{12}H_9BrN_2O_2$ requires C, 49.2; H, 3.1; N, 9.6%). $\nu_{max}$ 3540, 3420 (NH), 3150 (OH); 1670 $cm^{-1}$. $^1H$ n.m.r. (80 MHz) δ 6.46, d, J 6.9Hz, H5; 7.0-8.0, m, 7H (including 7.75, d, J 6.9Hz, H6); 12.95, br s, $W_{h/2}$ 26Hz, NH. $^{13}C$ n.m.r. ($CD_3SOCD_3$) δ 109.1, 120.6, 123.7, 127.4, 129.1, 129.4, 132.2, 136.2, 141.3, 153.9, 161.9, 165.8. Mass spectrum m/e 293, 291 (M), 213.

(ii) 2-[1-(2-Bromophenyl)-3-dimethylaminoprop-2-ethylidene]malononitrile (35) (711 mg, 2.35 mmol) was dissolved in 75% sulfuric acid (20 ml) at 80-100° and the solution was stirred for 4 h. The resulting solution was poured into water (20 ml) and then neutralized with sodium carbonate until the amide (39) precipitated. 4-(2-Bromophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (39) (648 mg, 92%) was collected and was identical with that obtained above.

4-(2-Bromophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic Acid (40).

(i) 4-(2-Bromophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (39) (212 mg, 0.72 mmol) was dissolved in 70% sulfuric acid (10 ml) at 80-100° with stirring. Then sodium nitrite (950 mg, c. 20 equiv.) was added portionwise over 2h. The reaction mixture was cooled and poured into water (50 ml). Sodium hydroxide solution (2M) was added until the acid (40) precipitated (pH2) and the solid (166 mg, 0.56 mmol, 78%) was collected.

The analytical sample was prepared by flash chromatography in ethylacetate/methanol (1:1). 4-(2-Bromophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (40) was recrystallized from ethanol/water and then from acetone/water and had m.p. 248-250° (Found: C, 48.9; H, 2.9; N, 4.9. $C_{12}H_8BrNO_3$ requires C, 49.0; H, 2.7; N, 4.8%). $\nu_{max}$ 3220, 3140, (NH, OH), 2700 (br) (OH), 1725, 1590, 1210 $cm^{-1}$. $^1H$ n.m.r. ($CD_3SOCD_3$, 80 MHz) $\delta$ 6.34, d, J 6.5Hz, H5; 7.1-7.7, m, 4H; 7.86, d, J 6.5Hz, H6. $^{13}C$ n.m.r. ($CD_3SOCD_3$) $\delta$ 111.2, 120.0, 127.5, 128.4, 129.7, 132.1, 132.6, 140.3, 157.6 164.2. Mass spectrum m/e 293, 291 (M-2), 251, 249.

(ii) 4-(2-Bromophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (37) (323 mg, 1.17 mmol) was dissolved in 75% sulfuric acid (10 ml) at 80-100° and stirred for 2h. Then sodium nitrite (c. 0.5 g) was added portionwise over 2h. The reaction mixture was worked up as above to give the carboxylic acid (40) (2.62 mg, 76%) m.p. 246-248°. The infrared spectrum was identical to that of the material isolated above.

(iii) 2-[1-(2-Bromophenyl)-3-dimethylaminoprop-2-ethylidene]malanonitrile (35) (789 mg, 2.61 mmol) was dissolved in 75% sulfuric acid (25 ml) at 100°. The solution was stirred for 4h. Sodium nitrite (768 mg, 2.6 equiv.) was added as before and the reaction mixture was worked up as described above. The yield of the carboxylic acid (40) was 698 mg (91%), m.p. 246-248°.

4-(2-Bromophenyl)-N-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (32).

4-(2-Bromophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (40) (276 mg, 0.94 mmol) was dissolved in dry tetrahydrofuran (30 ml) and 3,4-dimethoxyaniline (176 mg, 1.15 mmol, 1.2 equiv.) was added. The solution was cooled in ice and dicyclohexylcarbodiimide (255 mg, 1.25 mmol, 1.3 equiv.) was added. The solution was stirred under nitrogen at 15-20° for 14h, additional dicyclohexylcarbodiimide (100 mg) being added after 14h, and stirring was then continued for 14h. The reaction mixture was cooled in ice and the dicyclohexylurea was removed by filtration and the solvent evaporated. The residue was crystallized from dichloromethane/light petroleum to give 4-(2-bromophenyl)-N-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (32) as yellow needles (351 mg, 87%), m.p. 242-245°.

The analytical sample was prepared by flash chromatography in dichloromethane/methanol (94:6) then recrystallized from dichloromethane/light petroleum and had m.p. 247-249° (Found: C, 55.6; H, 4.2; N, 6.5. $C_{20}H_{17}BrN_2O_4$ requires C, 56.0; H, 4.0; N, 6.5%). $\nu_{max}$ 3350 (NH), 3150 (br) (OH), 1735, 1680, 1540, 1515 $cm^{-1}$. $^1H$ n.m.r. (80 MHz) δ 3.86, s, 2 x $OCH_3$; 6.34, d, J 6.9Hz, H5; 6.7-7.8, m, 8H (including 7.54, d, J 6.9Hz, H6); 11.15, br s, $W_{h/2}$ 7Hz, NH; 11.83, br s, $W_{h/2}$ 12Hz, NH. $^{13}C$ n.m.r. ($CD_3SOCD_3$) δ 55.5, 55.8, 104.9, 109.0, 111.6, 112.2, 120.4, 123.8, 127.4, 128.9, 129.5, 132.3, 136.2, 139.6, 140.6, 145.2, 148.7, 153.6, 161.7, 168.1. Mass spectrum m/e 430, 428 (M), 349 (M-Br).

Attempted Formation of 4-[2-(3,4-Dimethoxyphenylamino)phenyl]-2-oxo-1,2-dihyrodpyridine-3-carboxylic Acid (41).

(i) 4-(2-Chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (30) (269 mg, 1.08 mmol), 3,4-dimethoxyaniline (7) (189 mg, 1.1 equiv.), potassium carbonate (260 mg, 3.5 equiv.) and copper powder (83 mg, 30%) were heated in dimethylformamide (20 ml) at reflux for 8h. The reaction mixture was cooled and examined by t.l.c. but none of the required product was present,[59] although many other spots were seen.

(ii) The reaction was repeated using 4-(2-bromophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (40) (300 mg, 1 mmol), with 3,4-dimethoxyaniline (173 mg, 1.1 equiv.) potassium carbonate (0.5 g, 4 equiv), copper bronze (10 mg) and copper iodide (10 mg) in n-butanol (10 ml) but still no (41) was observed,[59] only a dark complex mixture was obtained.

