SYNTHESIS OF ANTICANCER COMPOUNDS

A thesis presented by

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ABSTRACT

This thesis discusses the synthetic procedures developed for the construction of platinum - intercalator compounds, potential anticancer agents.

Two synthetic areas have been investigated: the field of diamine synthesis is reviewed, and a mild new method of diamine formation has been developed. Also a concise method for the synthesis of the intercalator ellipticine has been achieved.

The basis for the new mild method of diamine formation was the predicted facile ring opening of 4,5-dihydro-2-trichloromethyl-imidazoles. These compounds were synthesised by a newly developed cyclisation of N-allylamidines.

In addition several new diamines were prepared via the hydrolysis of imidazolinones, synthesised from the cyclisation of isoureas, in turn prepared from the reaction of N-bromosuccinimide and cyanamide with alkenes.

Ellipticine was synthesised by the cycloaddition of 1,4-dimethyl-pyrano[3,4-b]indol-3-one to 3,4-didehydropyridine. Successful achievement of this synthesis involved the development of a new method of generating 3,4-didehydropyridine by thermal decomposition of 3-(3,3-dimethyltriazen-1-yl)pyridine-4-carboxylic acid.

CONTENTS

ABBREVIATIONS

Apart from the usual chemical abbreviations, the following more specialised abbreviations were used in this thesis:-

THF - tetrahydrofuran

DMF - dimethylformamide

Py - pyridine

Bz - benzyl

Ph - phenyl

DEAD - diethylazodicarboxylate

Ts - p-toluenesulphonyl

NBS - N-bromosuccinimide

NCS - N-chlorosuccinimide

NIS - N-iodosuccinimide

Ac - acetyl

LTA - lead tetraacetate

^{n}Bu - n-butyl

DBU - 1,8-diazabicyclo[5.4.0]undec-7-ene

CHAPTER I

INTRODUCTION

1.0 PLATINUM COMPLEXES AS ANTICANCER COMPOUNDS

The anticancer activity of platinum complexes has been known for nearly twenty years.[1] As with many drugs the initial discovery was completely serendipitous. The first platinum anticancer complex was cis-platin (1),[2] the simplest of molecules.

$$H_3N\diagdown \atop H_3N\diagup Pt \diagup Cl \atop \diagdown Cl$$

(1)
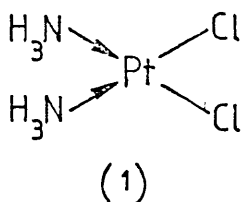
Such was the magnitude of the discovery of platinum anticancer compounds that virtually all modern interest in inorganic compounds as pharmaceuticals stems from it.

The clinical utility of platinum complexes is limited, however, by their toxic side effects,[3] the most serious of these being their nephrotoxicity,[4] although neurotoxicity and nausea are additional minor problems. Since the discovery of cis-platin an immense effort has been made to find out its mechanism of action.[5] This is to enable the design of new platinum complexes which retain the anticancer activity, but are devoid of the side effects.

The molecular mechanism of action of cis-platin is believed to involve interaction with D.N.A. Studies on D.N.A. with varying G:C - A:T ratios[6] suggest that guanine is a major reaction site. This is thought to be due to the formation of a closed ring chelate (2) of cis-platin with guanine.[7] The chelate is thought to form due to the fact that, once cis-platin has linked to the N-7 position of guanine, other base pairs are out of reach and it binds the guanine oxygen
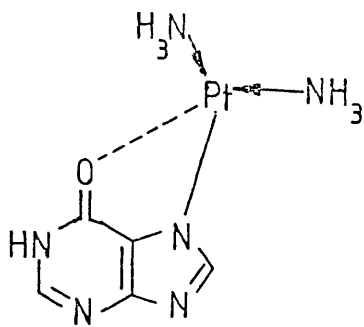
(2)

instead.   The control of replication occurs as the D.N.A. unwinds.

During the untwisting of the strands of D.N.A. base pairs on the

opposite strand approach the cyclic chelate close enough to enable the

oxygen ligand to be displaced for the nitrogen of a base pair.   This

forms a tetra-amine complex (3) which is very stable and thus stops

further replication.
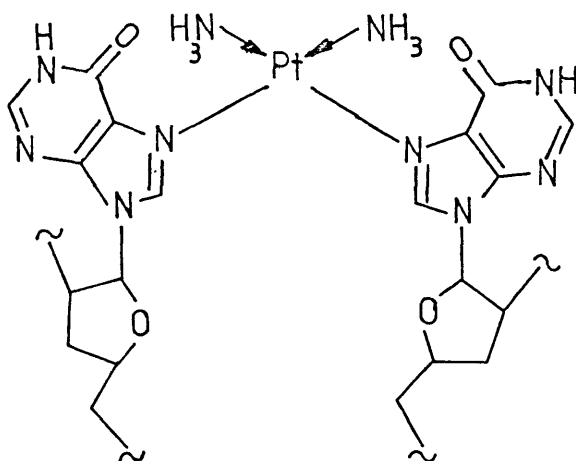
(3)

1.1 THE DEVELOPMENT OF NEW PLATINUM ANTICANCER COMPOUNDS

Attempts to improve the activity of platinum anticancer complexes and remove the side effects, have progressed since the discovery of cis-platin.   Structural changes to the amine side of the molecule have generally not been successful.[8] Anything except a primary aliphatic diamine seems to reduce the activity of the complex. Changes to the reactive side of the molecule are likewise difficult. Having a labile leaving group such as NO_3^- gives rise to highly toxic species.   Strongly bound ligands such as SCN^- and NO_2^- form inactive complexes.   The balance between the two is reached with Cl^- and Br^-.   Recently[9] an improvement in the activity of cis-platin has been achieved by the replacement of chlorine with a cyclic malonate ligand.   This has given rise to a second platinum anticancer drug carbo cis-platin (4).
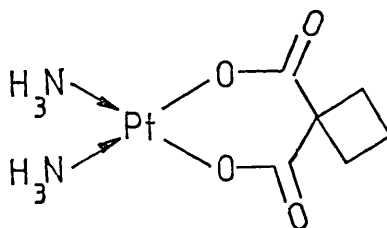
(4)

1.2 INTERCALATORS AS ANTICANCER COMPOUNDS

Another class of anticancer compounds which has been the subject of much research is that of intercalators.[10] The term intercalator is used collectively and refers to their mode of action. The process of intercalation[11] takes place when the drug inserts itself between the coiled strands of D.N.A. Hydrogen bonds are then formed between the intercalator and the four adjacent base pairs, preventing the D.N.A. from unwinding. Several antitumour drugs such as ellipticine (5)[12]

$$CH_3$$

(5)
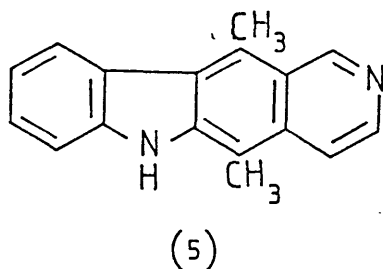
and amino acridines (6)[13] interact with D.N.A. via intercalation.

$$CH_3 \diagdown N \diagup CH_3$$
$$(CH_2)_3$$
$$RN \qquad NO_2$$

$$R = H, CH_3$$

(6)
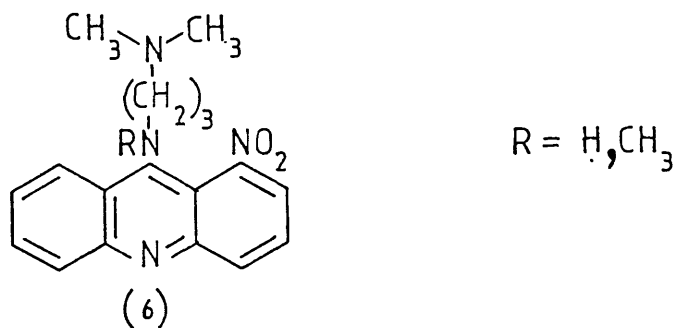
The major problem with this class of compound is that they don't necessarily stay between the base pairs, once intercalation has taken place. Thus there exists an equilibrium between intercalation and non-intercalation. Several methods have been tried to increase the residence time in between D.N.A. base pairs by using bis[14] and tris[15] intercalators. Although these do show increased activity, the same fundamental problem still prevails.

1.3 PLATINUM-INTERCALATOR COMPOUNDS

In view of the immense number of different combinations of ligands tried as a platinum complex, it would appear from an inorganic standpoint that the limits of molecular manipulation have been reached.

In order to improve further the anticancer activity of platinum complexes, it would seem necessary to incorporate them into a molecule capable of delivering them to the active site. Thus this would avoid the toxic side effects.

In principle the type of molecule which would fulfil the requirements would show a selectivity for cancer cells. Thus the anticancer activity of the combined molecule would be synergically increased. This requirement would be met by a molecule such as an intercalator. If the two parts of the molecule thus envisaged were suitably linked together then each should be able to interact with D.N.A. Thus there would be a synergistic increase in the activity. In the type of molecule conceived, the possibilities for incorporating the correct transport and solubility properties are numerous. Thus it should be possible to achieve the right balance.

1.4 THE RETROSYNTHETIC APPROACH

The platinum-intercalator molecules thus conceived in its simplest

form is shown below (7).
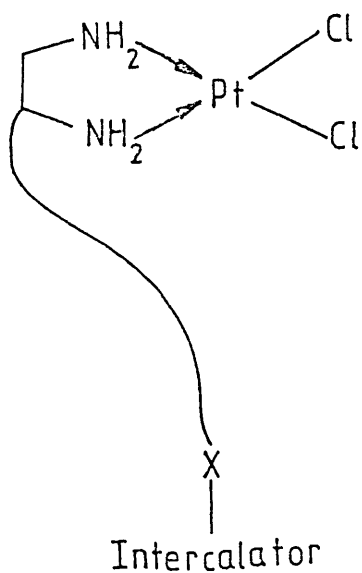
(7)

The fundamental disconnection of the molecule into simpler synthetic

targets is as follows (Scheme 1).
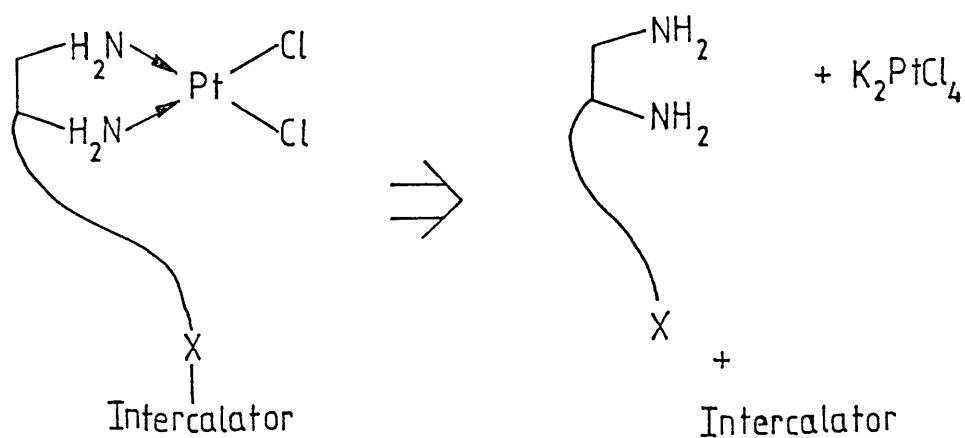
(Scheme 1)

The basic synthetic fragment then, is that of a functionalised 1,2-diamine.

In the current literature there are but a handful of methods by which functionalised diamines are available. All have little scope for flexibility, and use harsh conditions at some point in their synthesis. The development of new facile syntheses of functionalised diamines, has been the main aim of the research described in this Thesis. Similarly intercalators are difficult to prepare and generally are not commercially available. Thus simpler methods of producing intercalators have also been a target.

CHAPTER II

METHODS OF 1,2-DIAMINE SYNTHESIS

2.0 CLASSICAL METHODS

The original approaches to the synthesis of diamines were in effect duplicated methods of amine synthesis. Early attempts involved the reaction of dihalides with ammonia, but this method is very low yielding as might be expected. Ammoniolysis of 2,3-dibromobutane[16] yields mostly 2-bromobut-2-ene, with only a very small amount of 2,3-diaminobutane being produced.

Reduction of dinitro[17] and dioxime[18] type compounds was also explored in attempts to synthesise diamines. Although this type of reduction can proceed in reasonable yield, the actual production of the dinitro or the dioxime is very low yielding. This makes this type of synthesis of little use.

A bis Curtius rearrangement[19,20,21] has also been used as a pathway to diamines starting from diesters. Again the yield is somewhat disappointing.

The first practical approach to diamines was via the ring opening of epoxides and aziridines.[22] In the former method sodium azide is used to ring open an epoxide, forming an azido alcohol (Scheme 2).
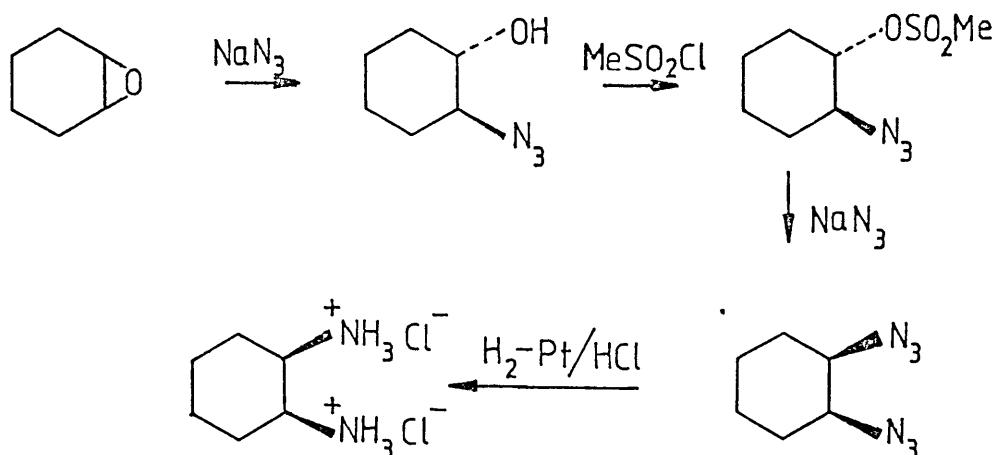
(Scheme 2)

This is then mesylated followed by displacement with sodium azide, yielding a diazide which is then reduced to the diamine. In the case of aziridines, ring opening with sodium azide yields an amino azide (Scheme 3). This is then reduced to the diamine.
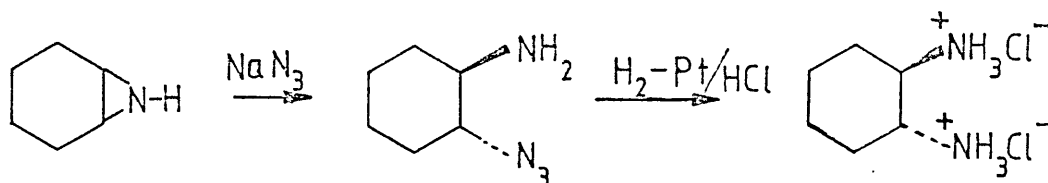
(Scheme 3)

These two methods although several steps long were the first routes to producing stereospecific diamines in good yield.

The use of amino acids as starting materials for diamines is amongst the earliest approaches used. Originally degradation of amino acids to diamino acids was used as a means of clarifying their structures.[23] Later, diamino acids were recognised as being important components of natural products. The two amino acids most suitable for conversion into diamino acids are serine and asparagine. The conversion of serine into 2,3-diaminopropionic acid was first described in 1907 by Emil Fischer[24] (Scheme 4).
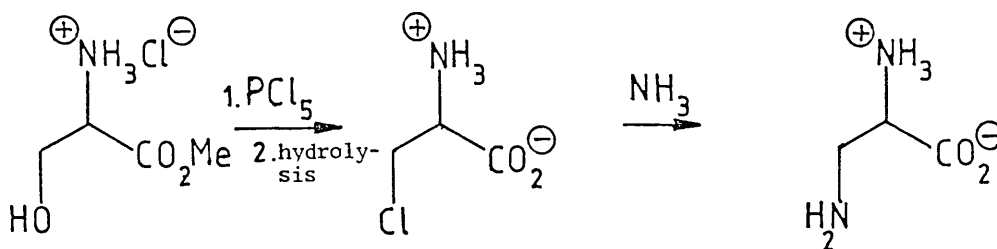
(Scheme 4)

Serine methyl ester hydrochloride is first converted to the chloride

using phosphorus pentachloride.   Hydrolysis of the ester followed by

treatment with ammonia gives the diamino acid.   The later stages of

this procedure are not particularly high yielding.   However, the

recognition of the importance of 2,3-diaminopropionic acid in natural

product synthesis has lead to an improved procedure using the Mitsunobu

reaction.[25]   In this method a displacement of the hydroxy group of

serine with azide, is followed by a mild reduction to give the diamino

acid (Scheme 5).
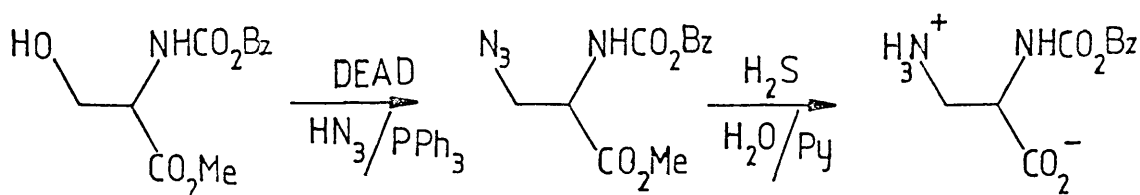
(Scheme 5)

Diaminopropionic acid can also be obtained from asparagine via

a Hofmann rearrangement.   This was first carried out on the N-acetyl

derivative which yielded an imidazolinone (Scheme 6).[26]
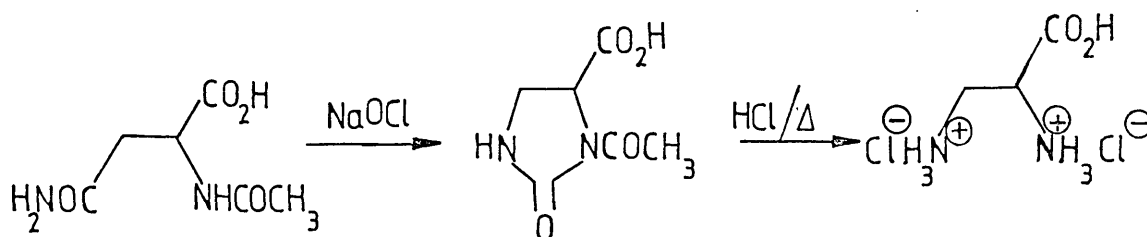
(Scheme 6)

Hydrolysis of the imidazolinone with 5M HCl gave the dihydrochloride of 2,3-diaminopropionic acid. The overall procedure gives a poor yield of the diamino acid. Using the *N*-tosyl derivative of asparagine however, the intermediate imidazolinone does not form and the yield is quite respectable.[27]

Recently a procedure for the conversion of the commercially available *N*-benzyloxycarboxyl-L-asparagine to N^2-benzyloxycarboxyl-2,3-diaminopropionic acid has appeared.[28] This takes place under relatively mild conditions using bis[trifluoroacetoxy]iodobenzene (Scheme 7).
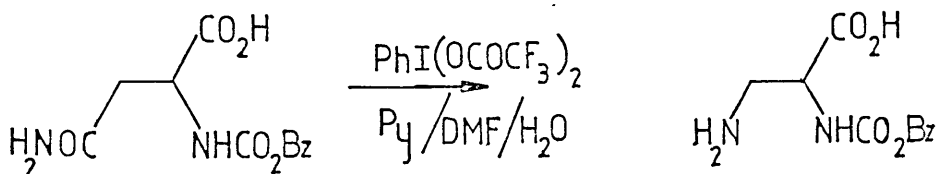
(Scheme 7)

This procedure works in good yield and uses commercially available starting material. Thus it avoids the need to manipulate asparagine into a suitably protected form.