Reaction of 4-(2-Bromophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (37) with Copper Bronze.

4-(2-Bromophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (37) (429 mg, 2.18 mmol), copper iodide (15 mg), copper bronze (4 mg), and potassium carbonate (0.55 g, 4 equiv.) were mixed in refluxing n-butanol (20 ml). After 8h no exchange in the nitrile (37) could be observed by t.l.c. The solvent was removed and the residue was acidified (3M HCl, 10 ml) and extracted with dichloromethane (4 x 10 ml). The extract was identical with the starting nitrile (37) by t.l.c. and $^{1}H$ n.m.r.

Attempted Reaction of 4-(2-Bromophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (39) with Copper Bronze.

4-(2-Bromophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (39) (278 mg, 0.95 mmol) in n butanol (6 ml) with copper bronze (2 mg), copper iodide (3 mg), and potassium carbonate (450 mg, 3.5 equiv.) were heated to reflux but after 8h no change was observed and the amide (39) was recovered unchanged.

Ethyl 2-Cyano-5-dimethylamino-3-phenylpenta-2,4-dienoate

Ethyl 2-cyano-3-phenylbut-2-enoate[130] (1.42 g, 6.58 mmol) was stirred under nitrogen at 20° and dimethylformamide dimethyl acetal was added. The mixture was stirred until it solidified (1h) and was then left for a further 2h. The volatile material was removed under vacuum and the solid which remained was chromatographed on alumina with dichloromethane. Ethyl 2-cyano-5-dimethylamino-3-phenylpenta-2,4-dienoate was recrystallized as a mixture of isomers from dichloromethane/light petroleum as yellow prisms, m.p. 138-139° (1.65 g, 93%)

(Found: C, 71.4; H, 6.5; N, 10.3. $C_{16}H_{18}N_2O_2$ requires C, 71.1; H, 6.7; N, 10.4%). $\nu_{max}$ 2200 (CN), 1680, 1615 $cm^{-1}$. $^1H$ n.m.r. $\delta$ 1.10, t, J 7Hz; 1.33, t, J 7Hz; 1.45, t, J 7Hz, 3H; 2.93, s, 6H, 2 x $NCH_3$; 3.93, q, J 7Hz; 4.22, q, J 7Hz, 2H; 5.82, 6.28, ABq, J 12Hz; 6.38, d, J 14Hz; 7.0-7.5, m, 7H. Mass spectrum m/e 270 (M), 225 (M-$OCH_2CH_3$).

Ethyl 2-Oxo-4-phenyl-1,2-dihydropyridine-3-carboxylate

Ethyl 2-cyano-5-dimethylamino-3-phenylpentadienoate (585 mg, 2.17 mmol) was dissolved in refluxing 80% acetic acid (50 ml). The yellow-green solution was refluxed for 3h by which time the solution had changed to a dark colour. The solvent was removed under vacuum. The residue was dissolved in dichloromethane (50 ml) and washed with saturated sodium hydrogen carbonate solution (20 ml). The aqueous solution was extracted with dichloromethane (2 x 20 ml), the combined organic extracts were dried and the solvent was removed under vacuum. The solid residue (539 mg) was chromatographed on Sorbsil with dichloromethane/acetic acid (90:10) which gave ethyl 2-oxo-4-phenyl-1,2-dihydropyridine-3-carboxylate (461 mg, 87%). Recrystallization from dichloromethane/light petroleum gave ethyl 2-oxo-4-phenyl-1,2-dihydropyridine-3-carboxylate as off-white plates, m.p. 183-185° (Found: C, 69.2; H, 5.5; N, 5.9. $C_{14}H_{13}NO_3$ requires C, 69.1; H, 5.4; N, 5.8%). $\nu_{max}$ 1735, 1625 $cm^{-1}$. $^1H$ n.m.r. (80 MHz) $\delta$ 0.99, t, J 7.5Hz, 3H; 4.16, q, J 7.5Hz, 2H; 6.39, d, J 7Hz, 1H, H5; 7.44, s, 5H; 7.52, d, J 7Hz, 1H, H6. $^{13}C$ n.m.r. ($CD_3SOCD_3$) $\delta$ 13.7 (q), 61.0 (t), 106.9 (d), 123.9 (s), 127.7 (d), 129.0 (d), 129.5 (d), 136.7 (d), 137.6 (s), 151.5 (s), 160.2 (s), 166.6 (s). Mass spectrum m/e 243 (M), 198 (M-$OCH_2CH_3$).

2-Bromo-4-(2-bromophenyl)-pyridine-3-carbonitrile

2-[1-(2-Bromophenyl)-3-dimethylaminoprop-2-ethylidene]malononitrile (35) (1.58 g, 5.24 mmol) was heated in 48% hydrogen bromide in acetic acid (25 ml) at 50-60° for 2h, the green colour faded, although not all the compound dissolved. The mixture was cooled and poured onto water (20 ml) and the acid was neutralized with sodium carbonate and extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dired and the solvent was removed leaving a white solid (1.77 g) which was chromatographed on alumina with light petroleum/dichloromethane (1:1). 2-Bromo-4-(2-bromophenyl)pyridine-3-carbonitrile (1.70 g, 96%) was recrystallized from dichloromethane/light petroleum which gave clear prisms m.p. 125-126° (Found: C, 43.05; H, 1.90; N, 8.47. $C_{12}H_6Br_2N_2$ requires C, 42.64; H, 1.79; N, 8.29%). $\nu_{max}$ 2248 (CN), 1595, 1575 $cm^{-1}$. $^1H$ n.m.r. (80 MHz) $\delta$ 7.1-7.5, m, 4H (including 7.23, d, J 5Hz, H5), 7.6-7.8, m, 1H; 8.51, d, J 5Hz, H6. $^{13}C$ n.m.r. $\delta$ 114.5 (s), 115.0 (s), 121.6 (d), 124.2 (d), 128.0 (d), 130.3 (d), 131.7 (d), 133.7 (d), 136.3 (s), 145.0 (s), 152.2 (d), 155.5 (s). Mass spectrum m/e 340, 338, 336 (M), 249, 247 (M-Br), 178 (M-$Br_2$).

Attempted Reduction of 4-(2-Chlorophenyl)-N-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (31).

(i) The amide (31) (83 mg, 0.22 mmol) was dissolved in tetrahydrofuran (20 ml) and a solution of sodium bis(methoxyethoxy)aluminium hydride in benzene (2M, 3 ml, excess) was added under nitrogen. The solution was stirred at reflux but after 2h no evidence for reduction products could be obtained.

(ii) The amide (31) (285 mg, 0.76 mmol) was partly dissolved in tetrahydrofuran (40 ml) and lithium aluminium hydride (0.1 g) was added and the mixture was refluxed under nitrogen. After 4h no change in the amide (31) was observed.

(iii) The amide (31) (293 mg, 0.76 mmol) was dissolved in tetrahydrofuran (20 ml) under nitrogen then borane-dimethyl sulfide (10M, 0.2 ml, 2 mmol, 3 equiv.) was added and the solution was stirred at reflux for 3 days. None of the starting amide (31) remained and the reaction was quenched by pouring into 3M hydrochloric acic (10 ml) and neutralized with sodium carbonate. The solution was extracted with dichloromethane (5 x 20 ml). The combined organic extracts were dried and evaporated to dryness, which gave an intractable mixture. Under similar conditions and using the workup procedure described by Brown et al.[73,74] the amide (32) also gave only intractable mixtures.

Dehydroperloline (6-(3,4-Dimethoxyphenyl)benzo[c][2,7]naphthyridine-4,5(3H,6H)-dione) (3)

(i) 4-(2-Bromophenyl)-N-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (32) (223 mg, 0.52 mmol) was partly dissolved in dry tetrahydrofuran (20 ml) at -70° under nitrogen and lithium diisopropylamide in dry tetrahydrofuran (10 ml) at -70° [prepared from diisopropylamine (0.4 ml, 2.9 mmol, 5.5 equiv.) and n-butyllithium (2.5 ml, 1.0M, 2.5 mmol, 4.8 equiv.) in tetrahydrofuran (10 ml)] was added over 10 min. The reaction mixture was allowed to warm slowly to 20° and became homogeneous during warming. The solution changed colour from orange to dark burgundy over 2h. After 4h the solution was poured into 3M hydrochloric acid (10 ml) followed by brine (20 ml). The

layers were separated and the aqueous phase was extracted with dichloromethane (5 x 15 ml). The combined organic extracts were dried and the solvent was removed under vacuum.

The residue was purified by preparative t.l.c. on silica with dichloromethane/ethanol (90:10), the plate being run twice. The components which fluoresced intensely under 366-nm light were collected and further purified by chromatography on a commercial alumina t.l.c. plate with dichloromethane/ethanol (85:15). The band which fluoresced under 366-nm light was collected and recrystallized from dichloromethane/light petroleum to give colourless needles of dehydroperloline, m.p. 276-283° (Lit. 284°) (21 mg, 12%).

The aqueous solution was neutralized with sodium carbonate, which caused a colour change from yellow to red. The neutral solution was extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried and the solvent was removed under vacuum. The residue was purified by preparative t.l.c. on silica with dichloromethane/methanol (95:5). The component at $R_F$ 0.65 was identified by $^1H$ n.m.r. spectrscopy and by t.l.c. comparison as 3,4-dimethoxyaniline (12 mg, 15%).

(ii) 4-(2-Bromophenyl)-N-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (32) (453 mg, 1.06 mmol) was partly dissolved in dry tetrahydrofuran (20 ml) at -60°, then lithium hexamethyldisilazide (4.1 equiv.) [prepared from n-butyllithium (4.3 m, 1.0 M, 4.1 equiv.) and hexamethyldisilazane (0.95 ml, 730 mg, 4.5 mmol, 4.3 equiv.) in tetrahydrofuran (10 ml) at -60°] was added slowly over 10 min. The reaction mixture became homogeneous on warming and was then refluxed.

The progress of the reaction was followed by t.l.c.; after 4 days no starting amide (32) remained. The solution was poured into 3M hydrochloric acid (10 ml), then brine (10 ml) was added, the layers were separated and the aqueous phase was extracted with dichloromethane (4 x 15 ml). The combined organic extracts were dried and evaporated to dryness. Flash chromatography of the residue with dichloromethane/ethanol (80:20) gave dehydroperloline (3) (317 mg, 86%) m.p. 283-287°. The sample was recrystallized from ethanol, which gave 6-(3,4-dimethoxyphenyl)benzo[c][2,7]naphthyridine-4,5(3H,6H)-dione (3) as white crystals, m.p. 284-287° (Found: $M^{+\cdot}$ 348.1103. Calc. for $C_{20}H_{16}N_2O_4$: $M^{+\cdot}$ 348.1110). $\nu_{max}$ 3340, 1695, 1630, 1585 $cm^{-1}$. $^1H$ n.m.r. ($CD_3SOCD_3$, 80 MHz) δ 3.72, s, 3H, $OCH_3$; 3.85, s, 3H, $OCH_3$; 6.62, d, J 7Hz, 1H, H1; 6.8-8.2, m, 7H; 8.40, d, J 7Hz, 1H, H2. Mass spectrum m/e 348 (M).

(iii) The reaction was repeated using 4-(2-chlorophenyl)-N-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (31) (170 mg, 0.44 mmol) and lithium hexamethyldisilazide (4 equiv.), refluxed for 4 days. Dehydroperloline (3) was obtained in 50% yield (77 mg), m.p. 282-287°, and was identical by t.l.c. with that obtained above.

(iv) 4-(2-Bromophenyl)-N-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (32) (175 mg, 0.41 mmol), potassium carbonate (225 mg, 4 equiv.), copper bronze (2 mg, 1%) and copper (I) iodide (2 mg, 1%) were mixed in butan-1-ol and the mixture was refluxed for 2h.

The solvent was removed and the residue was dissolved in a mixture of dichloromethane and 1M hydrochloric acid. The layers were separated and the aqueous phase was extracted with dichloromethane (4 x 15 ml). The combined organic extracts were

dried and the solvent removed under vacuum, leaving dehydroperloline (103 mg, 73%) which was identical by t.l.c. analysis (silica, dichloromethane/ethanol (9:1)) with that obtained above.

Reaction of 4-(2-Bromophenyl)-N-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (32) with Hexamethyldisilazane.

4-(2-Bromophenyl)-N-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (32) (124 mg, 0.29 mmol) was partly dissolved in dry tetrahydrofuran (5 ml) and hexamethyldisilazane (0.2 ml, 3 equiv.) was added and the solution was refluxed for 16h. The solvent and any other volatile material was removed under vacuum (0.001 mm). The residue (140 mg, 96%) was found to be a mono-silylated product. $\nu_{max}$ ($CDCl_3$) 3380 (NH), 1660, 1590, 1570 $cm^{-1}$. $^1H$ n.m.r. $\delta$ 0.42, s, 9H, $(CH_3)_3Si$; 3.75, s, 6H, 2 x $OCH_3$; 6.6-6.9, m, 3H; 6.9-7.0, m, 1H; 7.0-7.3, m. 3H; 7.3-7.7, m, 1H; 8.0-8.3, m, 2H.