The production of diamines via the reduction of azides figures among many diamine syntheses. Recently there has been much interest in the addition of azides to double bonds,[29,30] the diazide formed being a precursor to diamines. The diazides are formed by reaction of the double bond with sodium azide, in the presence of either manganese (III) acetate[29] or iodosobenzene[30] (Scheme 8). The mechanism of diazide formation is thought to be of a radical nature, involving some kind of manganese-azide or iodosobenzene-azide complex.

$$\text{NaN}_3 + \text{CH}_3\text{CO}_2\text{H} + 2\,\text{PhIO}$$

$$\text{Mn(III)(OAc)}_3 + \text{NaN}_3$$
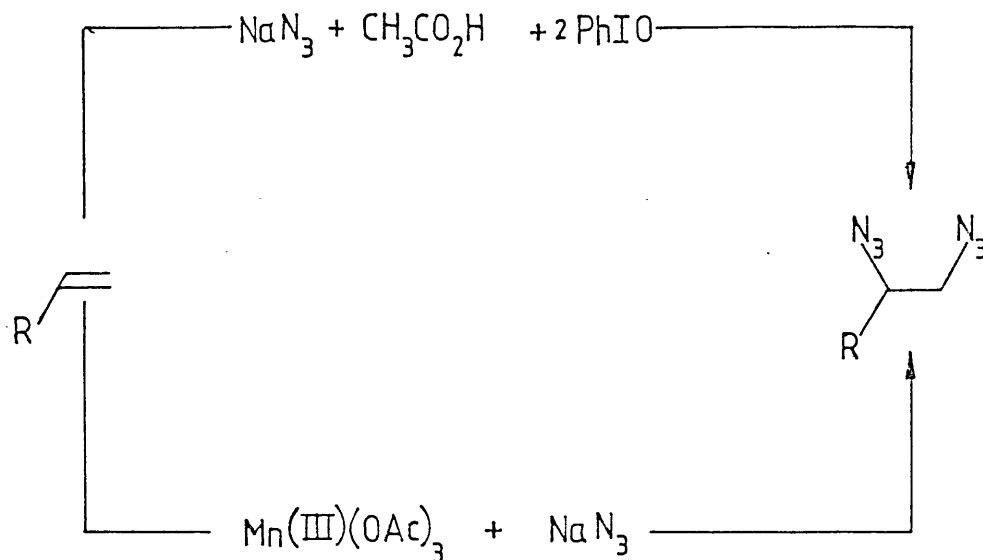
(Scheme 8)

The yields of diazides are high, and the methods seem applicable to a large number of alkenes. The subsequent reduction has been achieved under a variety of conditions with good overall yields.

An alternative to diazide procedures has been demonstrated in the addition of N,N-dichlorourethane to an alkene.[31] This is followed by the displacement of the chloride with a suitable nucleophile (Scheme 9).

$$\text{Cl}_2\text{NCO}_2\text{CH}_2\text{CH}_3 \quad / \quad \text{NaHSO}_3 \qquad \text{Nu}^\ominus$$
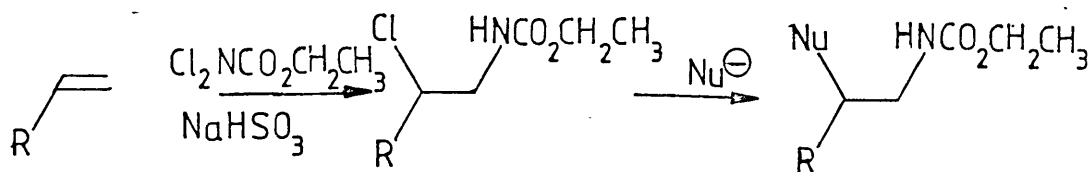
(Scheme 9)

High regioselectivity is obtained when using unsymmetrical alkenes, and the reaction can also proceed stereospecifically. Overall the conditions used are quite mild, however the nucleophiles that can be used are limited to either sodium azide or aromatic amines.

2.1 ORGANOMETALLIC METHODS

The concept of diamine formation via the reaction of alkenes with an organometallic complex, in an analogous manner to diol synthesis, has been a tempting ideal for many chemists. This was first attempted using osmium reagents[32] to mimic the osmium tetraoxide mediated synthesis of diols. The reagent envisaged would be one in which all the oxygens of osmium tetraoxide are replaced by nitrogen. The nearest possible structure to this which is sufficiently stable would be tetrakis(tert-butylimido) osmium (8).

(8)
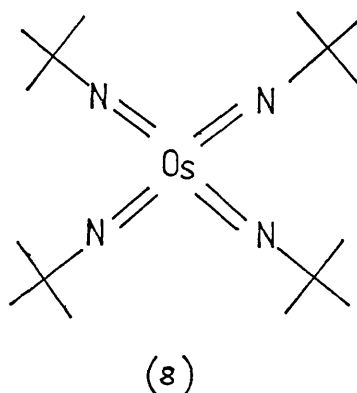
Approaches to this compound have included the reaction of osmium tetraoxide with N-tert-butyl-tri-n-butylphosphinimine (Scheme 10), but only three of the oxygen atoms have been successfully replaced in this way.
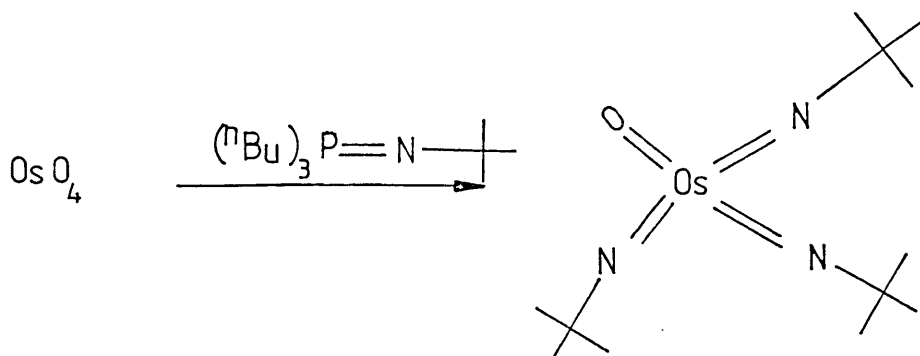
(Scheme 10)

However, using oxotris(tert-butylimido) osmium, diamines have been
synthesised from alkenes in high yield (Scheme 11). Only traces of
amino-alcohols are produced thus implying a strong preference for
nitrogen to add across the double bond.
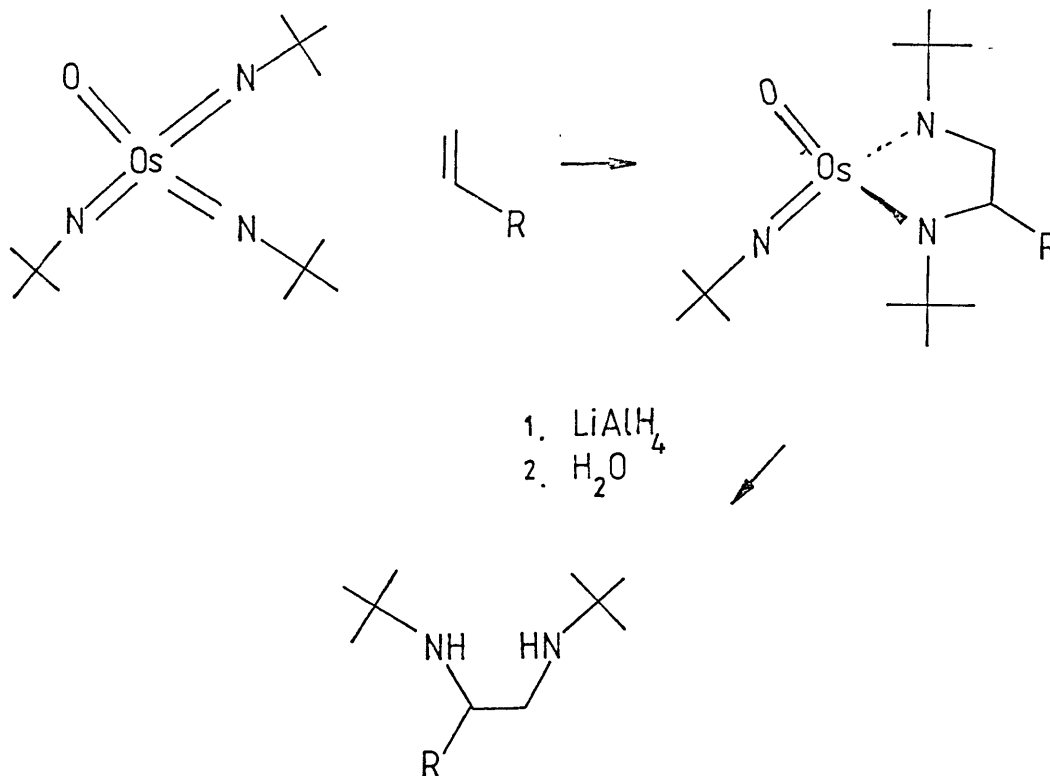
(Scheme 11)

The diamine is then released by reduction of the complex with LiAlH$_4$.
The diamines produced using this method are *cis*-diamines as would be
expected. Although this procedure is effectively one pot, it suffers
from the disadvantage that only ditertiary butyl diamines can be
synthesised in this way.

This problem has been overcome by using organo-cobalt reagents.
Brunner[33] showed that a cyclopentadienylnitrosocobalt dimer could form
an adduct with strained alkenes (Scheme 12). However, it was nine

years later that it was recognised as a potential source of diamines. The work was repeated[34,35] and found to be general for any simple alkene.
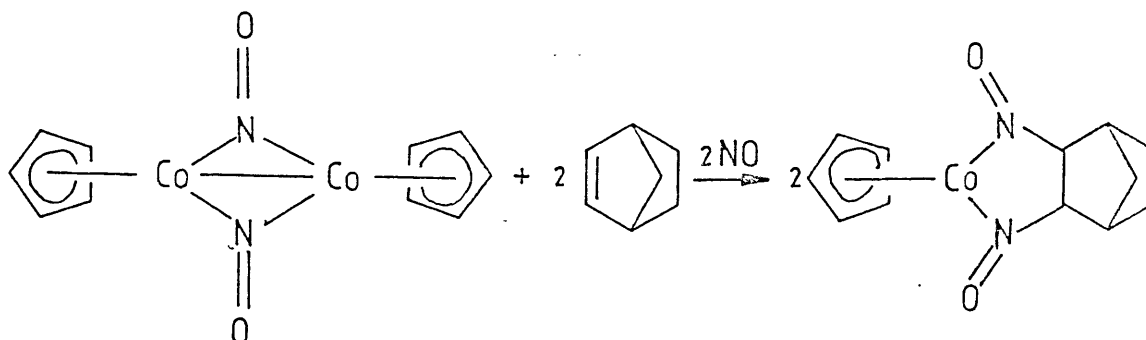
(Scheme 12)

The diamines are liberated from the cobalt complex by reduction using LiAlH₄ (Scheme 13). Yields of diamines produced using metal hydride reductions are high.
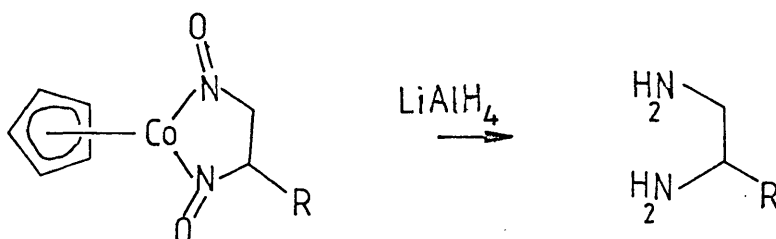
(Scheme 13)

Other methods of removing cobalt from the diamine, such as ligand exchange were not successful. Thus the functional groups with which this method can be used are limited to ones that resist LiAlH₄.

In contrast to the use of osmium and cobalt as a means of inserting ligands into a double bond, diamines have been synthesised from alkenes by the initial formation of a metal alkene complex. First attempts

were made using thallium triacetate alkene complexes.[36]   It was found

that in the presence of aromatic amines a good yield of the diamine was

achieved (Scheme 14).
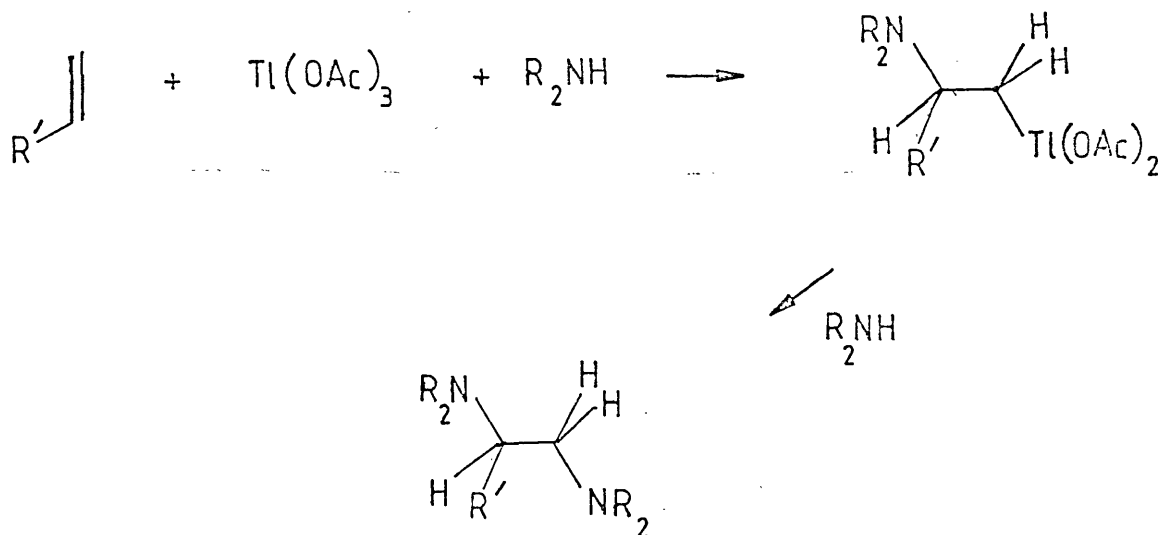
(Scheme 14)

However, the process is strictly limited to aromatic amines as aliphatic

amines do not add to the alkenes.

This type of approach was also attempted using mercury oxide-

tetrafluoroboric acid complexes.[37]   Using this reagent, high yields of

diamines can be achieved.   Again the method is strictly limited to

aromatic amines.

The limitations of the latter methods have been eased slightly by

the use of bis(benzonitrile) palladium dichloride.[38]   The reaction of

alkenes with this compound in the presence of amines gives rise to an

aminopalladation reaction.   These amino palladium compounds are then

converted to diamines by a mild oxidation in the presence of an excess

of the amine (Scheme 15).

$$R-\overset{\|}{\diagup} \quad \longrightarrow \quad \left[\begin{array}{c} R_2N \diagdown \overset{H}{\diagup}H \\ H \diagup \overset{\displaystyle R}{\diagdown} \overset{\displaystyle PdCl}{|} \end{array} \right] \quad \underset{R_2NH}{\overset{\text{OXIDATION}}{\longrightarrow}} \quad R_2N \diagdown \diagup NR_2 \\ \overset{\displaystyle R}{}$$
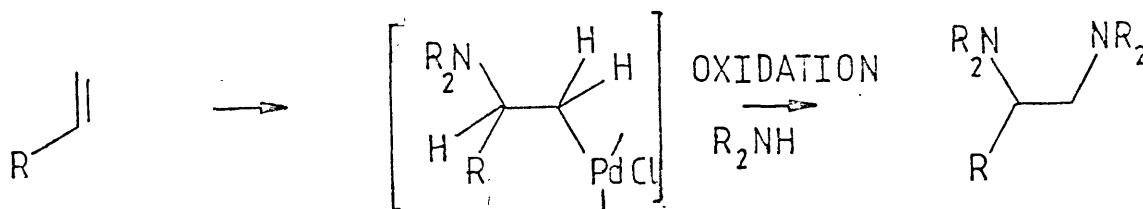
(Scheme 15)

Although it is possible to use aliphatic amines with this procedure, they must be secondary ones.   Also the process only gives small yields with anything other than terminal alkenes.   This is due to the steric requirements of the palladium.

A novel approach to diamines has been made using bisimide type reagents.   The first of this type of compound to be used was a selenium diimide species.[39]   These compounds react with dienes in a Diels-Alder type reaction (Scheme 16) to give selenolactams, which undergo a rearrangement to give protected diamines.   The yield using this reagent however is quite low.

Recently, however, a significant improvement to this type of approach has been effected by using sulphur dioxide bis(imides).[40]   These also react with dienes in a Diels-Alder fashion to give thiazine-1-imines (Scheme 17).   A rearrangement is then undergone, either on treatment with phenylmagnesium bromide, or on heating.   Both methods give rise to protected diamines in high yields.
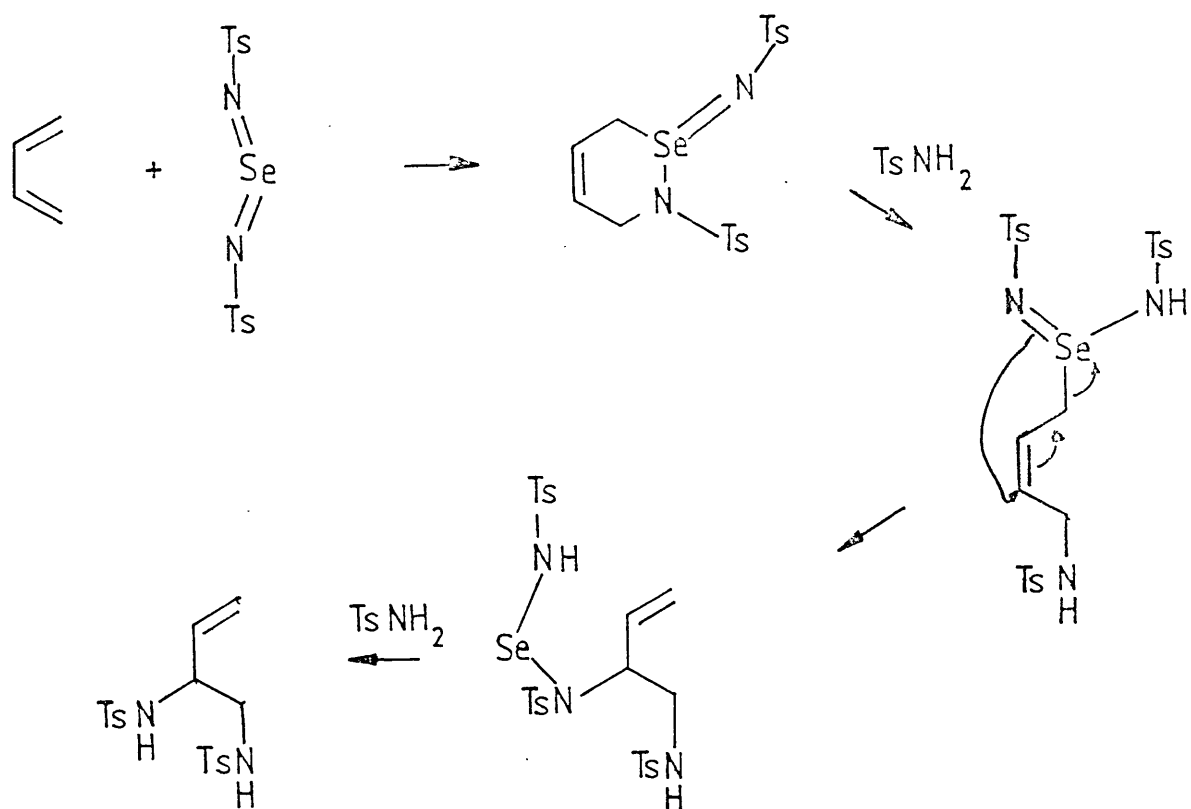
(Scheme 16)
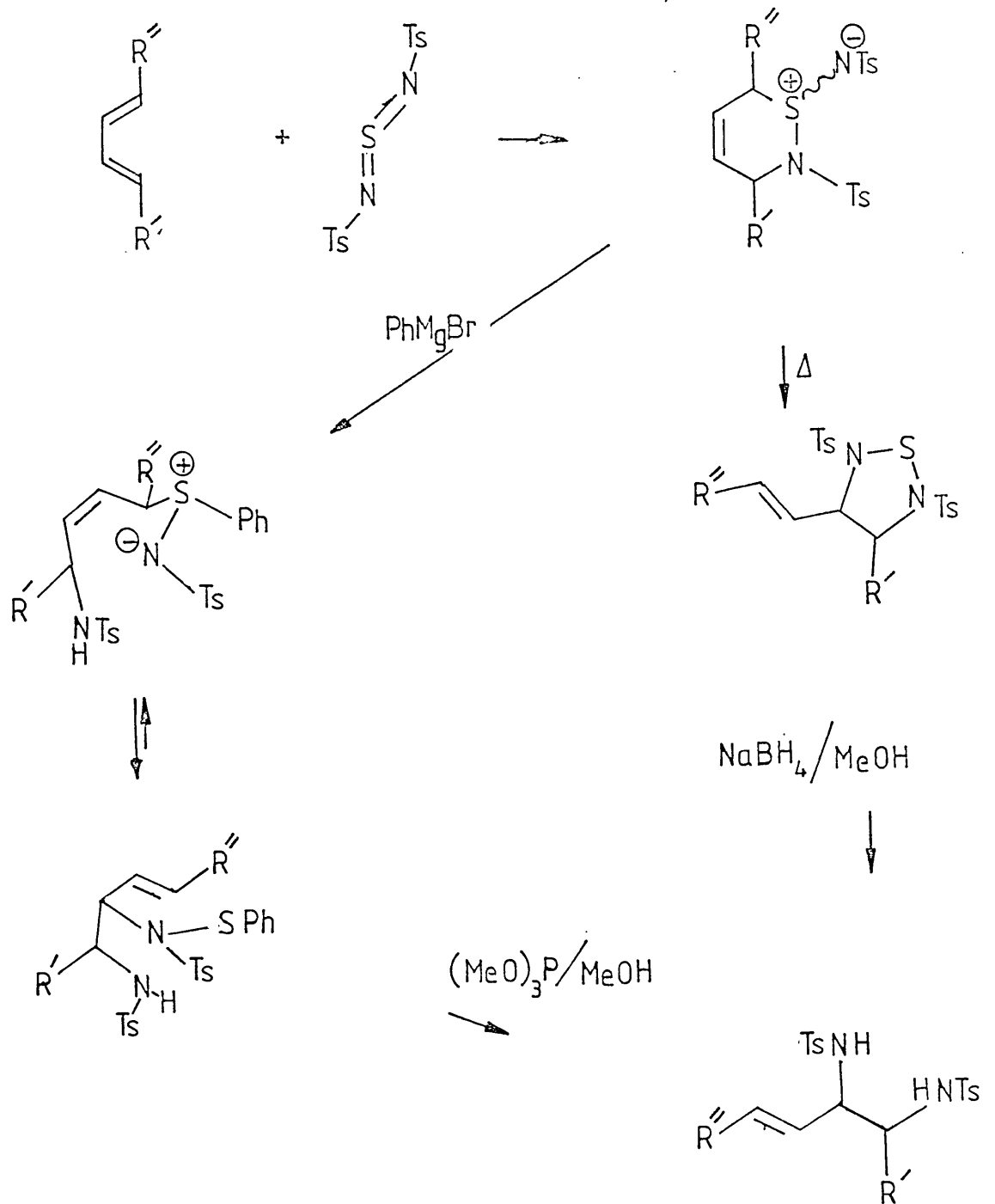
(Scheme 17)

2.2 DIAMINES VIA IMIDAZOLINONES

The cleavage of the imidazolinone ring systems, has traditionally formed the basic method by which diamines are available to the organic chemist. Although the conditions for achieving this cleavage are somewhat harsh there has never been a feasible alternative.

Work on the use of imidazolinones in diamine synthesis has been solely concentrated on constructing the imidazolinone unit on to other molecules. The first method by which this was achieved involved the cycloaddition of an imidazolone in either a (2+2) or (2+4) manner.

Imidazolones are accessible from the commercially available 2-imidazolinones, via oxidation,[41] or from hydantoins by reductive elimination of water.[42]

The method of choice for using imidazolones in cycloaddition reactions is (2+2) photocyclisation.[42,43,44,45] This has been achieved using a range of alkenes to give fused ring imidazolinones in reasonable yield. The (4+2) cycloaddition has also been effected,[42] but the dienes with which this has been successful are limited in number (Scheme 18).

An alternative to the introduction of the imidazolinone unit by cycloaddition is to build this ring system on to some functional group. The functional group of choice has been an alkene. Kohn[46,47] has used this approach with great success (Scheme 19). The reaction of an alkene with cyanamide and N-bromosuccinimide effectively builds on an iso-urea unit. This is then subsequently cyclised to give an imidazoline.
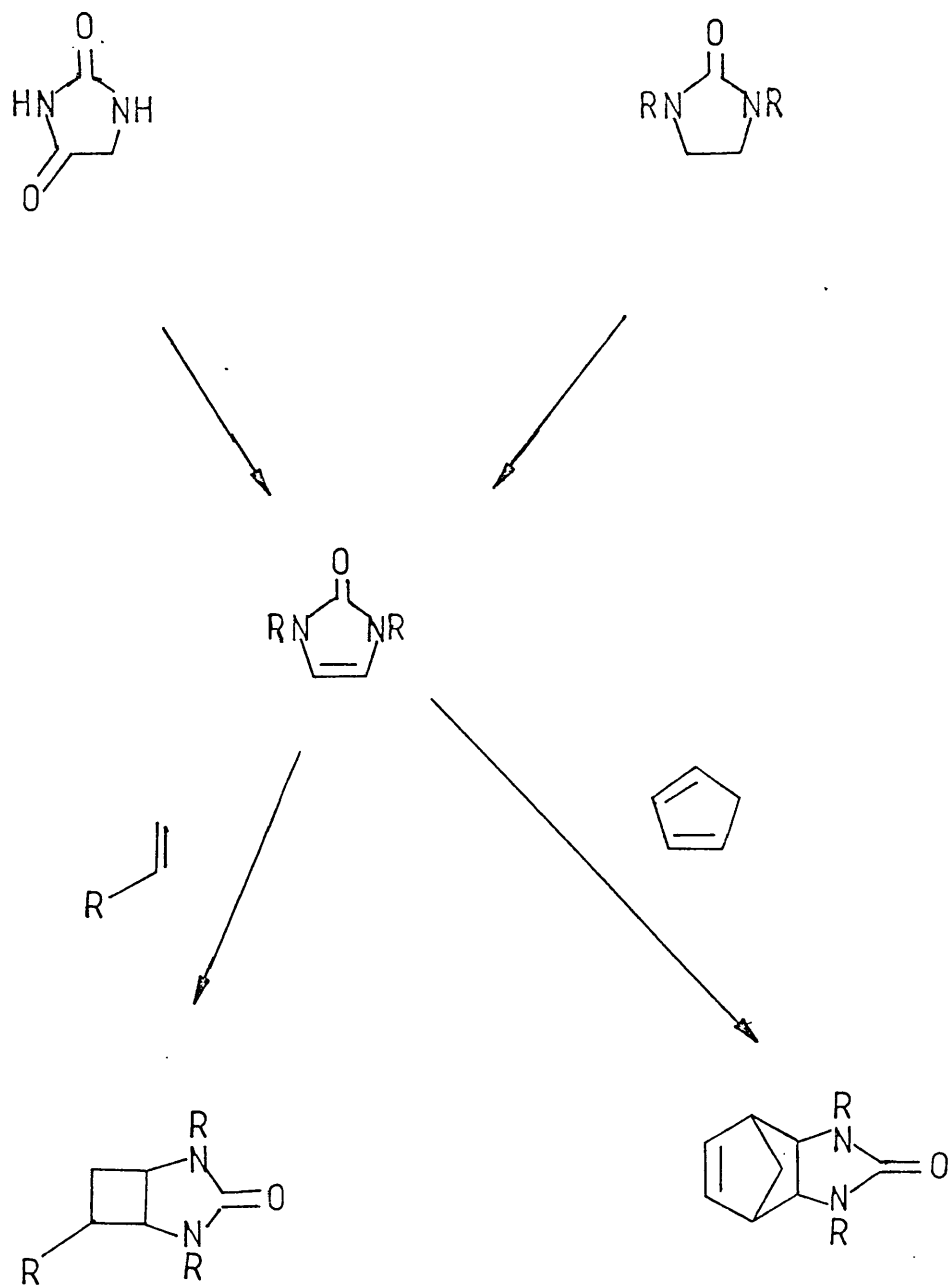
(Scheme 18)
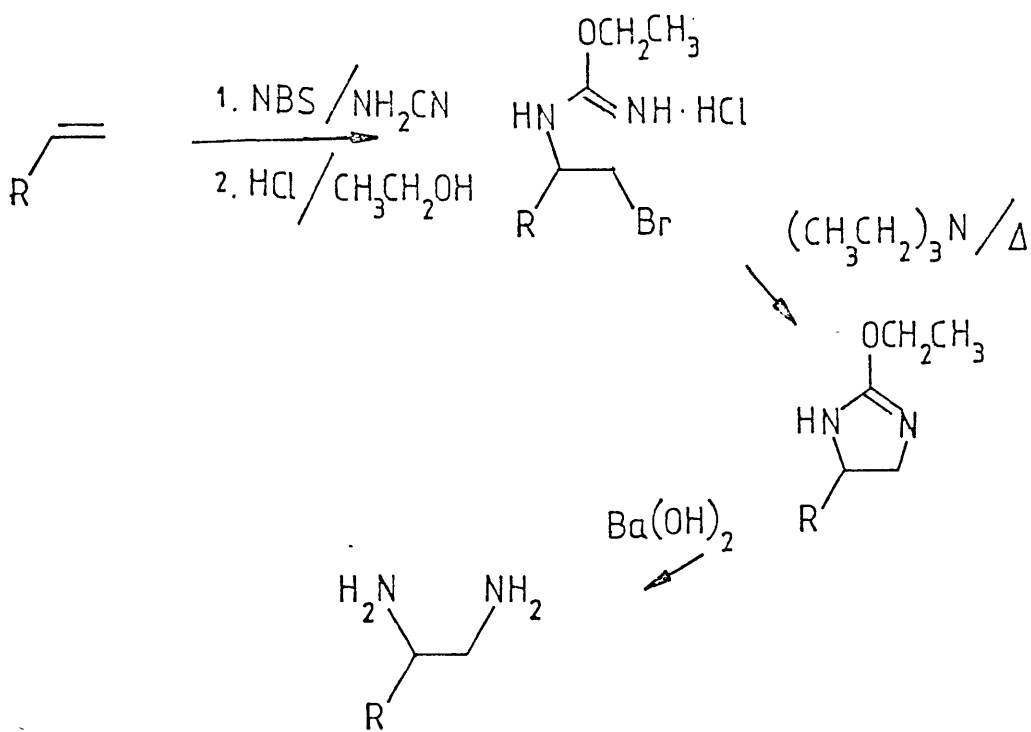
(Scheme 19)

The synthesis overall uses quite mild conditions and has been used with a range of alkenes to give imidazolines in high yield.

The conversion of alkenes to imidazolinones has also been accomplished using a shorter procedure (Scheme 20).[48] Treatment of an alkene with silver isocyanate and iodine gives an iodoisocyanate which on treatment with ammonia followed by acid, leads to an imidazolinone.
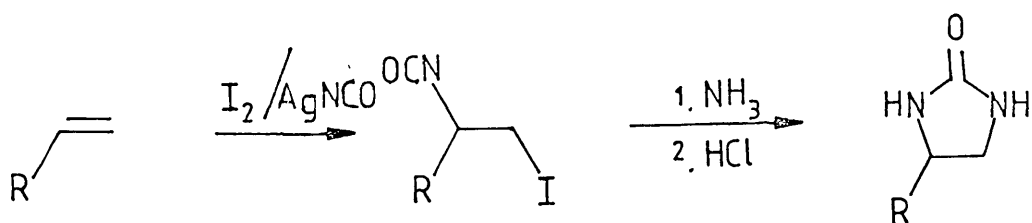
(Scheme 20)

Although somewhat simpler the overall yield of this procedure is not as high as that of Kohn's.

Imidazolinones have been reported to be produced on reduction of hydantoins. However, the original work claimed six products from the reduction of hydantoin. This work was reinvestigated by Kohn,[49] who showed that reduction of hydantoins can lead exclusively to 4-hydroxy imidazolinones. It was also found that reductions at higher temperatures, such as refluxing THF leads to diamines (Scheme 21).
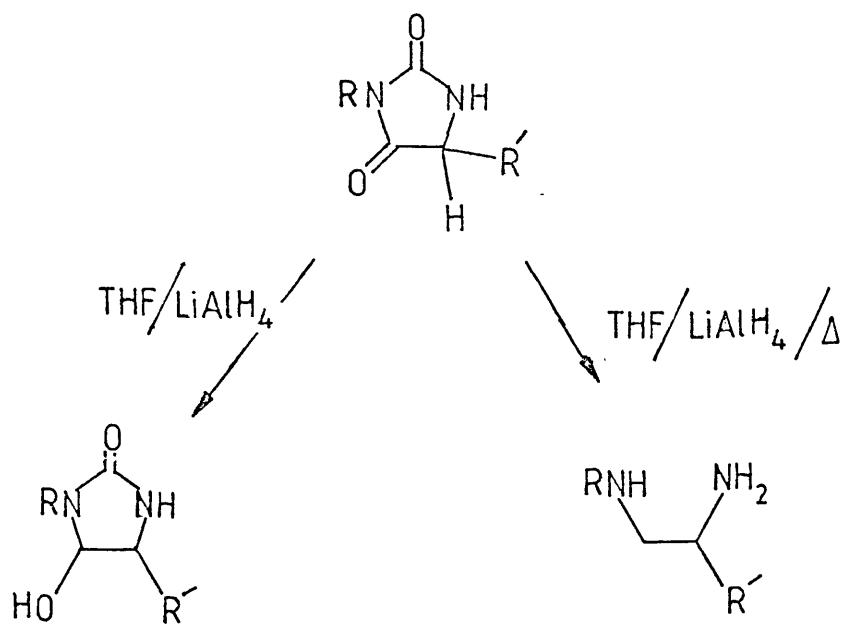
(Scheme 21)

Kohn later used this procedure to build an imidazolinone unit into another molecule.[50,51] Reduction of a 3,3-disubstituted hydantoin, followed by the elimination of water gave rise to an N-amidoyliminium ion (Scheme 22). This was then reacted intramolecularly with an alkene

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CHAPTER III

DISCUSSION : DIAMINE SYNTHESIS

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to give a fused imidazolinone - Kohn showed that this type of cyclis-
ation was possible for both alkenes and alkynes.
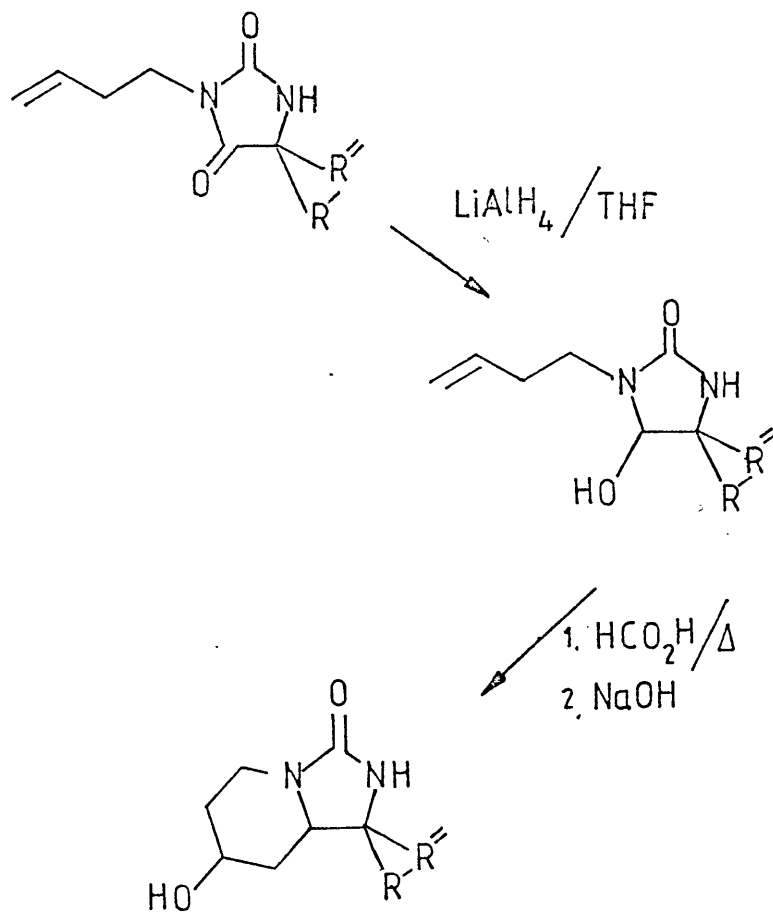
(Scheme 22)

3.0 INTRODUCTION

The type of platinum complex mentioned previously can basically
be constructed from a primary 1,2-diamine containing some functional
group. It is thus necessary to have a method of synthesising such
primary 1,2-diamines.

In the current literature there exists no method of diamine syn-
thesis that has been used with a range of functional groups. There
are, however, certain methods which would appear to have the potential
to be developed for use in the synthesis of functionalised 1,2-diamines.
In deciding which method would be most suitable, the main criteria
were simplicity, and the avoidance of methods using expensive or
delicate reagents. It was found that these criteria were best
satisfied by using imidazolinones as precursors to primary 1,2-diamines.
A recently developed method[46,47] of imidazolinone synthesis had con-
siderably improved the means by which they were available. This
method also appeared to hold the most potential in terms of the
synthesis of functionalised imidazolinones.