Attempted Cyclization of 4-(3-Bromophenyl)-N-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (58).

4-(3-Bromophenyl) N-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (58)[12,83] (6 mg, 14 μmol) was refluxed for 4 days with lithium hexamethyldisilazide (1 ml, 1M, excess), as with (31) and (32) above. The reaction was followed by t.l.c. comparison with an authentic sample of dehydroperloline (3). No dehydroperloline was observed, even after concentration of the corresponding $R_F$ material by thin-layer chromatography.

6-(3,4-Dimethoxyphenyl)-5-hydroxy-5,6-dehydrobenzo[c][2,7]naphthridin-4(3H)-one (Perloline) (1).

6-(3,4-Dimethoxyphenyl)benzo[c][2,7]naphthyridine-4,5 (3H, 6H)-dione (3) (156 mg, 0.45 mmol) was partly dissolved in dry tetrahydrofuran (10 ml) at 20°, then sodium bis(methoxyethoxy)aluminium hydride (1 ml, 2M, 2 equiv.) was added. The mixture became homogeneous and after 2 min the solution was poured into 3M hydrochloric acid (10 ml) followed by brine (10 ml). The layers were separated and the aqueous phase was extracted with dichloromethane (4 x 15 ml). The combined organic extracts were dried and evaporated to dryness. The residue was chromatographed on alumina with dichloromethane/ethanol (9:1) which gave 6-(3,4-dimethoxyphenyl)-5-hydroxy-5,6-dihydrobenzo[c][2,7]-naphthyridin-4(3H)-one (1) (111 mg, 0.32 mmol, 70%) identical by t.l.c. (alumina and silica) with an authentic sample of perloline hydrochloride. The mass spectrum and m.p. and mixed m.p., (220-225°), were identical with those of the authentic sample.

3.2 Reaction of Vinylisocyanate (59) with 1-Pyrrolidin-1-ylcyclopent-1-ene (60)

1-Pyrrolidin-1-ylcyclopent-1-ene (60)[131] (1 ml, 6.9 mmol) was dissolved in the solvent, thermally equilibrated and then vinylisocyanate[100] (0.34 ml, 1.0 equiv.) was added. The mixture was stirred for 30 min and then equilibrated to 10°. Any solid formed was collected and recrystallized from degassed acetonitrile under nitrogen. N-Ethenyl-2-pyrrolidin-1-ylcyclopent-1-ene-1-carboxamide (61) crystallized as white needles and had m.p. 128-131° (Found: C, 69.8; H, 8.4; N, 13.4. $C_{12}H_{18}N_2O$ requires C, 69.9; H, 8.8; N, 13.6%). $\nu_{max}$ 3275, 1635, 1605,

1570 $cm^{-1}$. $^1H$ n.m.r. δ 1.5-2.0, m, 6H; 2.57, t, J 7Hz, 4H; 3.2-3.5, m, 4H; 4.16, d, J 8Hz, 1H, 4.39, d, J 15.5Hz, 1H; 6.5-7.3, m. 2H (including 7.06, dd, J 8, 15.5Hz).

The residue after filtration was chromatographed on silica with dichloromethane, 1,3,5-triethenyl-S-triazine-2,4,6(1H,3H,5H)-trione (62) was isolated and distilled, b.p. 85-95°, 0.01-0.03 mm (lit. 114-116, 0.17 mm[99]). $\nu_{max}$ 1710 $cm^{-1}$. $^1H$ n.m.r. δ 5.28, d, J 9Hz, 1H; 5.74, d, J 16Hz, 1H; 6.63, dd, J 9,16Hz, 1H.

The results are summarized in Table 1 (see page 40).

Attempted Cyclization of N-Ethenyl-2-pyrrolidin-1-ylcyclopent-1-ene-1-carboxamide (61) by Heating

N-Ethenyl-2-pyrrolidin-1-ylcyclopent-1-ene-1-carboxamide (61) (53 mg, 0.25 mmol) was dissolved in acetonitrile (10 ml) and refluxed for 16h after which time no change was observed and (61) was recovered.

Reaction of N-Ethenyl-2-pyrrolidin-1-ylcyclopent-1-ene-1-carboxamide (61) with Bistrimethysilylacetamide

N-Ethenyl-2-pyrrolidin-1-ylcyclopent-1-ene-1-carboxamide (61) (90 mg, 0.44 mmol) was partially dissolved in toluene (10 ml) and bistrimethylsilylacetamide (0.13 ml, 1.2 equiv.) was added with stirring. The solution became homogeneous after 10 min and stirring was continued for 1h. Then the solution was poured into 1M hydrochloric acid (5 ml), the layers were separated and the aqueous solution was extracted with dichloromethane (2 x 10 ml). The combined organic extracts were dried and evaporated to dryness. The residue (53 mg) was examined by $^1H$ n.m.r. spectroscopy but only aliphatic material was observed.

Reaction of N-Ethenyl-2-pyrrolidin-1-ylcyclopent-1-ene-1-carboxamide (61) with Base

(i) N-Ethenyl-2-pyrrolidin-1-ylcyclopent-1-ene-1-carboxamide (61) (90 mg, 0.44 mmol) was dissolved in dry tetrahydrofuran (20 ml) and sodium hydride (20 mg, 50% dispersion in oil, 0.95 equiv.) was added under nitrogen. The solution was stirred at reflux for 30 min then poured into 1M hydrochloric acid (5 ml) and brine (5 ml) was added. The layers were separated and the aqueous phase was extracted with ethyl acetate (3 x 10 ml). The combined organic extracts were dried and evaporated to dryness. The $^1$H n.m.r. spectrum showed only aliphatic compounds had been isolated.

(ii) N-Ethenyl-2-pyrrolidin-1-ylcyclopent-1-ene-1-carboxamide (61) (145 mg, 0.71 mmol) was dissolved in dry tetrahydrofuran and methyllithium (0.85M, 0.8 ml, 1 eq.) was added and the solution was refluxed for 1h. The reaction was worked up as above. $^1$H n.m.r. spectroscopy showed that no reaction had occurred, but the starting material had partly decomposed during work-up.

Methyl Hydrogen Maleate

Sodium (8.9 g) was dissolved in methanol (200 ml), the resulting solution of sodium methoxide was added to maleic anhydride (38 g, 0.39 mol). The solution was cooled, the solvent was removed and the residual gum was acidified with 3M hydrochloric acid (50 ml) and then extracted with dichloromethane (4 x 30 ml). The combined organic extracts were dried and evaporated to dryness leaving methyl hydrogen maleate. $^1$H n.m.r. $\delta$ 3.78, s, 3H; 6.28, s, 2H; 9.93, s, 1H.

Methyl (E) Chloroformylpropenoate

Methyl hydrogen maleate (50 g, 0.38 mmol) was heated with thionyl chloride (30 ml, 1.1 equiv.) at 40° for 30 min. The volatile material was removed under reduced pressure leaving methyl (E) chloroformyl-propenoate $\nu_{max}$ 1780 $cm^{-1}$.

Methyl (E) 3-Isocyanatopropenoate (64).

(i) Methyl (E) chloroformylpropenoate (from above) was immediately dissolved in toluene (100 ml) and cooled to 5° and added to a solution of sodium azide (31 g, 1.3 equiv.) in water (150 ml) at 5°. The two phase mixture was stirred vigorously for 5 min. An infrared spectrum of the toluene phase showed that the acyl azide had formed and that no acyl chloride remained ($\nu_{max}$ 2150, 1760 $cm^{-1}$). The phases were separated and the organic phase was washed successively with aqueous sodium carbonate (3 x 20 ml) and water (3 x 20 ml). The organic solution was then dried with anhydrous calcium chloride.

The acyl azide was then decomposed by refluxing the toluene solution over 1,3-dinitrobenzene for 2h. The toluene was then removed under reduced pressure and the residue was distilled at 50°/0.01 mm. Methyl (E) 3-isocyanatopropenoate (64) was collected as a solid 3.5 g (7% overall) m.p. 52-54° (Found: $M^{+\cdot}$ 127.02710. Calc. for $C_5H_5NO_3$: $M^{+\cdot}$ 127.02694). $\nu_{max}$ 2270 (NCO), 1725, 1645 $cm^{-1}$. $^1H$ n.m.r. $\delta$ 3.68, s, 3H, $OCH_3$; 5.71, d, J 13Hz, 1H, N-C=CH; 7.15, d, J 13Hz, 1H N-CH=C. Mass spectrum m/e 128 (M+1), 127 (M), 96 (M-$OCH_3$).

Methyl (E) 3-(Methoxycarbonylamino)propenoate

Methyl (E) 3-isocyanatopropenoate (64) (347 mg, 2.73 mmol) was

cooled in ice and methanol (111 µl, 87 mg, 1 equiv.) was added; the reaction was instantaneous and left a white powdery solid (399 mg, 2.51 mmol, 92%). Recrystallization from methanol afforded methyl (E) 3-(methoxycarbonylamino)propenoate as white crystals m.p. 172.5-173° (Found: C, 45.5; H, 5.9; N, 8.8. $C_6H_9NO_4$ requires C, 45.3; H, 5.7; N, 8.8%). $\nu_{max}$ 3280 (NH), 1750, 1705, 1695, 1630 $cm^{-1}$. $^1H$ n.m.r. δ 3.67, s, 3H, $OCH_3$; 3.77, s, 3H, $OCH_3$; 5.32, d, J 13Hz, 1H, N-C=CH; 7.0-7.7, m, 2H. Mass spectrum m/e 159 (M), 128 (M-OCH ), 100 (M-$CO_2CH_3$), 96 (M-(2 x $OCH_3$ + H)).

Methyl (E) 3-(2-Pyrrolidin-1-ylcyclopent-1-en-1-ylcarbonylamino)-propenoate (65).

Methyl (E) 3-isocyanatopropenoate (64) (415 mg, 3.27 mmol) was dissolved in dry acetonitrile (10 ml) under nitrogen with stirring, 1-pyrrolidin-1-ylcyclopent-1-ene (60) (0.48 ml, 1 equiv.) was added and the solution was stirred for 10 min and then cooled in ice. The solid which formed was collected and washed with cold dry acetonitrile. Methyl (E) 3-(2-pyrrolidin-1-ylcyclopent-1-en-1-ylcarbonylaminopropenoate (65) (143 mg, 17%) was recrystallized from dry degassed acetonitrile and was collected as colourless needles m.p. 165-166° (Found: C, 63.6; H, 7.2; N, 10.3. $C_{14}H_{20}N_2O_3$ requires C, 63.6; H, 7.6; N, 10.6%). $\nu_{max}$ 1715, 1665, 1615, 1600 $cm^{-1}$. $^1H$ n.m.r. δ 1.6-2.1, m. 6H; 2.4-2.6, m, 4H; 3.2-3.6, m, 4H; 3.64, s, 3H, $OCH_3$; 5.20, d, J 13Hz, 1H, N-C=CH; 7.23, d, J 12Hz, $W_{h/2}$ 7Hz, 1H, NH; 8.08, dd, J 12,13Hz, 1H, N-C(H)=C. Mass spectrum m/e 264 (M), 164.

Methyl (Z) 3-(2-Pyrrolidin-1-ylcyclopent-1-en-1-ylcarbonylamino)-propenoate (66).

(i) Methyl (E) 3-(2-pyrrolidin-1-ylcyclopent-1-en-1-ylcarbonylamino) propenoate (65) (31 mg, 0.12 mmol) was dissolved in dry tetrahydrofuran (5 ml) with stirring under nitrogen, then sodium hydride (8.5 mg, 1.5 equiv.) was added and the mixture was stirred at 20° for 1h. The solution was poured into 1M hydrochloric acid (5 ml) and the layers were shaken and separated, the aqueous phase was extracted with dichloromethane (3 x 5 ml) the combined organic extracts were dried and the solvent removed. Methyl (Z) 3-(2-pyrrolidin-1-ylcyclopent-1-en-1-ylcarbonylamino)propenoate (66) (24 mg, 78%) was isolated as a white solid (Found: $M^{+\cdot}$ 264.14855. Calc. for $C_{14}H_{20}N_2O_3$, $M^{+\cdot}$ 264.1474). $\nu_{max}$ ($CCl_4$) 3350 (NH), 1730, 1695, 1615, 1550 $cm^{-1}$. $^1H$ n.m.r. $\delta$ 1.6-2.1 m, 6H; 2.4-2.9, m, 4H; 3.2-3.6, m, 4H; 3.67, s, 3H, $OCH_3$; 4.88, d, J 9Hz, 1H, N-C=CH; 7.50, dd, J 9, 10Hz, 1H, N-C(H)=C; 10.12, d, J 10Hz, NH. Mass spectrum m/e 264 (M), 164.