3.1 LONG ALKYL CHAIN DIAMINES

One of the fundamental requirements for the type of platinum complex concerned, is that the reactive parts of the molecule must be separated by a certain distance. This is to enable the intercalator-platinum molecule to interact with D.N.A. in the desired manner. Thus it is necessary to have a spacer group between the platinum complex and the intercalator.
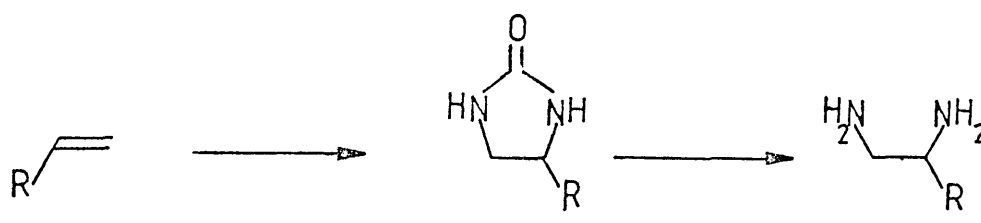
The basic handling problem encountered with platinum complexes formed from diamines is their acute insolubility. It is possible that better solubility could be effected by increasing the organic character of the platinum complex. Thus if the spacer group between the platinum complex and the intercalator was a long alkyl chain then it might be possible to overcome the problem of insolubility in organic solvents.

To ascertain whether the above method of overcoming the insolubility problem was viable, a series of 1,2-diamines containing long alkyl chains were synthesised using the method of Kohn (Section 2.3, Scheme 19). Using this method the imidazoline (9) is usually isolated prior to release of the diamine. This was always achieved previously using distillation, and was not found to be viable with imidazolines other than the simple ones described by Kohn.[46,47] It was found to be somewhat easier to characterise the imidazolinone (9a) instead of
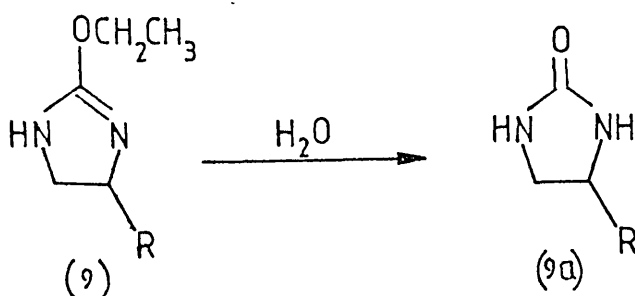
the diamine or the imidazoline (12) as in Kohn's method. Imidazolinones (9a) are in general more crystalline and less prone to hydrolysis. A series of 4-alkylimidazolinones was thus produced in good yield (Table 1)

The hydrolysis of the imidazolinones did not proceed in particularly good yield when using barium hydroxide as in Kohn's[46,47] procedure. The use of 50% potassium hydroxide in aqueous methanol produced the diamine in far higher yields (Table 1).

R		
$CH_3(CH_2)_3CH{=}CH_2$	54%	–
$CH_3(CH_2)_5CH{=}CH_2$	89%	71%
$CH_3(CH_2)_7CH{=}CH_2$	80%	88%
$CH_3(CH_2)_9CH{=}CH_2$	94%	–
$CH_3(CH_2)_{15}CH{=}CH_2$	85%	60%

(Table 1)

3.2 PLATINUM COMPLEXES

The long alkyl chain diamines produced as described above, were converted into the diaminodichloroplatinum(II) complex using a procedure developed from that used by Dhara.[52] In this method the diamine is first converted to the diaminodiiodoplatinum(II) complex (Scheme 23), and then the iodine ligands exchanged for chlorine. This procedure is preferred to the direct reaction of diamines with potassium tetrachloro-platinum(II),[53] which is sluggish and proceeds in poor yield. Diamino-dichloroplatinum(II) complexes were produced using the former procedure
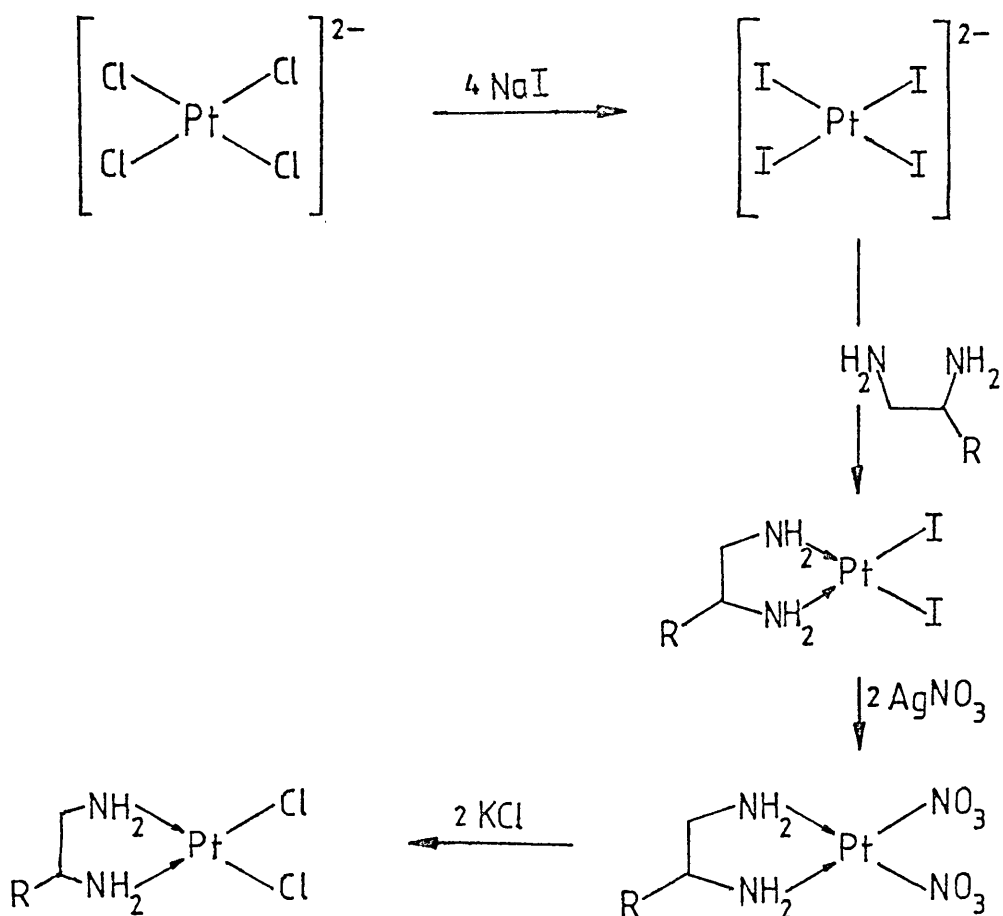
(Scheme 23)

in good yield. The expected improvement in solubility properties of the platinum complexes was not realised however, as the complexes were found to be totally insoluble in all organic solvents, dissolving only in aqueous acidic media. The insolubility of these compounds led to considerable purification problems, and as a result of this, complete characterisation was not possible.

3.3 THE SYNTHESIS OF FUNCTIONALISED IMIDAZOLINONES

From the careful consideration of the conditions used in Kohn's method,[46,47] it was clear that unprotected functional groups would not be compatible with this. Also aldehydes and ketones even in a protected form would not be able to survive the experimental conditions.

The extension of Kohn's method to the synthesis of functionalised imidazolinones was first attempted with the unsaturated esters (10) and (11). It was found that this type of compound could be readily

R'	R'
CH_2=$CH(CH_2)_8CO_2Me$ (10)	68%
CH_2=$CH(CH_2)_{14}CO_2Me$ (11)	70%
CH_2=$CH(CH_2)_9OCONHPh$ (12)	54%
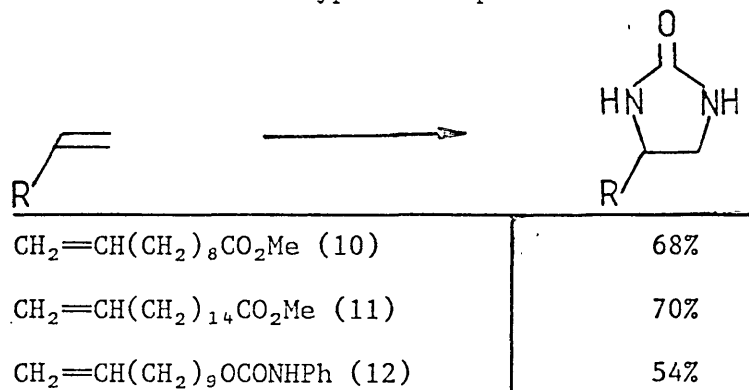
(Table 2)

transformed into the imidazolinone using Kohn's procedure, the function-alised imidazolinone being produced in reasonable yield (Table 2). The procedure of Kohn was also applied to alcohols protected in the form of N-phenylcarbamates (12) but in this case the yield of the functionalised imidazolinone was lower.

With the extension of Kohn's method to the synthesis of the afore-mentioned functionalised imidazolinones, it was thought that it may be possible to carry a simple intercalator through the synthesis. 11-Aminoundecene hydrochloride was reacted with 9-phenoxyacridine (Scheme 24), using a literature procedure,[54] to give (13), which was acetylated to give the substituted acridine (13a). This acridine (13a) was then subjected to the procedure developed from that of Kohn.
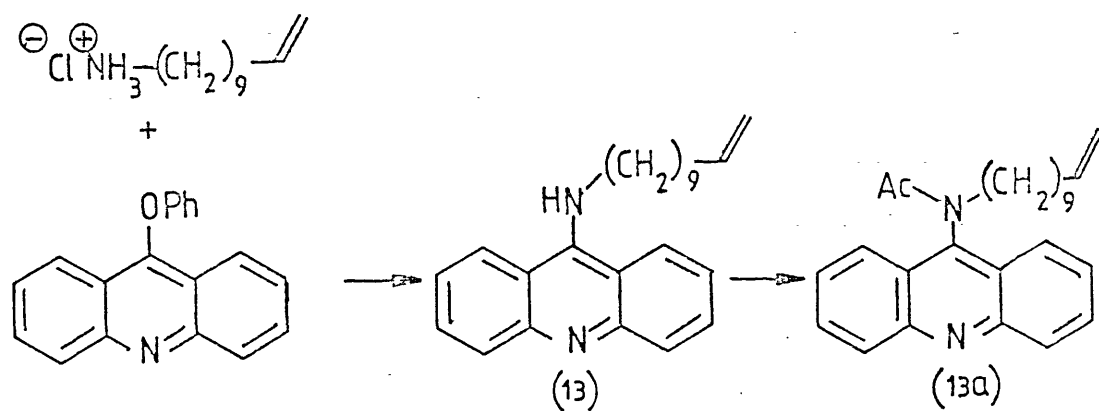
(Scheme 24)

However, after the first stage of the synthesis it was found that the intercalator had been cleaved (Scheme 25), a process thought to be due to acridine removing a proton from the bromo-cyanamide (14), thus leading to the cleavage of the intercalator during aqueous work-up.
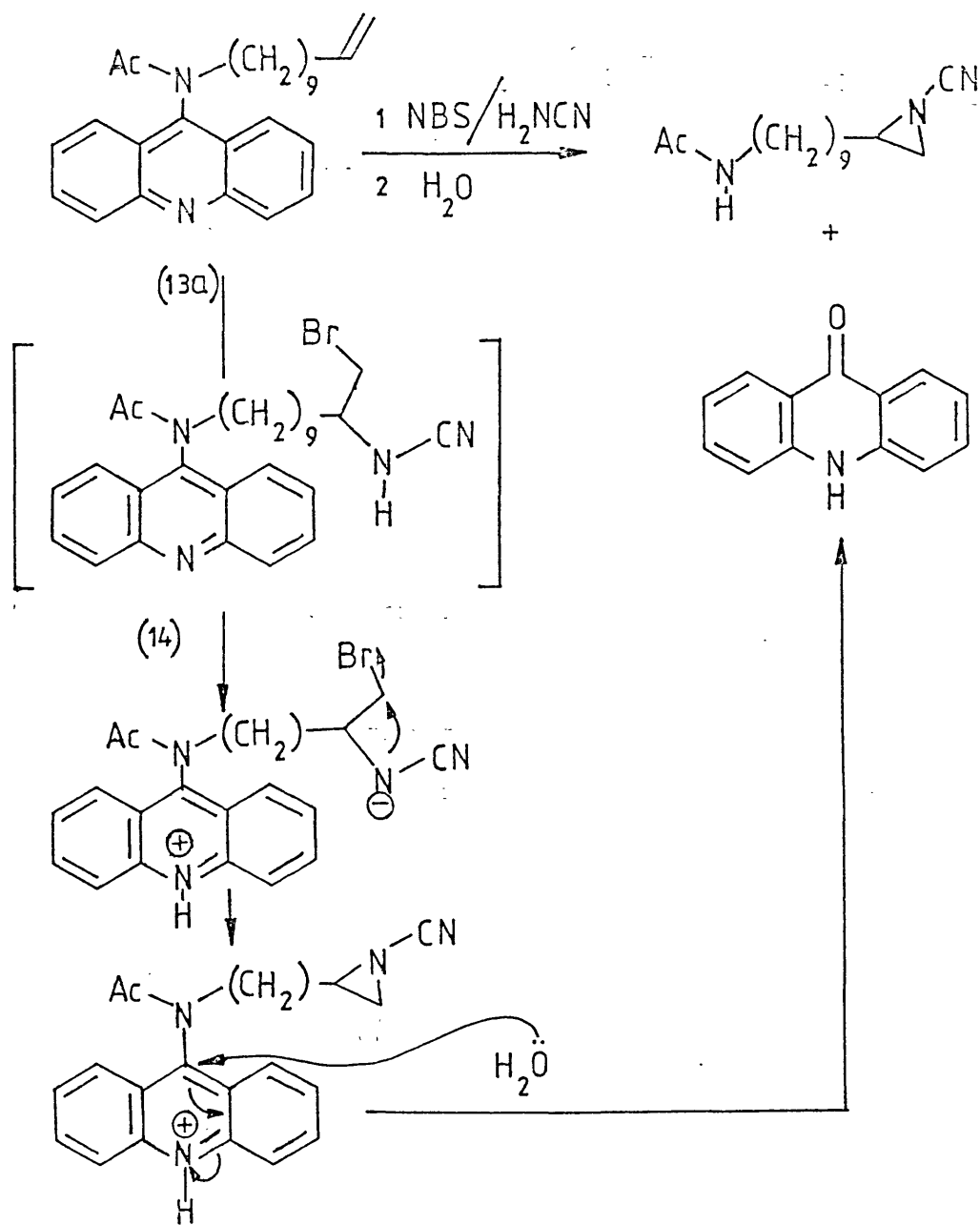
(Scheme 25)

3.4 DIAMINES VIA TRICHLOROMETHYLIMIDAZOLINES

It was clear from the attempted extension of Kohn's method of diamine synthesis, that none of the existing methods would be satisfactory for use in producing functionalised diamines.

The basic problem is common to all existing methods of diamine synthesis, that is, they all involve harsh conditions or reagents at some point in the synthesis. The use of such drastic conditions leads to methods being inflexible and only useful for producing simple diamines.

Thus it is a priority of any new method of diamine synthesis to keep conditions and reagents as mild as possible. It is also necessary to work with the diamine in a suitably protected form, due to its sensitive nature, prior to its use. This means that the final step in any diamine synthesis must be its deprotection, the problem step in the majority of syntheses. An easy release of the diamine is thus an essential requirement for a new method of diamine formation.

In terms of the aforementioned requirements there has been no actual progress in the field of diamine synthesis. In the related field of 1,2-amino alcohol synthesis, however, flexible methods have been developed which use mild conditions. In particular the use of 2-trichloromethyloxazolines[55] as labile intermediates, has been investigated in the formation of 1,2-amino alcohols. One of the greater synthetic advantages of these intermediates is the relatively easy conversion of the 2-trichloromethyloxazoline to the 1,2-amino alcohol (Scheme 26). The oxazoline is also formed so as to produce an alkyl iodide side chain which has been shown[56] to lend itself to the incorporation of a variety of other functionalities. If 1,2-diamines could be produced in an analogous manner then this would constitute a

very mild and flexible method of diamine synthesis.   As amino alcohols
are produced in this method from 2-trichloromethyloxazolines, diamines
could be formed from 2-trichloromethylimidazolines (Scheme 27).   The
latter compounds could also be produced in a similar manner by the
cyclisation of N-allyltrichloroacetamidines.
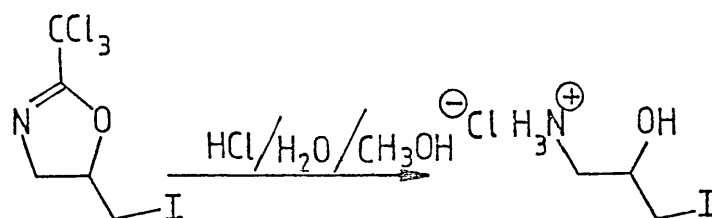
(Scheme 26)
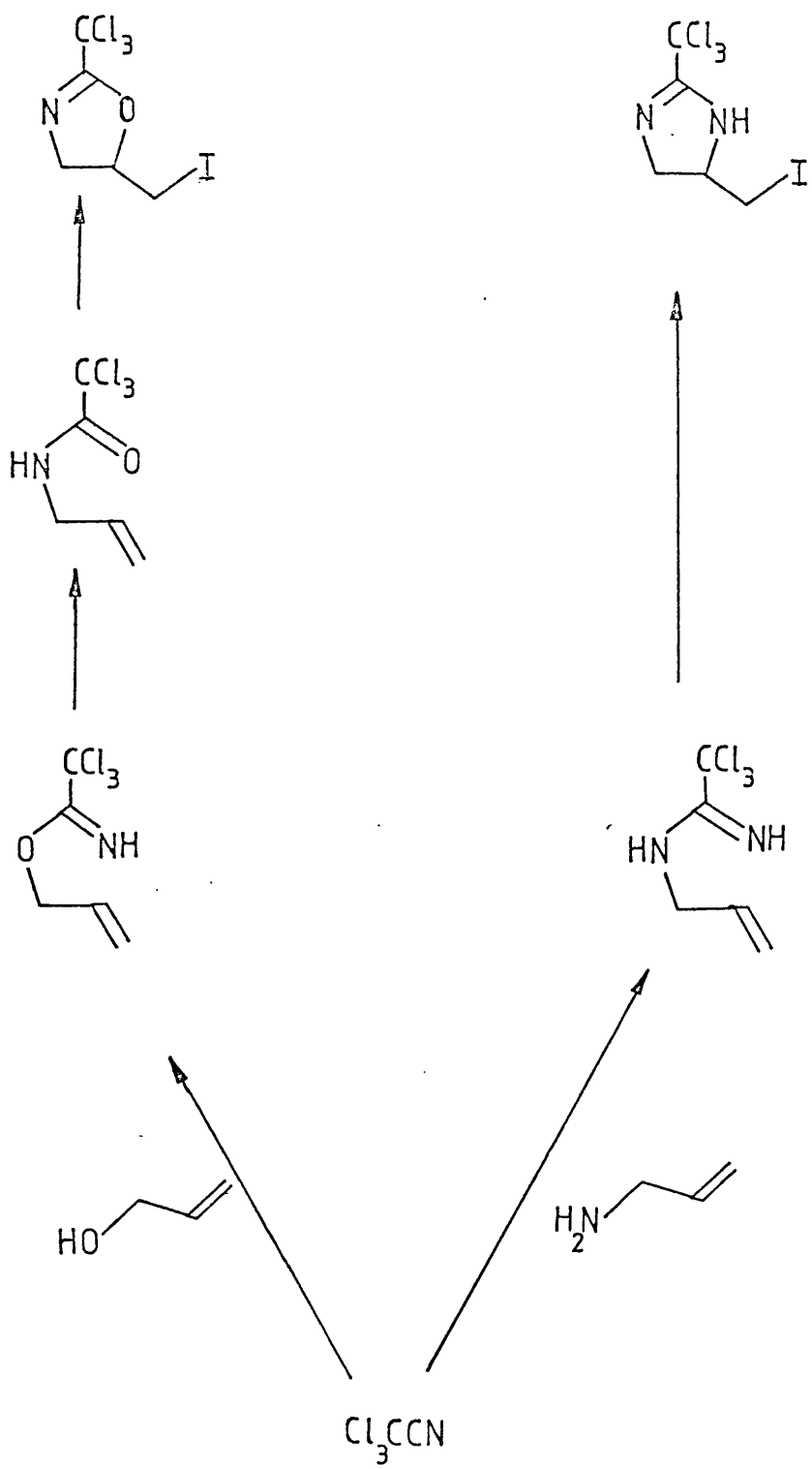
(Scheme 27)

3.5 THE SYNTHESIS OF N-ALLYL AMIDINES

In order to investigate the cyclisation of N-allylamidines in general, model studies were carried out on N-allylbenzamidines. N-Allylbenzamidine was first reported[57] to be produced on heating benzonitrile and allylamine together in a sealed tube, although in very low yield.   It was later shown that the use of a Lewis acid in the synthesis of amidines greatly improved[58] the yields when using unreactive nitriles like benzonitrile.   This type of approach was found to work well in the synthesis of N-allylbenzamidines.

For the synthesis of N-alkyl-2,2,2-trichloroacetamidines, however, Lewis acid catalysis need not be used, trichloroacetonitrile being sufficiently reactive.   N-Allyl-2,2,2-trichloroacetamidine was produced according to the method of Dachlauer[59] in high yield.

3.6 THE CYCLISATION OF N-ALLYLAMIDINES

Initial attempts to cyclise N-allylbenzamidine (15) using pyridine and iodine in THF (Method A) were not particularly successful. Only a small yield of the desired imidazole (16) was recovered along with most of the starting amidine (15).

A. I_2/Py
B. NIS
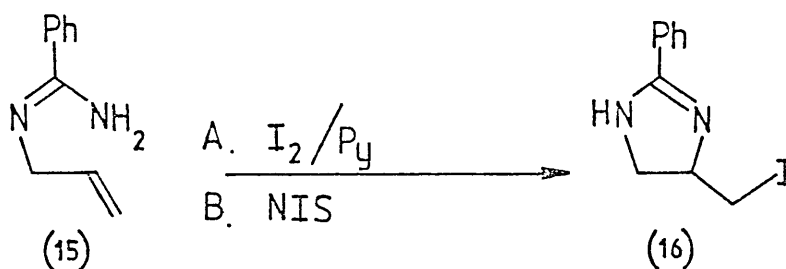
The use of N-iodosuccinimide in THF (Method B) instead of iodine and pyridine led to a much improved yield of the desired imidazoline.

Treatment of N-allylbenzamidine with N-bromosuccinimide also led to cyclisation; however, the product was later found to be not a dihydroimidazole (16) but a tetrahydropyrimidine (17) the alternative cyclisation product.

NBS
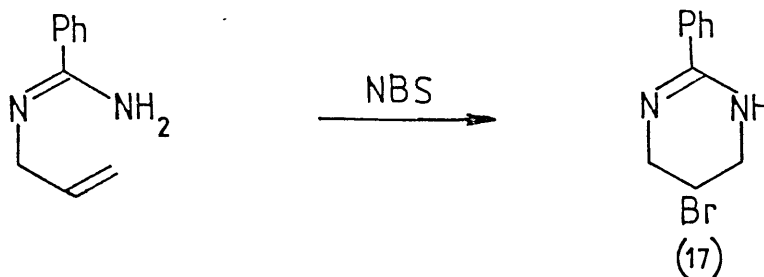
The structure of the product (17) was confirmed by X-ray crystallography

(Appendix 1). This change in products by simply using N-bromo-

succinimide instead of N-iodosuccinimide was both surprising and

puzzling. It was hard to understand why this simple change had such a

marked effect. Light was thrown on this problem when it was observed

that the reaction of N-allylbenzamidine with N-chlorosuccinimide gave

an N-allyl-N'-chlorobenzamidine (Scheme 28).
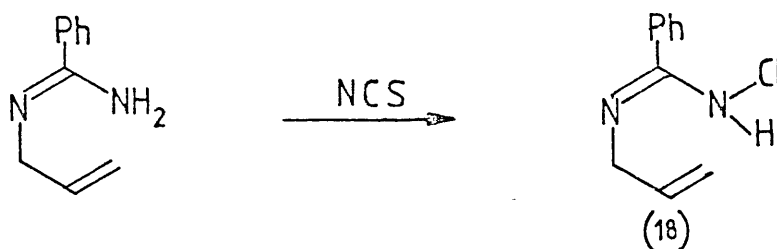
(Scheme 28)

Although complete characterisation of this compound (18) could not be

achieved, all spectra data is consistent with it being the N-chloro

derivative of N-allylbenzamidine (18). In addition to this, an aqueous

solution of this compound turned starch-iodide paper blue.

It would thus seem probable that both NBS and NIS also react via

N-halo compounds. The stability of the N-bromo and N-iodo compounds

would, however, be far less than that of the N-chloro - the difference

between bromine and iodine being,that the nitrogen-bromine bond is more

likely to cleave heterolytically, and the nitrogen-iodine bond

homolytically. Thus it can be seen (Scheme 29), how the two products

could arise. Homolytic cleavage of the nitrogen-iodine bond produces

an iodine radical, which reacts with the olefinic bond to give the most

stable radical. Coupling of the radicals thus gives the observed five

membered ring. In the case of the nitrogen-bromine bond, heterolytic

cleavage leads to a bromonium species. This intermediate ring opens to give the greatest relief of strain and thus forms a six-member ring.
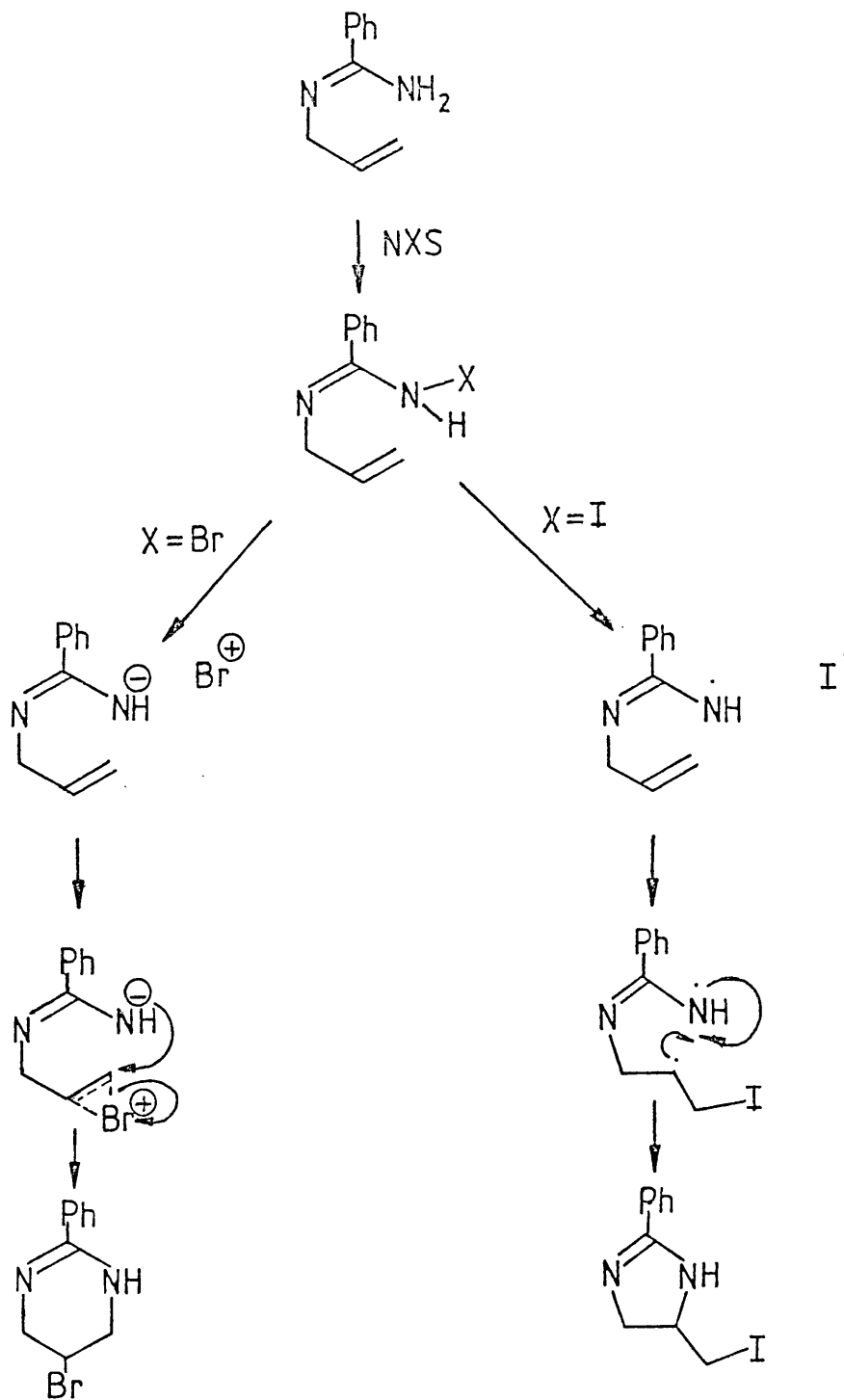
(Scheme 29)

In the case of N-allyl-N-2,2,2-trichloroacetamidine (19), treatment with N-iodosuccinimide failed to give any products. Use of the original conditions of iodine and pyridine however, gave the desired dihydroimidazole (20) in good yield.
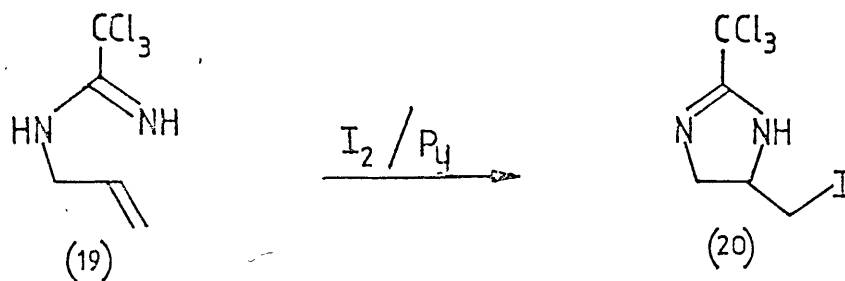
It was also observed that pyridine and bromine again gave the tetra-hydropyrimidine (21) in good yield.
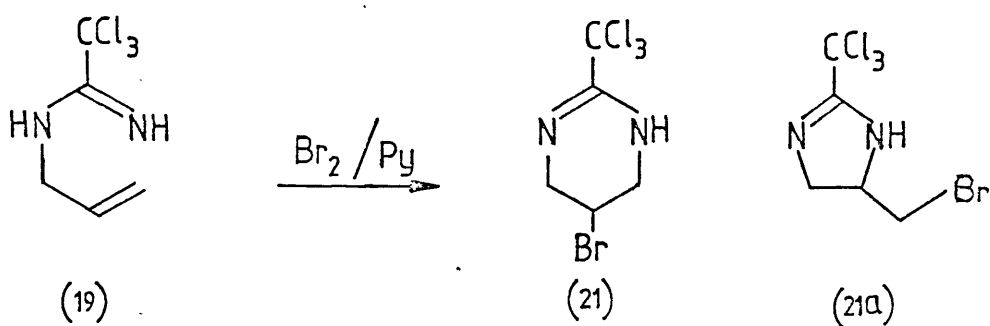
In this case small amounts of the dihydroimidazole (21a) were also observed in the NMR spectrum of the crude product.

3.7 STABILITY OF DIHYDROIMIDAZOLES

On recrystallisation of 4,5-dihydro-4-iodomethyl-2-phenyl-imidazole (16), elemental analysis showed the crystallised material to be the hydroiodide salt (22) of the aforementioned imidazole. It was then realised that the dihydroimidazole (16) was a strong enough base to remove hydrogen iodide from another molecule, thus yielding the imidazole (23).
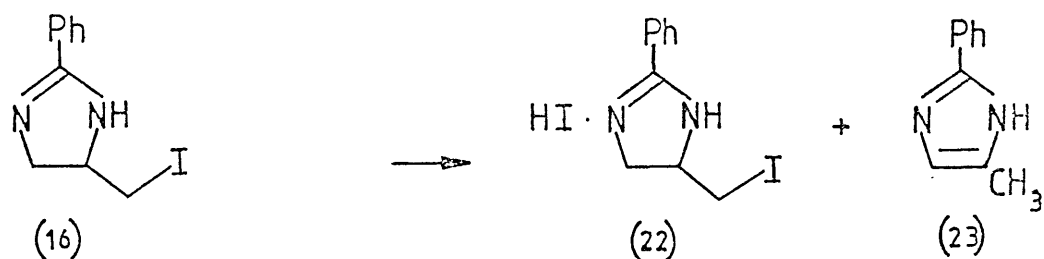
Treatment of the dihydroimidazole (16) with DBU in THF also gave the imidazole (23) in high yield. In a comparative experiment, treatment of 5-bromo-3,4,5,6-tetrahydropyrimidine (17) with DBU in a similar manner gave multiple minor products and not 1,6-dihydro-2-phenyl-pyrimidine.

3.8 THE SYNTHESIS OF N-METHALLYLAMIDINES

The facile elimination of HI from the dihydroimidazole posed a problem, in that it restricted the synthetic procedures with which it was compatible. It was decided, therefore, to block the elimination by the introduction of a methyl group adjacent to the iodine. This required the synthesis of N-methallylamidines, which are available from the reaction of methallylamine with a nitrile. Methallylamine is commercially available as its hydrochloride salt, and prior release of the free base is required. This was initially achieved by dissolving the hydrochloride salt in dichloromethane and releasing the free base with one equivalent of triethylamine. On treatment with benzonitrile and aluminium chloride, however, the dihydroimidazole (24) was recovered from the reaction.
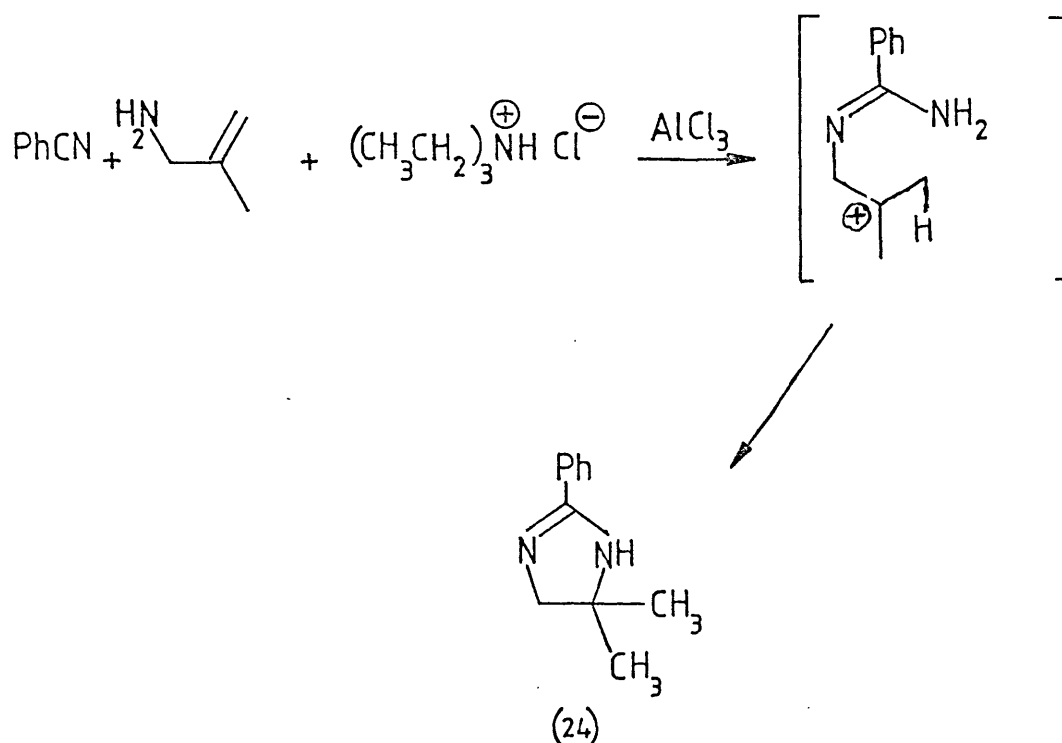
(Scheme 30)

This is thought to be due to the initially formed N-methallylbenzamidine undergoing an acid catalysed cyclisation (Scheme 30) due to the presence of triethylamine hydrochloride.   Removal of the triethylamine hydrochloride prior to reaction with benzonitrile gave the desired amidine (25) in good yield.

In the case of N-methallyl-2,2,2-trichloroacetamidine the reaction was carried out in benzene and the insoluble triethylamine hydrochloride was found not to interfere.   A good yield of N-methallyl-2,2,2-trichloroacetamidine was thus recovered.

3.9 THE CYCLISATION OF *N*-METHALLYLAMIDINE

N-Methallylbenzamidine (25) was cyclised using *N*-iodosuccinimide as in the case of its *N*-allyl isomer. The resulting dihydroimidazole (26) showed no signs of losing HI and proved to be quite stable.

NIS

(25)

(26)
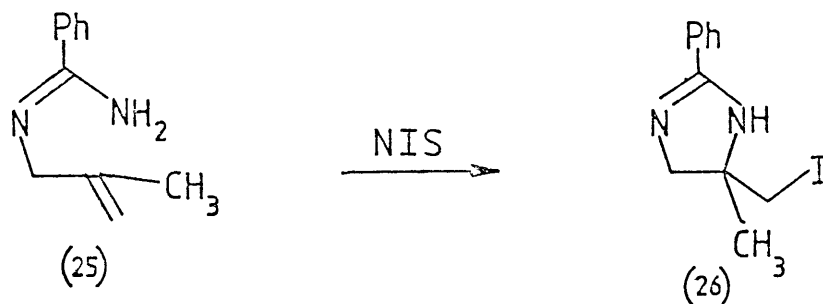
The cyclisation of *N*-methallyl-2,2,2-trichloroacetamidine again proceeded when using a pyridine-iodine mixture in THF, and not with *N*-iodosuccinimide. The product thus formed (27) was again thermally quite stable.