(ii) Methyl (E) 3-(2-pyrrolidin-1-ylcyclopent-1-en-1-ylcarbonylamino)-propenoate (65) (32 mg, 0.12 mmol) was dissolved in trifluoroacetic acid (0.5 ml) and equilibrated at 35°, the course of the reaction was followed by $^1H$ n.m.r. spectroscopy. After 10 min the spectrum was of the starting material (65). $^1H$ n.m.r. ($CF_3CO_2H$) $\delta$ 2.1 2.6, m, 8H; 2.8-3.2, m, 2H; 3.7-4.3, m, 7H (including $\delta$ 3.86, s, 3H, $OCH_3$); 5.94, d, J 14Hz, 1H, N-C=CH; 7.93, dd, J 14, 11Hz, 1H, N-C(H)=C; 9.43, d, J 11Hz, 1H, NH.

After 60h $^1H$ n.m.r. ($CF_3CO_2H$) $\delta$ 2.1-2.6, m, 8H; 2.8-3.2, m, 2H; 3.7-4.3, m, 7H (including 3.86, s, 3H); 5.60, d, J 9Hz, 0.7H; 5.95,

d, J 14Hz, 0.3H; 7.43, dd, J 9,11Hz, 0.7H; 7.93, dd, J 14,11Hz, 0.3H.

There was no change in the $^1$H n.m.r. spectrum after 130h. So a 7:3 mixture of (66) and (65) had been formed.

(iii) Methyl (E) 3-isocyanatopropenoate (64) (1.41 g, 11.1 mmol) and 1-pyrrolidin-1-ylcyclopent-1-ene (60) (1.62 ml, 11.1 mmol) were mixed in benzene and refluxed for 20h. On cooling the crystallized product was collected (490 mg, 17%). The product, methyl (Z) 3-(2-pyrrolidin-1-ylcyclopent-1-en-1-ylcarbonylamino)propenoate (66) was identical with that obtained above.

Reaction of Methyl (E) 3-(2-Pyrrolidin-1-ylcyclopent-1-en-1-ylcarbonyl-amino)propenoate (65) with Methyl Toluenesulfonate

Methyl (E) 3-(2-pyrrolidin-1-ylcyclopent-1-ene-1-ylcarbonyl-amino)propenoate (65) (104 mg, 0.39 mmol) was dissolved in acetonitrile (10 ml) and methyl toluenesulfonate (87 mg, 1.2 equiv.) was added and the solution was refluxed for 12h. The solvent was removed and the $^1$H n.m.r. spectrum revealed a complex mixture.

The Reaction of Vinylisocyanate (59) with 5,5-Dimethyl-3-pyrrolidin-1-ylcyclohex-2-en-1-one (67).

5,5-Dimethyl-3-pyrrolidin-1-ylcyclohex 2-en-1-one (67)[106] (1.48 g, 7.7 mmol) was dissolved in acetonitrile (20 ml) at 20° and vinylisocyanate (59) (0.8 ml, 2 equiv.) was added. After stirring for 30 min the solvent was removed under reduced pressure. $^1$H n.m.r. spectroscopy showed that the residue was a mixture of the starting ketone (67) and 1,3,5-triethenyl-s-triazine-2,4,6 (1H,3H,5H)-trione (62) and nothing else. $^1$H n.m.r. $\delta$ 1.08, s; 1.8-2.1, m; 2.12, s; 2.27, s; 3.31,

br s, $W_{h/2}$ 16Hz; 4.93, s; 5.28, d, J 9Hz, 5.74, d, J 16Hz, 6.63, dd, J 9, 16Hz. The spectrum of (67) is $^1$H n.m.r. δ 1.08, s, 6H; 1.8-2.1, m, 4H; 2.12, s, 2H; 2.27, s, 2H; 3.31, br s, $W_{h/2}$ 16Hz, 4H; 4.93, s, 1H.

Reaction of Methyl 3-Isocyanatopropenoate (64) with 5,5-Dimethyl-3-pyrrolidin-1-ylcyclohex-2-en-1-one (67).

Methyl (E) 3-isocyanatopropenoate (64) (441 mg, 3.47 mmol) and 5,5-dimethyl-3-pyrrolidin-1-ylcyclohex-2-en-1-one (67) (682 mg, 3.53 mmol, 1.0 equiv.) were mixed together in acetonitrile (5 ml) and the solution was refluxed for 30 min. On cooling the solvent was removed. $^1$H n.m.r. spectroscopy revealed that the starting enaminoketone (67) remained and a trace of a decomposed isocyanatoester was present.

Attempted Thioketalization of 4,4-Dimethyl-3-pyrrolidin-1-ylcyclohex-2-en-1-one (67).

The method of Sondheimer and Rosenthal[132] was used. 5,5-Dimethyl-3-pyrrolidin-1-yl-cyclohex-2-en-1-one (67) (6 g, 31 mmol) and 1,2-ethanedithiane (7 ml, 83 mmol, 2.7 equiv.) were cooled in ice and then boron trifluoride etherate (7 ml) was added to the suspension. The mixture was stirred and became homogeneous after 30 min. Then methanol (60 ml) was added and the solution was cooled in ice. The volatile material was removed and the residual oil was examined by $^1$H n.m.r. spectroscopy. Crude material $^1$H n.m.r. δ 1.12, s, 6H; 1.9-2.7, m, 8H; 3.5-4.0, m, 6H (including 3.89, s); 7.64, br s $W_{h/2}$ 6Hz, 1H. The material decomposed on attempted crystallization from ether/light petroleum.

Attempted Reduction of 5,5-Dimethyl-3-pyrrolidin-1-yl)cyclohex-2-en-1-one (67)

5,5-Dimethyl-3-pyrrolidin-1-ylcyclohex-2-en-1-one (67) (4.7 g, 24 mmol) was dissolved in dry ether (30 ml) and lithium aluminium hydride (0.5 g, 2 equiv.) was added. The mixture was stirred at 20° for 14h under nitrogen, the yellow colour of (67) faded leaving a clear solution. The reaction was quenched with saturated sodium sulfate, the layers were separated and the aqueous layer was extracted with ether (2 x 30 ml). The combined organic extracts were dried and evaporated to dryness. The solid residue was examined by $^1$H n.m.r. spectroscopy and consisted of 50% (67) and the remaining material was unknown. Crude material $^1$H n.m.r. δ 0.88, s; 1.08, s; 1.3-2.8, m (including 1.8-2.1 m; 2.12, s; 2.27, s); 3.31, br s, $W_{h/2}$ 16Hz; 4.93, s.

Attempted Reaction of 1,1-Dimethoxy-2-azabutadiene (69) with Indenone (70)

Methyl ethenyl carbamate[133] (2.02 g, 20 mmol) was dissolved in dry benzene (10 ml) and the solution was cooled in ice. Methyl fluorosulfonate (1.6 ml, 1 equiv.) was added dropwise with stirring under nitrogen. The solution rapidly turned dark. The solution was then stirred at 0-5° for 30 min. Triethylamine (2.8 ml, 1 equiv.) was added slowly with cooling, the solution turned a light brown colour. Indenone[111] (2.6 g, 20 mmol, 1 equiv.) was added and the solution was stirred for 1h at 5°. The reaction was examined by t.l.c. which showed that the indenone had been unaffected. Heating the solution caused polymerisation of the mixture.

Attempted Formation of 1,1-Dimethoxy-2-azabutadiene (69).

Methyl ethenylcarbamate[133] (1.01 g, 10 mmol) was dissolved in dry carbontetrachloride (10 ml) under nitrogen, the solution was cooled to 5° and methyl fluorosulfonate (0.8 ml, 1 equiv.) was added dropwise. After the addition the solution was stirred at 5° for 30 min and then filtered through a short column of dried potassium carbonate. The filtrate was examined by $^1$H n.m.r. spectroscopy which showed no olefinic material.

5,5-Dimethyl-3-oxocyclohex-1-en-1-yl Ethenylcarbamate (74).

5,5-Dimethylcyclohexane-1,3-dione (914 mg, 6.5 mmol) was partly dissolved in dry dichloromethane (20 ml), vinylisocyanate (0.4 ml, 1.2 equiv.) was added and the mixture was stirred at 20° until the solution became homogeneous (30 min). The solvent was removed under vacuum leaving a white solid (1.33 g). 5,5-Dimethyl-3-oxocyclohex-1-en-1-yl ethenylcarbamate (74) was recrystallized from dichloromethane and light petroleum (1.08 g, 79%) m.p. 147-149°. $\nu_{max}$ 3340, 1735, 1660, 1623 cm$^{-1}$. $^1$H n.m.r. $\delta$ 1.08, s, 6H, 2 x $CH_3$; 2.25, s, 2H, $CH_2$-C=O; 2.45, d, J 1Hz, 2H, $CH_2$-C=CH; 4.38, d, J 8Hz, 1H; 4.63, d, J 16Hz, 1H; 5.90, t, J 1Hz, 1H; 6.53, d,d,d, J 8,16,10Hz, 1H, HN-C(H)=$CH_2$; 7.63, d, J 10Hz, 1H, NH. A mass spectrum could not be obtained.

Reaction of 5,5-Dimethyl-3-oxocyclohex-1-en-1-yl Ethenylcarbamate (74) with Base.

(i) 5,5-Dimethyl-3-oxocyclohex-1-en-1-yl ethenylcarbamate (74) (124 mg, 0.59 mmol) was dissolved in dichloromethane (5 ml) and dry triethylamine (1 drop) was added, the solution was stirred at 20° for 10 days.

The solvent was removed under reduced pressure. The residue (107 mg) was examined by $^1$H n.m.r. spectroscopy and was identical with a mixture of 1,3,5-triethenyl-s-triazine-2,4,6(1H,3H,5H)-trione (62), dimedone, triethylamine, and some 1,8-dioxo-3,3,6,6,9-pentamethyl-1,2,3,4,5,6,7,8-octahydro-9(H)-xanthene (77), all identical by $^1$H n.m.r. spectroscopy and t.l.c. with authentic samples.

(ii) 5,5-Dimethyl-3-oxocyclohex-1-en-1-yl ethenylcarbamate (74) (545 mg, 2.6 mmol) was sealed in a test tube containing dry triethylamine (2 drops). The sealed tube was heated at 120° for 15 min. The resulting red oil was examined by $^1$H n.m.r. spectroscopy and was a mixture of 1,3,5-triethenyl-s-triazine-2,4,6(1H,3H,5H)-trione (62) and decomposed 5,5-dimethylcyclohexane-1,3-dione. $^1$H n.m.r. δ 1.08, s, 1.22, t, J 7Hz, 14H; 1.7-2.5, m, 8H; 2.93, q, J 7Hz, 2H; 5.28, d, J 9Hz, 1H; 5.74, d, J 16Hz, 1H; 6.63, dd, J 9,16Hz, 1H.

(iii) 5,5-Dimethyl-3-oxocyclohex-1-en-1-yl ethenylcarbamate (74) (553 mg, 2.6 mmol) was treated as above. The product obtained (412 mg) was a mixture of 5,5-dimethylcyclohexane-1,3-dione, 2,2'-ethylidenebis-[5,5-dimethyl-1,3-cyclohexanedione] (76), 3,4,6,7-tetrahydro-3,3,6,6,9,-pentamethylxanthene-1,8(2H,5H)-dione (77) and 1,3,5-triethenyl-s-triazine-2,4,6(1H,3H,5H)-trione (62), all were identical by $^1$H n.m.r. spectroscopy and t.l.c. with authentic samples.

Reaction of 5,5-Dimethylcyclohexane-1,3-dione with Sodium Hydride and Vinylisocyanate (59).

5,5-Dimethylcyclohexane-1,3-dione (931 mg, 6.65 mmol) was dissolved in dry tetrahydrofuran (20 ml) and sodium hydride (320 mg) was added. After stirring for 30 min at 20° vinylisocyanate (0.33 ml, 1 equiv.) was

added and the mixture was stirred for 30 min. The mixture was poured into 1M hydrochloric acid (5 ml) followed by brine (10 ml) and extracted with dichloromethane (3 x 15 ml). The combined organic extracts were dried and evaporated to dryness. The residue (1.12 g) was shown by $^1$H n.m.r. spectroscopy to be a mixture of 5,5-dimethylcyclohexane-1,3-dione and 1,3,5-triethenyl-s-triazine-2,4,5(1H,3H,5H)-trione (62).

Reaction of 5,5-Dimethyl-3-methoxycyclohex-2-en-1-one and 5,5-Dimethyl-3-oxocyclohex-1-en-1-yl Acetate with Vinylisocyanate.

The title compounds (0.4 ml) were separately mixed with vinylisocyanate (0.2 ml) in a n.m.r. sample tube and the reaction was followed by $^1$H n.m.r. spectroscopy. After 2 days no change in the starting materials could be observed.

Reaction of 5,5-Dimethylcyclohexane-1,3-dione with Vinylisocyanate (59) in Acetonitrile.