(27)
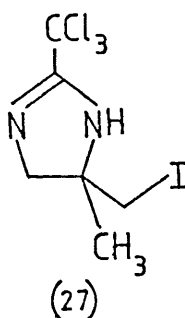
The dihydroimidazole (27) represents a stable precursor to functionalised diamine formation. The iodomethyl group is capable of being transformed into numerous functionalities prior to the deprotection of the diamine. Release of the diamine from the dihydroimidazole *via* hydrolysis should be

possible under both acidic and basic conditions. It should also be possible to produce the diamine by initially reducing the dihydro-imidazole (27) to an aminal before hydrolysis. The diamine could thus be released from the 4,5-dihydro-2-trichloromethylimidazole moiety under a variety of conditions making it compatible with a range of functional groups.

CHAPTER IV

THE SYNTHESIS OF ELLIPTICINE

4.0 ELLIPTICINE

The alkaloid ellipticine (5) was first isolated from the leaves of a small tropical evergreen *Ochrosia elliptica* Labill in 1959.[60] Later *Bleckeria vitiensis*, a small tree native to the island of Fiji, was found to be an especially rich source of ellipticines (Scheme 31).[61]

(Scheme 31)
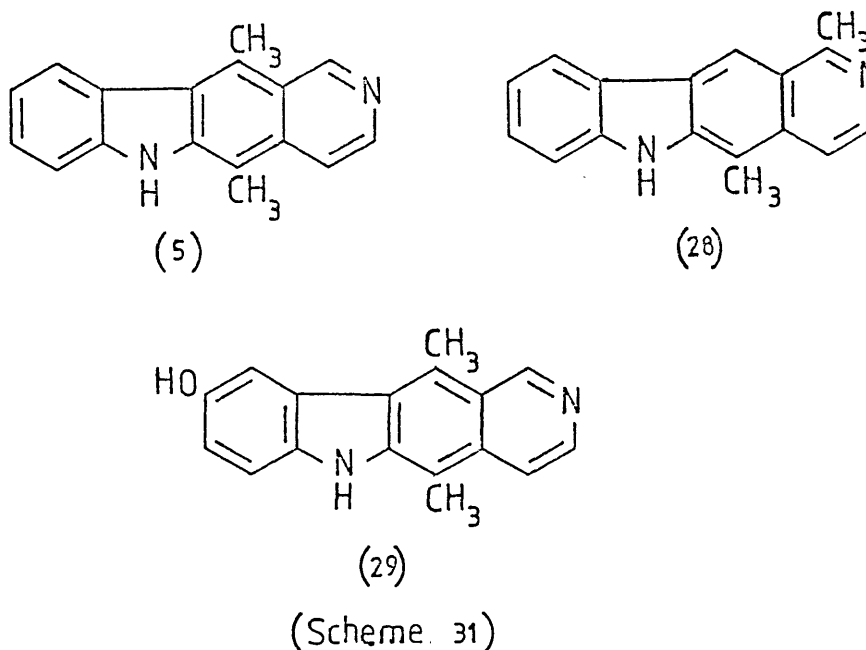
It was not until 1967 however that the anticancer activity of the ellipticine alkaloids was discovered.[62] As mentioned previously (Section 1.2), the mechanism of ellipticine's anticancer activity is by intercalation. The interest in the anticancer activity of ellipticine and related molecules has resulted in "Elliptinium" (30) becoming commercially available for clinical use in the treatment of some cancers.[63]
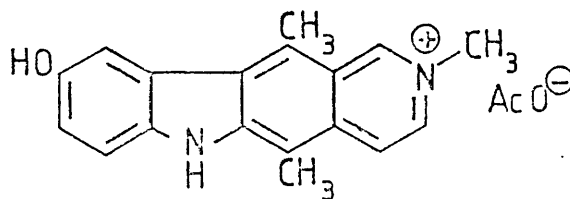
(30)

The need to obtain ellipticine as well as new derivatives and analogues for pharmacological evaluation has resulted in many syntheses of the alkaloids. The synthesis of ellipticine is the subject of no less than four[64,65,66,67] reviews, from which it can be seen that of the many syntheses, the majority are either long, or use select materials. Since it would be of interest to synthesise a platinum-ellipticine molecule of the general type discussed previously (Section 1.4), it was thought necessary to pursue new methods of syn-thesising ellipticine itself.

4.1 INDOLE-2,3-QUINODIMETHANES - POTENTIAL PRECURSORS TO ELLIPTICINE

In the synthesis of indole alkaloids indole-2,3-quinodimethanes
(31) have become of considerable interest.[68] This type of compound
(31) is not stable itself, but can be generated from stable precursors.
When generated it can react with dienophiles both intra- and inter-
molecularly leading to indole alkaloids.[69,70] It is possible to
imagine this type of synthetic approach being used in a synthesis of
ellipticine (Scheme 32).

(Scheme 32)

The concept of using an indole-2,3-quinodimethane (31) precursor
in a synthesis of ellipticine has also been conceived by other workers
although their paper appeared after the completion of our work. Their
approach uses an indolofuran (33) precursor,[71] synthesised in six steps
from 3-ethylindole. However, 3,4-didehydropyridine (32) generated
via organometallic methods failed to react with the indolofuran (33).
Recently 3,4-didehydropyridine (32) generated via an oxidative method
has been successfully reacted with the indolofuran (33) to give the
endoxide precursors (34) and (35) to ellipticine and isoellipticine.[72]

In the current literature there exists however, a synthetically

simpler precursor to indolo-2,3-quinodimethane based on the pyrano-

[3,4-b]indol-3-one (36) ring system.[73]
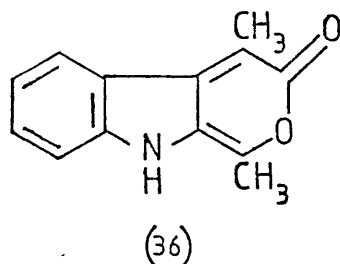
This type of precursor undergoes Diels-Alder reactions when heated with

acetylenes to give, with loss of carbon dioxide, carbazoles, and

although reported over twenty years ago is relatively forgotten.   It

also possesses several advantages over the indolofuran type precursor

(33) previously mentioned: the indole nitrogen need not be protected;

they are available in two steps from indole;   and they avoid the need

to remove the endoxide oxygen after reaction, losing carbon dioxide

spontaneously during the reaction.   The only requirement of this

type of compound when reacting it in a Diels-Alder fashion, is that the reaction must be a thermal process. It thus appeared possible to use the pyranoindole type precursor (36) in a very short synthesis of ellipticine (Scheme 33).
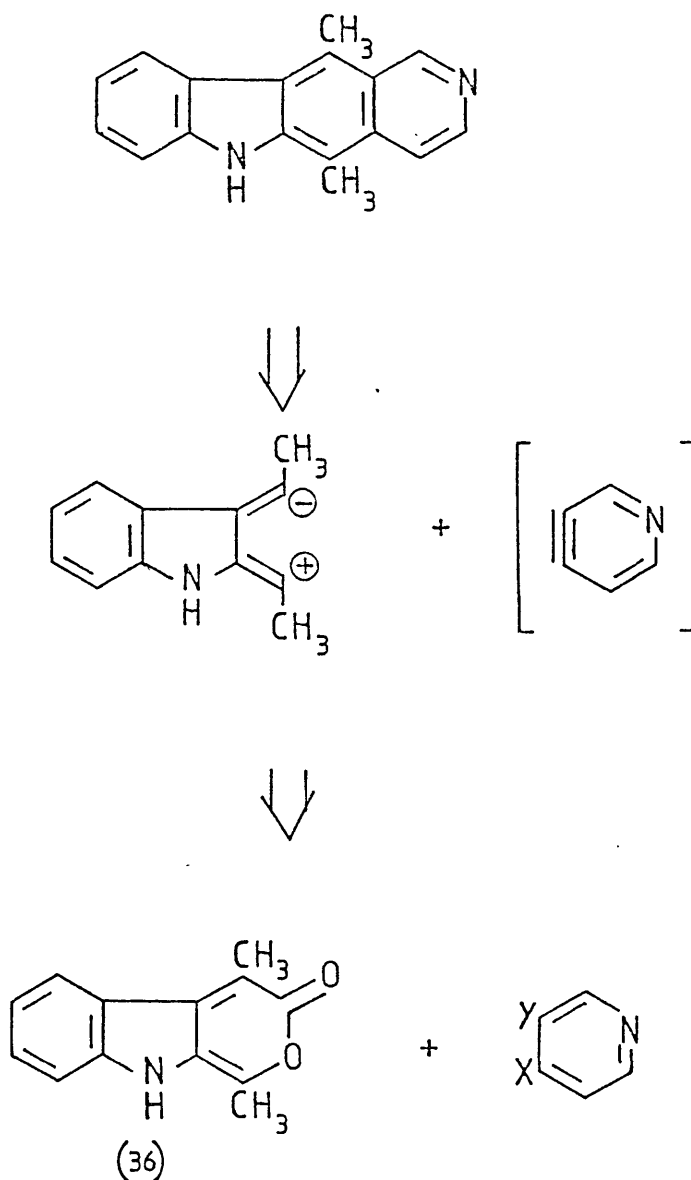
(Scheme 33)

From the disconnection (Scheme 33) it can be seen that the other necessary fragment is that of 3,4-didehydropyridine (32). The need for the reaction of pyranoindole to be carried out at elevated temperatures dictates that a thermally labile precursor to 3,4-didehydropyridine (32) is required in order for the synthesis to be realised.

4.2 THE GENERATION OF PYRIDYNE

Introduction

Pyridyne like benzyne is the reactive intermediate formally generated by removing two vicinal atoms or atomic groups from a parent aromatic molecule.[74] For benzene only one 1,2-didehydrobenzyne is possible, however for pyridine two didehydropyridines are possible. 3,4-Pyridyne (32) was the first hetaryne to be established and calculations[75] indicated that 3,4-pyridyne would be the most stable. Accordingly, the evidence for its transient existence is the most convincing for any hetaryne.
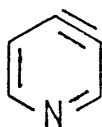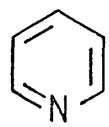
(32)   (37)

3,4-Didehydropyridine has been generated from several different precursors, and detected by both nucleophilic and diene traps.[36]

2,3-Didehydropyridine (37) has been calculated[75] to be far less stable than its 3,4-isomer. The generation and study of 2,3-didehydropyridine has met with considerably less success. Thus the evidence for its existence is far less extensive and convincing.

a.   Organometallic Methods

As with benzyne the hetaryne can be generated by treating a mono-halide with a strong base causing the elimination of HX[74] (Scheme 34). This phenomenon was first used to explain the formation of 4-amino-pyridine from the treatment of 3-bromopyridine with sodamide in liquid

ammonia.[77]   Later a more extensive investigation into the amination

of halopyridines,[78] showed that the reaction products were independent

of the position and nature of the halogen substituent.   It was also

shown that hetaryne formation was favoured by the use of heavier

halogens and by the use of bulkier strong bases.
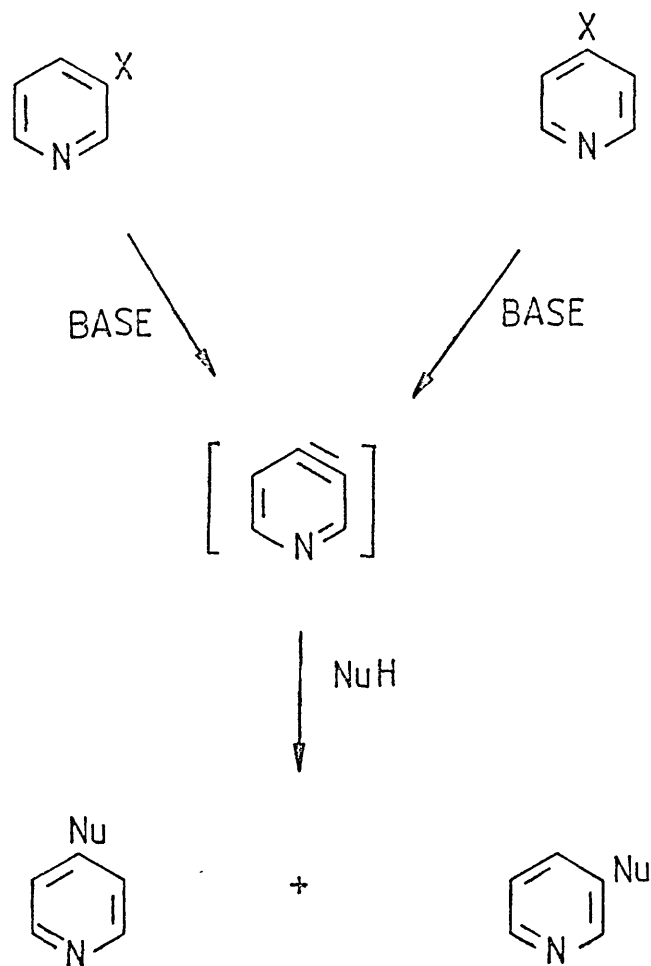
(Scheme 34)
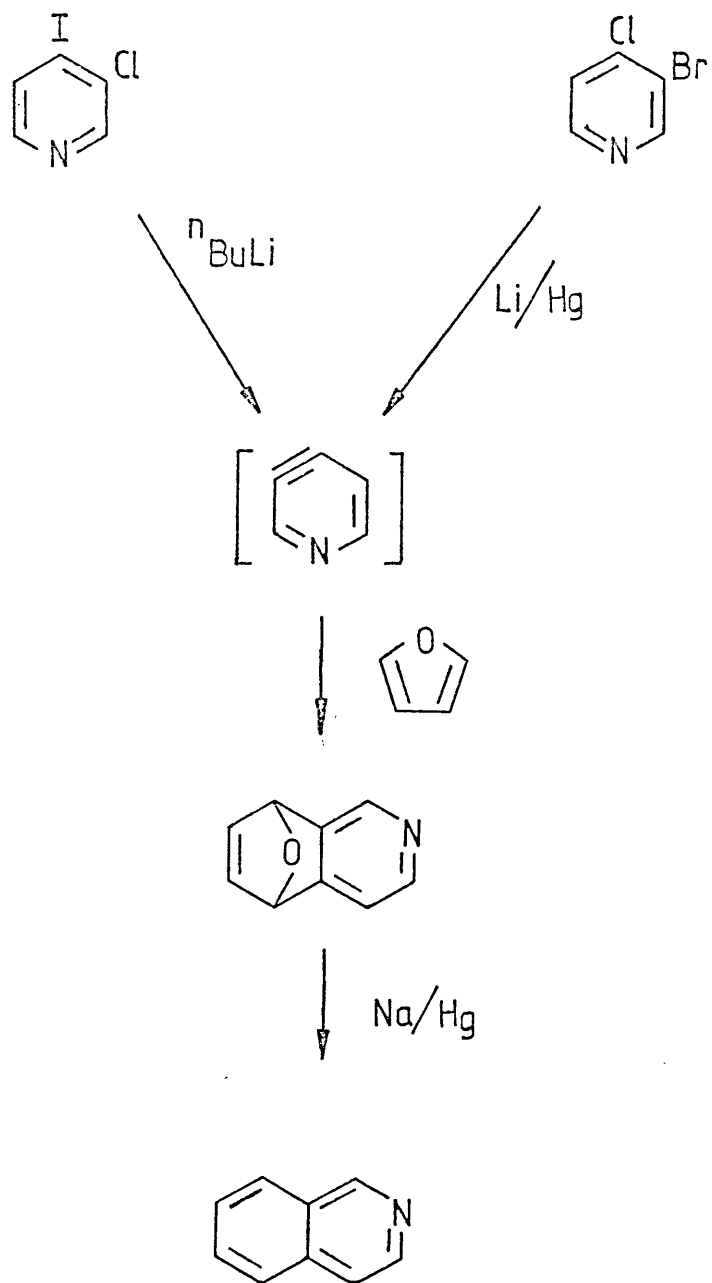
(Scheme 35)

The hetaryne was found to be less able to discriminate between two offered nucleophiles than benzyne,[79] as would be expected with the drop in stability. When 3-halopyridines are used to generate 3,4-dide-hydropyridine no products are detected that might arise from the formation of 2,3-didehydropyridine. This is thought to be due to the 2-anion being kinetically disfavoured,[80] because of the nitrogen - C2 lone pair interaction. Attempts to generate 2,3-didehydropyridine via 2-halopyridines have been without success.

Dihalopyridines are also a potential source of didehydropyridines via the elimination of a metal-halogen fragment (Scheme 35). This was first observed[81] when 3-bromo-4-chloropyridine was reacted with lithium amalgam in the presence of furan, when isoquinoline was isolated. The intermediate endoxide can be isolated from the reaction when 3-chloro-4-iodopyridine and butyl lithium[82] are used to generate 3,4-didehydro-pyridine.