(i) 5,5-Dimethylcyclohexane-1,3-dione (1.04 g, 7.44 mmol) was dissolved in dry acetonitrile (20 ml) and vinylisocyanate (59) (0.37 ml, 1.0 equiv.) was added at 20°. The mixture was stirred for 1h and the solvent was removed under reduced pressure. The residue (1.47 g, 96%) $\nu_{max}$ 3200, 1630 cm$^{-1}$. $^1$H n.m.r. $\delta$ 1.08, s, 6H, 2 x $CH_3$; 2.42, s, 4H, 2 x $CH_2$-CO; 4.54, d, J 8.5Hz, 1H; 4.78, d, J 15Hz, 1H; 6.93, ddd, J 8.5, 15, 11.5Hz, 1H, N-C(H)=C; 11.44, d, J 11.5Hz, 1H, NH. The compound decomposed on attempted purification and the compound was not stable to mass spectrometry conditions, but was identified as 4,4-dimethyl-2,6-dioxo-N-ethenylcyclohexan-1-ylcarboxamide (75).

(ii) 5,5-Dimethylcyclohexane-1,3-dione (870 mg, 6.21 mmol) was dissolved in dry acetonitrile (20 ml) and vinylisocyanate (59) (0.3 ml, 1.0 equiv.) was added at 20°, as above. The work up was as described for part (i). The product mixture consisted of 5,5-dimethyl-3-oxo-cyclohex-1-en-1-yl ethenylcarbamate (74) and 4,4-dimethyl-2,6-dioxo-N-ethenylcyclohexane-1-ylcarboxamide (75) (1:1) (1.21 g, 96%).

Reaction of 5,5-Dimethylcyclohexane-1,3-dione with Vinylisocyanate in the Presence of Boron Trifluoride

5,5-Dimethylcyclohexane-1,3-dione (1.17 g, 8.4 mmol) was partly dissolved in dry dichloromethane (20 ml) and boron trifluoride etherate (48%, 0.5 ml) was added and the solution became homogeneous. Vinylisocyanate (0.45 ml, 9 mmol, 1 equiv.) was added and the resulting solution was stirred at 15° for 15h. The solution was washed with 2M sodium hydroxide (10 ml), then washed with water (5 ml), dried and evaporated to dryness leaving a pale yellow viscous oil (1.41 g). The oil was chromatographed on silica with ethylacetate and two compounds were isolated. 4,7,7-Trimethyl-3,4,7,8-tetrahydrobenz[1,3]oxazine-2,5(6H)-dione (78) (0.79 g, 45%) was recrystallized from ether/light petroleum and gave white crystals m.p. 131-134° (Found: C, 63.55; H, 6.86; N, 6.36. $C_{11}H_{15}NO_3$ requires C, 63.14; H, 7.23; N, 6.69%). $\nu_{max}$ 3260, 1765, 1715, 1665, 1380 $cm^{-1}$. $^1H$ n.m.r. $\delta$ 1.11, s, 6H, 2 x $CH_3$; 1.34, d, J 6Hz, 3H; 2.28, s, 2H; 2.39, s, 2H; 4.32, dq, J 2,6Hz, 1H; 7.17, d, J 2Hz, 1H, N H. Mass spectrum m/e 209 (M).

The other compound was identified as 1,8-dioxo-3,3,6,6,9-pentamethyl-1,2,3,4,5,6,7,8-octahydro-9(H)-xanthene (77) (0.35 g, 29%), recrystallization from ether/light petroleum gave m.p. 176-177°

(lit. 176-177°[116]). $^1$H n.m.r. δ 1.08, s, 12H; 1.12, d, J 6Hz, 3H; 2.25, s, 4H; 2.35, s, 4H; 3.60, q, J 6Hz, 1H.

When the reaction was repeated the ring opened form of (77) was isolated. 2,2'-ethylidenebis[5,5-dimethyl-1,3-cyclohexanedione] m.p. 138-140° (lit. 140-141°[116]). $^1$H n.m.r. δ 1.03, s, 12H; 1.47, d, J 7.5Hz, 3H; 2.23, s, 8H; 4.06, q, J 7.5Hz, 1H.

Reaction of 3-Chloro-5,5-dimethylcyclohex-2-en-1-one (79) with the Anion of Methyl Ethenylcarbamate.

Methyl ethenylcarbamate (789 mg, 7.8 mmol) was dissolved in dry tetrahydrofuran (20 ml) at -60° and methyllithium (0.87M, 9.0 ml, 1 equiv.) was added, until a pink colour formed. Then 3-chloro-5,5-dimethylcyclohex-2-en-1-one (79) (1.24 g, 7.8 mmol, 1 equiv.) was added and the solution was warmed to 20° and stirred for 12h. The reaction was quenched with saturated sodium sulfate solution (30 ml) and then extracted with dichloromethane (4 x 20 ml). The combined organic extracts were dried and evaporated to dryness which left a residual oil (1.59 g).

The oil was chromatographed on silica with dichloromethane which gave methyl 5,5-dimethylcyclohex-1-en-3-on-1-ylcarbamate (81) (198 mg, 13%). $\nu_{max}$ (liquid film) 3340 (br), 1710, 1680, 1615 cm$^{-1}$. $^1$H n.m.r. δ 1.07, s, 6H; 2.23, s, 2H; 2.53, d, J=1.4Hz, 2H; 3.61, s, 3H, $OCH_3$; 6.12, t, J=1.4Hz, 1H. The compound decomposed on attempted purification.

Further elution with dichloromethane/ethyl acetate gave the second component, an oil (830 mg, 41%) which was distilled, methyl 1-(2-chloro-

4,4-dimethyl-6-oxocyclohex-1-en-1-yl)ethylcarbamate (82) had b.p. 120°/0.05 mm (Found: C, 55.2; H, 7.0; N, 5.6. $C_{12}H_{18}ClNO_3$ requires C, 55.5; H, 7.0; N, 5.4%). $\nu_{max}$ (film) 3420 (NH), 1720, 1665, 1610 $cm^{-1}$ $^1H$ n.m.r. $\delta$ 1.05, s, 6H, 2 x $CH_3$; 1.33, d, J 7Hz, 3H, $CH_3$; 2.28, s, 2H; 2.62, s, 2H; 3.61, s, 3H, $OCH_3$; 5.51, dq, J 7,10Hz, 1H, $CH_3CH$-NH; 6.02, br d, J 10Hz, 1H, NH. Mass spectrum m/e 261, 259 (M), 246, 244 (M-$CH_3$), 224 (M-Cl).

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