The 2,3-dihalopyridines have provided the most evidence for the existence of 2,3-didehydropyridine. Treatment of 2-chloro-3-bromo-pyridine with lithium amalgam in the presence of furan,[83] leads to the isolation of quinoline in low yield. The reaction of butyl lithium with 2,3-dihalopyridines leads to the isolation of the endoxide (Scheme 36),[84] but again the yield is quite low. The low yields are in line with 2,3-didehydropyridine being far less stable than its 3,4-isomer.
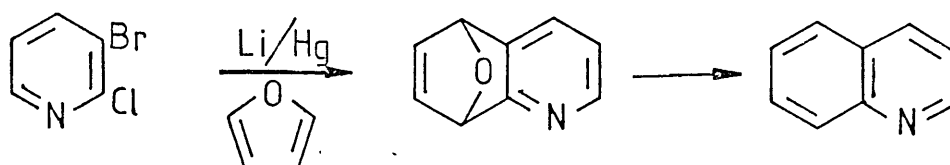
(Scheme 36)

b.   Thermal Methods

Unlike benzyne where several thermally labile precursors have been studied, the use of thermal precursors to generate pyridyne has not been widely investigated.   The first thermal precursor to be used was 3-diazoniumpyridine-4-carboxylate[85] (Scheme 37).   It was shown that the thermal decomposition of this compound in the presence of furan leads to the isolation of the desired endoxide in up to 60% yield. This 3,4-didehydropyridine precursor also reacts with cyclopentadiene[86] but not in the same manner as benzyne.   The product is thought to be a (2+2) adduct although this is not proven.   The latter two reactions are the only reported successful reactions using this precursor.
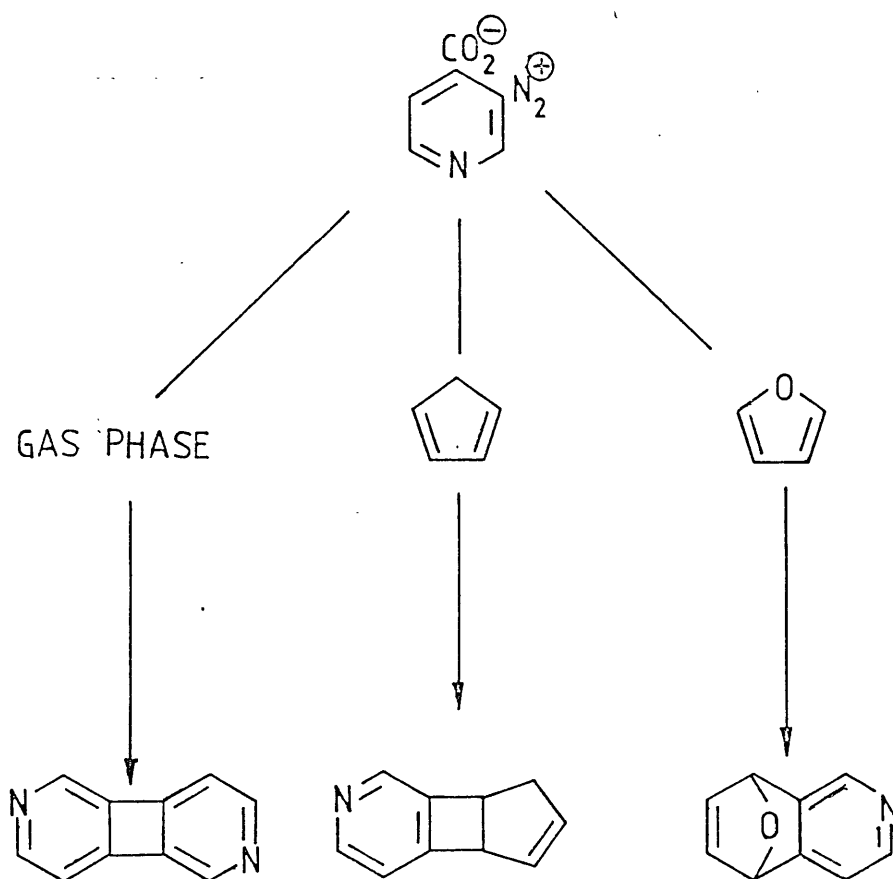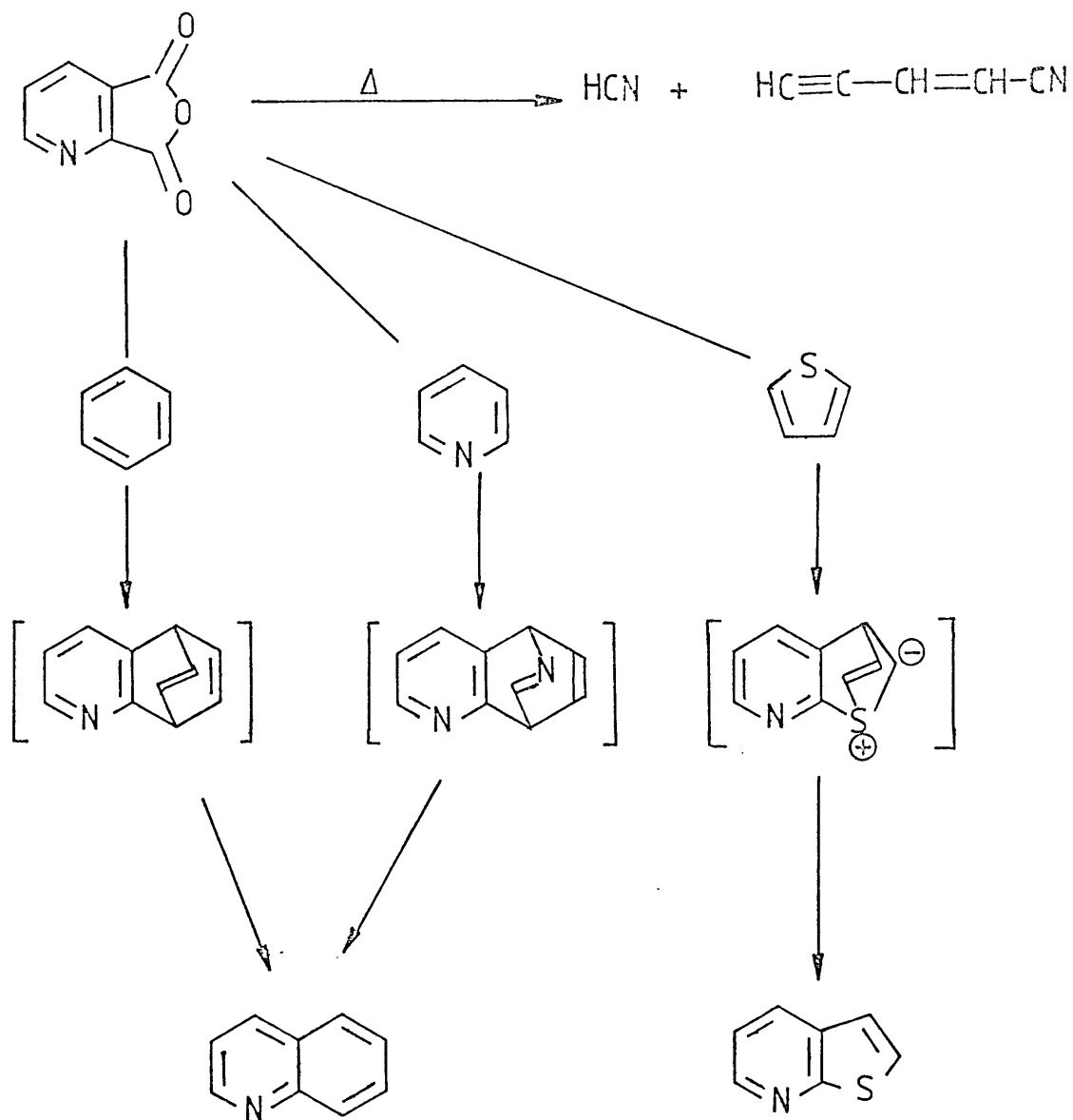
GAS PHASE

(Scheme 37)

(Scheme 38)

The production of a dimer in an analogous manner to the production of biphenylene from benzyne has only been reported as occurring in the gas phase.[87] Its non-occurrence in solution is believed to be due to the relative ease, when compared to benzyne, with which the unimolecular ring opening of pyridyne takes place.

The generation of 3,4-didehydropyridine via aprotic diazotisation has been claimed, appearing as a footnote in a short communication.[83] The consequent absence of any literature on the subject however, must cast doubt on the validity of this statement.

The generation of 2,3-didehydropyridine via 3-diazoniumpyridine-2-carboxylate has never been reported. However, attempts have been made to trap 2,3-didehydropyridine generated by the pyrolysis of the anhydride of pyridine-2,3-dicarboxylic acid.[89] This did not lead to the expected dimer only to the recovery of HCN and an unsaturated nitrile (Scheme 38). Pyrolysis in the presence of pyridine and benzene[90] lead to the recovery of quinoline, which is claimed to arise by an insertion reaction. In the presence of thiophene,[91] a product which is said to have arisen from a (3+2) cycloaddition[92] was obtained. These strange results must cast some doubt as to whether 2,3-didehydropyridine is in fact the reactive species generated during pyrolysis.

c.   Oxidative Methods

The two forms of didehydropyridine have been generated, like benzyne, via the oxidation of N-aminotriazoles[93] with lead tetra-acetate (Scheme 39). In contrast to the generation of benzyne, N-aminotriazolopyridines when oxidised in the absence of trapping agents do not dimerise. This is a property for which the benzene analogue is especially well known. 3,4-Didehydropyridine generated using this method has not only been trapped with tetracyclone and furan but also
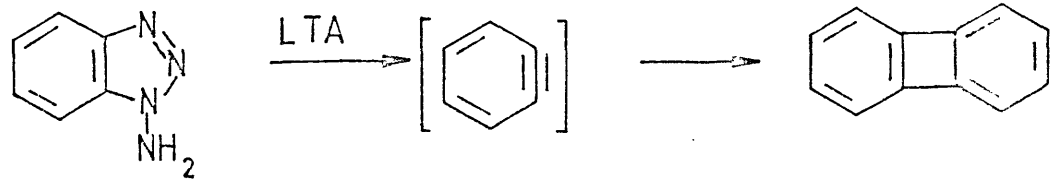
(Scheme 39)
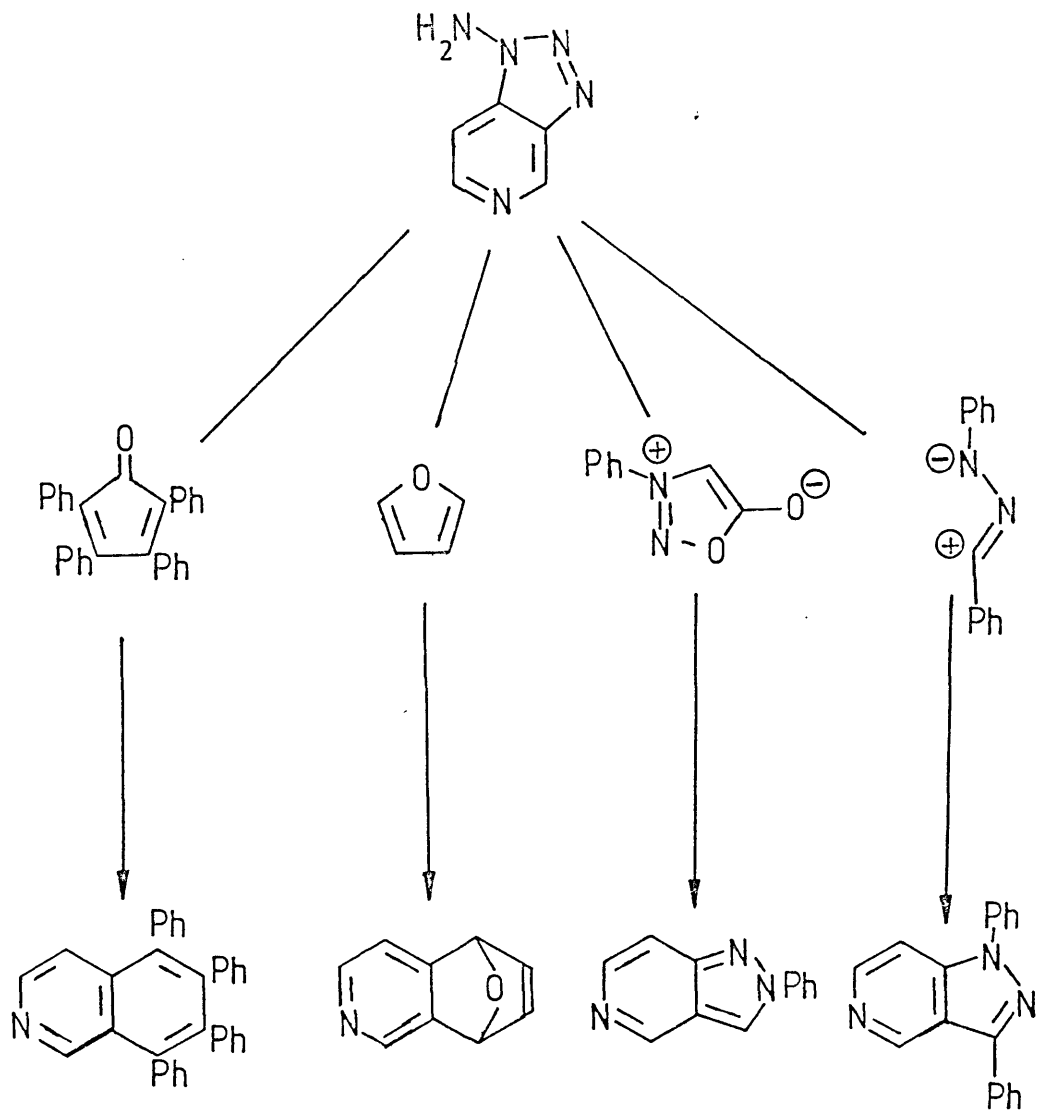
(Scheme 40)

1,3-dipoles (Scheme 40).[94]   This reaction is unique to this method of
generating 3,4-didehydropyridine.   The reaction of 3-diazonium-
pyridine-4-carboxylate with phenyl azide is reported not to give an
adduct.
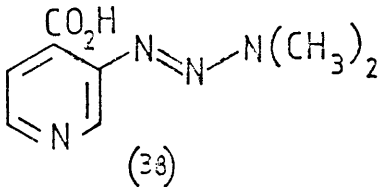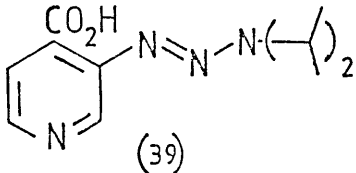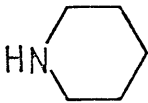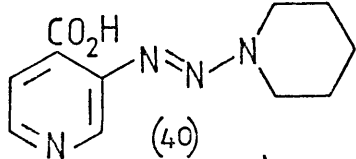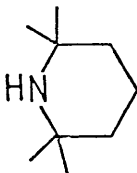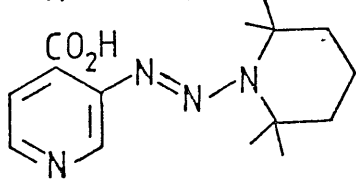
2,3-Didehydropyridine generated from the *N*-aminotriazole can also
be trapped with tetracyclone; the yield of the adduct is, however,
very low.   This is in keeping with the predicted drop in stability
compared with the 3,4-isomer.

4.3 A NEW PRECURSOR TO 3,4-DIDEHYDROPYRIDINE

It can be seen from the preceding review that the only existing

method of generating 3,4-didehydropyridine thermally is that using

3-diazoniumpyridine-4-carboxylate.[85] All attempts to synthesise this

precursor from 3-aminopyridine-4-carboxylic acid[95] using the published

procedure failed. This was due to the extreme insolubility of

3-aminopyridine-4-carboxylic acid. Therefore, it was clear that a

new thermal method of generating 3,4-didehydropyridine would be

required if the synthesis of ellipticine was to be realised. For a

solution to this problem, thermal methods of generating benzyne were

looked at with the possibility of extending one of these methods to the

generation of 3,4-didehydropyridine.

The use of triazenes[96] for the generation of benzyne was found

to meet the necessary requirements. 2-(3,3-Dimethyltriazen-1-yl)

benzoic acid[97] is a thermally labile precursor to benzyne, synthesised

from anthranilic acid, and is soluble in a range of organic solvents.

This triazene is synthesised by diazotisation in aqueous acidic media,

followed by coupling to dimethylamine in aqueous alkali.

This method seemed especially suitable since it was carried out

in aqueous media, the only solvent in which 3-aminopyridine-4-carboxylic

acid was appreciably soluble. A procedure modelled on the production

of 2-(3,3-dimethyltriazen-1-yl)benzoic acid from anthranilic acid was

used with 3-aminopyridine-4-carboxylic acid. This gave the desired

product (38) in good yield. Two other triazenes were also prepared,

using diisopropylamine (39) and piperidine (40) as secondary amines

(Table 3).

Amine	Triazene	Yield (%)
$HN(CH_3)_2$	(38)	72
$HN-(\!-\!\langle\ \rangle)_2$	(39)	30
	(40)	43
		0

(Table 3)

An attempted coupling with 2,2,6,6-tetramethylpiperidine failed. It is thought to be due to the amine being too sterically hindered as the yield of the triazene seemed to drop with the increasing steric hindrance of the amines.

4.4 THE GENERATION OF 3,4-DIDEHYDROPYRIDINE *VIA* TRIAZENES

Initial experiments to generate 3,4-didehydropyridine (32) using 3-(3,3-dimethyltriazen-1-yl)pyridine-4-carboxylic acid (38) were carried out in chlorobenzene, as with its benzene analogue. Using tetracyclone as a trap, 5,6,7,8-tetraphenylisoquinoline was isolated in 13% yield. The low yield was thought to be due to the incomplete solubility of the triazene (38) in chlorobenzene. Changing the solvent to acetonitrile led to an increased yield of 25%.

It was known[97] that in the case of 2-(3,3-dimethyltriazen-1-yl)-benzoic acid, that the addition of one equivalent of trichloroacetic acid to the reaction facilitated its decomposition. An experiment in which 3-(3,3-dimethyltriazen-1-yl)pyridine-4-carboxylic acid was decomposed in the presence of trifluoroacetic acid and tetracyclone led to a much improved yield of 45% of 5,6,7,8-tetraphenylisoquinoline. The three triazenes (Table 4) were decomposed under the latter conditions giving the yields of 5,6,7,8-tetraphenylisoquinoline shown (Table 4).

Two of the triazenes (38,40) were also decomposed in the presence of 2,5-dimethylfuran. This was initially carried out by heating the reaction at reflux. It was found, however, that carrying the reaction out in a sealed vessel at 130°C led to an improved yield (Table 4). It can be seen from these yields (Table 4) that there is no benefit in using triazenes other than the dimethyltriazene (38).

To assess the range of dienes with which 3-(3,3-dimethyltriazen-1-yl)pyridine-4-carboxylic acid could successfully be used as a precursor to 3,4-didehydropyridine, the triazene (38) was reacted with a range of dienes (Table 5). It would appear from these results that dienes must fulfil two requirements: they must possess sufficient reactivity,
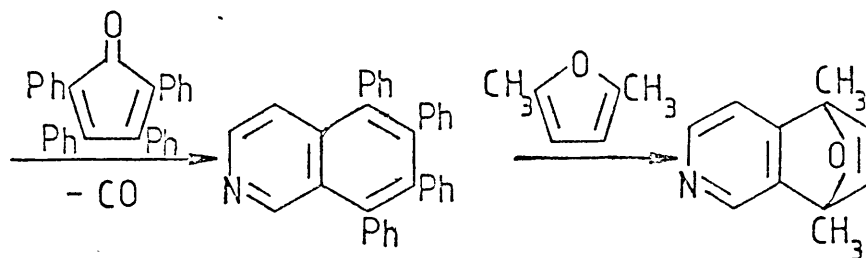
	45 %	40 %
(38)		
(39)	35 %	
(40)	43 %	38 %

(Table 4)

and have enough thermal stability to withstand the conditions used to decompose the triazene (38).

	Sufficient reactivity	Sufficient thermal stability	Yield
	Yes	No	0%
	Yes	Yes	40%
	No	Yes	0%

(Table 5)

As well as the aforementioned requirements, the diene must be cyclic.

A range of acyclic dienes all failed to react with 3,4-didehydro-

pyridine generated *via* the triazene (38).

4.5 PHOTOCHEMICAL DECOMPOSITION

Although thermal decomposition of a triazene is the normal method of generating the aryne from it, it is possible to achieve its decomposition *via* photochemical means.[98] This was found to be the case when 3-(3,3-dimethyltriazen-1-yl)pyridine-4-carboxylic acid was irradiated in the presence of tetracyclone, when a yield of 17% of 5,6,7,8-tetraphenylisoquinoline was recovered. However, a similar experiment using 2,5-dimethylfuran as a trap failed to give any trace of the Diels-Alder adduct, and therefore thermal generation of the reactive intermediate was the preferred method.

4.6 2,3-DIDEHYDROPYRIDINE

2,3-Didehydropyridine has never been generated thermally, and the methods by which it has been claimed to have been trapped are by no means proof of its generation.   It was thought that since 3,4-didehydropyridine could be generated so conveniently from a triazene type precursor, that it may be possible to generate 2,3-didehydropyridine in a similar fashion. 3-(3,3-Dimethyltriazen-1-yl)pyridine-2-carboxylic acid was synthesised from 3-aminopyridine-2-carboxylic acid[99] in 26% yield.   Decomposition using a variety of conditions and traps failed, however, to show any signs of products arising from the trapping of 2,3-didehydropyridine.

4.7 3,4-DIDEHYDRO-2-METHYLPYRIDINE

Olivacine (28) is a member of the same family of alkaloids as ellipticine, it is very similar both structurally and in its anticancer activity. It is also possible to conceive a short synthesis of olivacine using pyranoindoles. Applying the same synthetic strategy to olivacine as was done in the case of ellipticine (Scheme 41), it can be seen that the reactive intermediate required is 3,4-didehydro-2-methylpyridine (41).
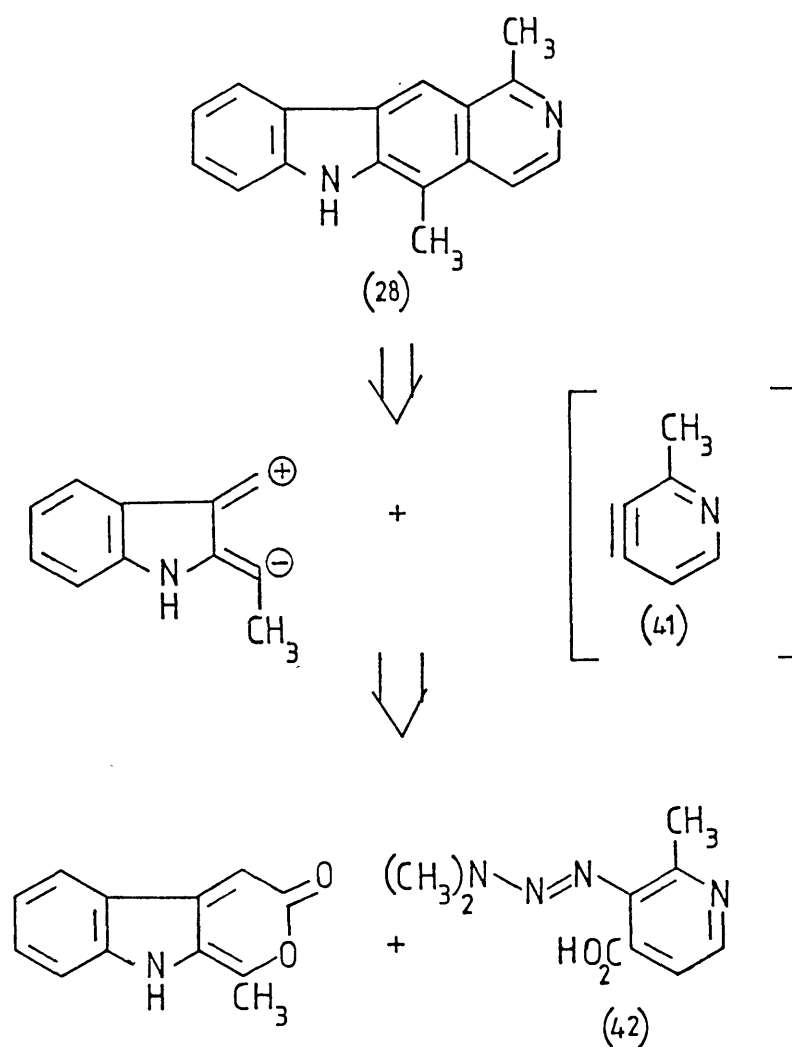
(Scheme 41)

Again, it was thought that this reactive intermediate could be possibly generated *via* the triazene (42). The requisite amino-acid (43) was synthesised from 2-methylpyridine-3,4-dicarboxylic acid in 46% overall yield using standard procedures.[95] Attempted diazotisation of the amino-acid (43), however did not lead to the desired triazene (42). The major product from the reaction was the acid (44), the triazene (42) only being detected in trace amounts. This was thought to be due to the 2-methyl group being too reactive, forming the intermediate (45), which is hydrolysed by the alkaline condition used in coupling (Scheme 42). Intermediates of the type (45) are known to form when amines are diazotised adjacent to reactive methyl groups under strongly acidic conditions.[100,101]
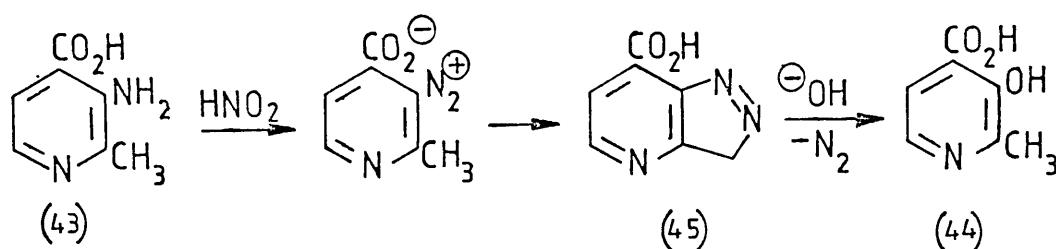
(Scheme 42)

4.8 THE SYNTHESIS OF ELLIPTICINE

The pyrano-indole (36) was heated with an excess of the triazene

(38) in refluxing acetonitrile. This gave (Scheme 43) ellipticine (5)

together with an equal amount of isoellipticine (46), appearing as

yellow and orange u.v. fluorescent spots on TLC. These two compounds

were readily separable by medium pressure chromatography, and the

spectra of the ellipticine produced were identical with those of an

authentic sample. Catalysing the reaction with trifluoroacetic acid

or carrying out the reaction at higher temperatures, only led to

reduced yields of the two products in the same ratio. An attempt to

increase the ratio of ellipticine produced by using BF_3-etherate as a

Lewis acid led to no products being observed at all.
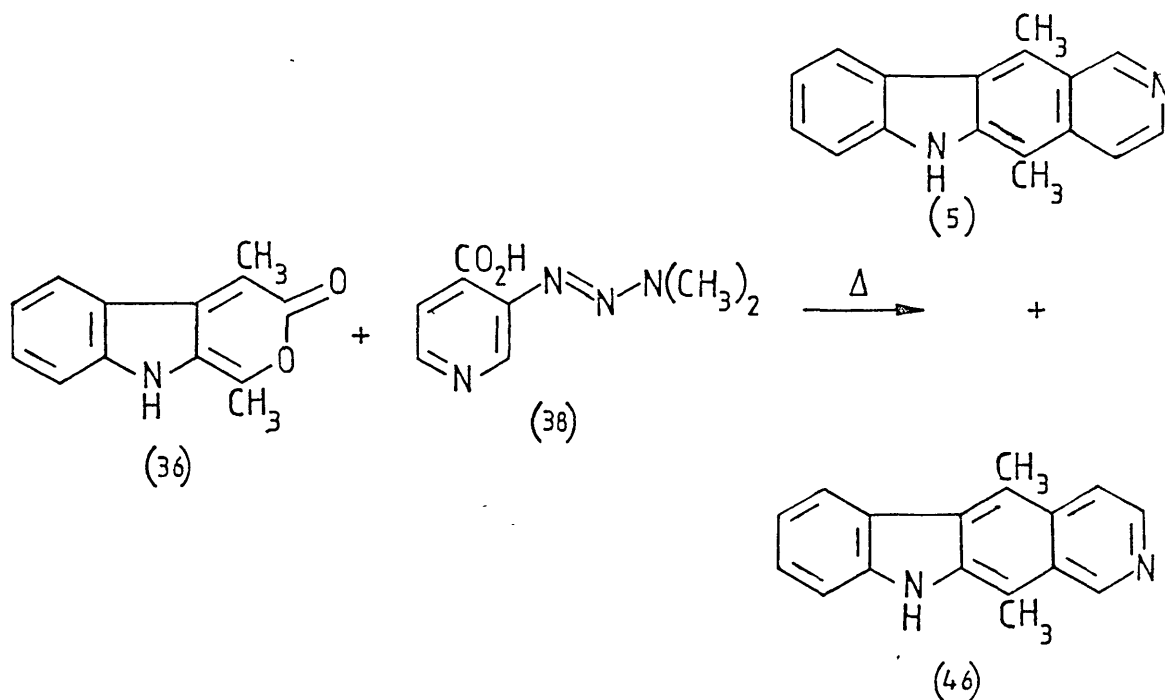
It is known, however, that the pyranoindole (36) gives mixtures of

isomers with unsymmetrical acetylenes.[102] Also that 3,4-didehydro-

pyridine gives mixtures of isomers with unsymmetrical dienes,[72] and

nucleophiles.[76] It would thus appear that the ratio of ellipticine

to isoellipticine is characteristic of the reaction. Nevertheless,

this route represents the shortest synthesis of ellipticine to date,

being just three steps from indole.

CHAPTER V

CONCLUSION

5.0 CONCLUSION

The aim of this work was to develop synthetic methods from which a new type of platinum anticancer compound could be constructed. Two synthetic areas have been investigated, that of functionalised diamine synthesis, and the synthesis of the intercalator ellipticine.

Attempts to synthesise precursors to functionalised diamines initially tried to extend Kohn's method of imidazoline synthesis. However, these attempts were only partially successful. Although simple functionalised imidazolinones could be synthesised, the method did not have the scope and flexibility to produce the range of functionalised diamines required.

A new route to functionalised diamines was thus developed using 2-trichloromethylimidazolines as a nucleus for mild diamine formation. From these studies an easily prepared precursor to diamines was synthesised, this precursor also having the potential for the incorporation of a variety of functional groups, and the capability to be used with a range of synthetic procedures.

The intercalator ellipticine has been synthesised in three steps from indole using procedures readily repeatable, and with the potential to be used on a large scale. During the work on this synthesis, a convenient new precursor to 3,4-didehydropyridine was developed. The triazene (38) is a stable solid which decomposes on heating to generate 3,4-didehydropyridine, which can be intercepted by a variety of diene traps. Not all diene traps tried, however, reacted with 3,4-didehydropyridine generated via the triazene, thus confirming the unpredictability of 3,4-didehydropyridine compared to 1,2-didehydrobenzene.

CHAPTER VI

EXPERIMENTAL

GENERAL

Starting materials. Starting materials were prepared according to literature procedure as indicated, and if no reference is quoted are available commercially.

Solvents. Petrol refers to petroleum ether, b.p. 60-80°C, and was distilled before use. Dichloromethane and acetonitrile were dried by refluxing over phosphorus pentoxide, followed by distillation and storage over molecular sieves 4A. Benzene, ether and THF were dried over sodium wire or over potassium-benzophenone as required .

Chromatography. Column chromatography was carried out using Merck kieselgel 60 (70-230 mesh). Flash chromatography used Merck kieselgel H (type 60) or Merck alumina GF_{254}, under pump pressure.

Melting points. Melting points were determined on a kofler hot stage apparatus and are uncorrected.

Spectra. Infra-red (i.r.) spectra were recorded in the range 4000-600 cm^{-1} using Perkin Elmer 257 and 298 spectrophotometers. Unless otherwise stated, spectra of solids were run as Nujol mulls, and spectra of liquids and oils as thin films between sodium chloride plates.

Proton nuclear magnetic resonance (n.m.r.) spectra were recorded using Varian EM 360A (60 MHz), Perkin-Elmer R32 (90 MHz) or Bruker WM 250 (250 MHz) instruments. Tetramethylsilane was used as an internal reference and signals are quoted as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) or broad (br).

Low and high resolution mass spectra were recorded on A.E.I.
MS 12 and VG Micromass 7070B instruments, at 70 eV using a direct
insertion probe.

Photolysis.   Photochemical reactions were carried out using a
Rayonet photochemical reactor with lamps of 300 nm wavelength.   No
external cooling was applied, so reactions proceeded at slightly above
ambient temperature.

PART A

EXPERIMENTAL FOR CHAPTER III

General procedure for the preparation of 4-alkylimidazolinones

The alkene (50 mmol) was dissolved in dichloromethane (200 ml) containing N-bromosuccinimide (50 mmol). To this cyanamide (200 mmol) was added and the reaction stirred for 72h. The reaction mixture was washed with water (3 × 50 ml), dried (MgSO$_4$), and concentrated. The residual gum was dissolved in ethanol containing HCl (50 mmol), and stirred for 6h. Triethylamine (100 mmol) was added, and the reaction mixture was heated at reflux for 1h. The reaction mixture was concentrated, dissolved in water (100 ml), and the resulting solution extracted with chloroform (3 × 25 ml). The combined organic layers were dried (MgSO$_4$), and concentrated to give the crude imidazolinone, which was recrystallised ("light petroleum" : chloroform) to give the product.

4-Butylimidazolin-2-one

1-Hexene (4.2g, 50 mmol) was converted into the imidazolin-2-one as described above. After recrystallisation the title compound was obtained as a colourless solid (3.85g, 54%), m.p. 97°C.

(Found: C, 58.8; H, 9.9; N, 19.4. C$_7$H$_{14}$N$_2$O requires C, 59.1; H, 9.8; N, 19.7%.)

ν_{max}(CHCl$_3$) 3460, 3300 and 1705 cm^{-1};

δ_H(90 MHz; CDCl$_3$) 0.9 (3H, t), 1.1 - 1.7 (4H, br s), 3.1 - 3.9 (3H, m), 4.4 (1H, br s), 4.6 (1H, br s).

m/z 142 (M^+).

4-Hexylimidazolin-2-one

1-Octene (5.6g, 50 mmol) was converted into the imidazolin-2-one as described above. After recrystallisation the <u>title compound</u> was obtained as a colourless solid (7.6g, 90%), m.p. 108-110°C.

(Found: C, 63.35; H, 10.8; N, 16.5. $C_9H_{18}N_2O$ requires C, 63.5; H, 10.5; N, 16.4%.)

$\nu_{max}(CHCl_3)$ 3460, 3300 and 1705 cm^{-1};

δ_H(250 MHz; CDCl$_3$) 0.9 (3H, t), 1.3 (10H, br s), 1.45 - 1.7 (2H, br m), 3.15 (1H, m), 3.6 (1H, m), 3.8 (1H, m), 4.4 (1H, br s), 4.6 (1H, br s).

m/z 170 (M^+).

4-Octylimidazolin-2-one

1-Decene (7.0g, 50 mmol) was converted into the imidazolin-2-one as described above. The <u>title compound</u> was obtained as a colourless solid after recrystallisation (7.9g, 80%), m.p. 114°C.

(Found: C, 66.6; H, 11.5; N, 14.2. $C_{11}H_{22}N_2O$ requires C, 66.6; H, 11.1; N, 14.1%.)

$\nu_{max}(CHCl_3)$ 3460, 3300 and 1705 cm^{-1};

δ_H(90 MHz; CDCl$_3$) 0.9 (3H, t), 1.2 - 1.8 (14H, m), 3.15 (1H, m), 3.6 (1H, m), 3.8 (1H, m), 4.4 (1H, br s), 4.6 (1H, br s).

m/z 198 (M^+).

4-Decylimidazolin-2-one

1-Dodecene (8.4g, 50 mmol) was converted into the imidazolin-2-one as described above. After recrystallisation the <u>title compound</u> was obtained as a colourless solid (10.6g, 94%), m.p. 96°C.

(Found: C, 68.8; H, 11.8; N, 12.1. $C_{13}H_{26}N_2O$ requires C, 68.9; H, 10.6; N, 12.4%.)

$\nu_{max}(CHCl_3)$ 3460, 3300 and 1705 cm^{-1};

δ_H(90 MHz; $CDCl_3$) 0.8 (3H, t), 1.1 - 1.7 (18H, m), 3.15 (1H, m), 3.6 (1H, m), 3.8 (1H, m), 4.4 (1H, br s), 4.6 (1H, br s).

m/z 226 (M^+).

4-Hexadecylimidazolin-2-one

1-Octadecene (12.6g, 50 mmol) was converted into the imidazolin-2-one as described above. After recrystallisation the <u>title compound</u> was obtained as a colourless solid (13.1g, 85%), m.p. 119-120°C.

(Found: C, 73.5; H, 12.45; N, 9.1. $C_{19}H_{38}N_2O$ requires C, 73.5; H, 12.3; N, 9.0%.)

$\nu_{max}(CHCl_3)$ 3460, 3300 and 1705 cm^{-1};

δ_H(90 MHz; $CDCl_3$) 0.9 (3H, t), 1.1 - 1.7 (30H, m), 3.1 (1H, m), 3.6 (1H, m), 3.8 (1H, m), 4.4 (1H, br s), 4.6 (1H, br s).

m/z 310 (M^+).

General procedure for the hydrolysis of 4-alkylimidazolin-2-ones

The imidazolin-2-one (10 mmol) was dissolved in an aqueous methanol (50:50) solution of KOH (50%; 25 ml). This solution was placed into an autoclave and maintained at 180°C for 24h. After cooling to room temperature, water (100 ml) was added and the resulting solution extracted with ether (3 × 30 ml). The combined organic layers were dried (Na$_2$SO$_4$), concentrated, and the residual oil was distilled to give the product.

1,2-Diamino octane

4-Hexylimidazolin-2-one (1.0g, 5.8 mmol) was hydrolysed to the diamine as described above, to give the title compound as a colourless oil (0.61g, 71%), m.p. (dihydrochloride) 128°C.

(Found: C, 43.2; H, 10.2; N, 12.5. C$_8$H$_{12}$N$_2$Cl$_2$ requires C, 43.4; H, 10.15; N, 12.5%.)

ν_{max}(film) 3380, 3300, 3200, 1580 and 1460 cm^{-1};

δ_H(250 MHz; CDCl$_3$) 0.9 (3H, t), 1.2 - 1.5 (10H, m), 1.75 (4H, br s), 2.4 - 2.8 (2H, m), 3.1 - 3.7 (1H, m).

m/z 145 (MH)$^+$.

1,2-Diamino decane

4-Octyl imidazolin-2-one (1.5g, 7.5 mmol) was hydrolysed to the diamine as described above, to give the title compound as a colourless oil (1.15g, 88%), m.p. (dihydrochloride) 174-175C.

(Found: C, 48.9; H, 10.9; N, 11.4. C$_{10}$H$_{26}$N$_2$Cl$_2$ requires C, 48.9; H, 10.7; N, 11.4%.)

ν_{max}(film) 3360, 3300, 2920, 2860 and 1460 cm^{-1};

δ_H(90 MHz; CDCl$_3$) 0.9 (3H, t), 1.1 - 1.4 (14H, m), 1.5 (4H, br s), 2.4 - 2.9 (2H, m), 3.1 - 3.7 (1H, m).

m/z 173 (MH)$^+$.

1,2-Diamino octadecane

4-Hexadecyl-imidazolin-2-one (2g, 6.45 mmol) was hydrolysed to the diamine as described above, to give the title compound as a colourless solid (0.67g, 46%), m.p. 43-44°C.

(Found: 285.3264;   C$_{18}$H$_{40}$N$_2$ requires 285.3269.)

ν_{max}(film) 3360, 3280, and 1460 cm^{-1};

δ_H(90 MHz; CDCl$_3$) 0.9 (3H, t), 1.1 - 1.4 (30H, m), 1.5 (4H, br s), 2.4 - 2.8 (2H, m), 3.1 - 3.6 (1H, m).

m/z 285 (MH)$^+$.

Methyl-9-(imidazolin-2-on-4-yl)nonanoate

Methyl undec-10-enoate (3.25g, 16.2 mmol) was dissolved in dichloromethane (200 ml) containing N-bromosuccinimide (2.9g, 16.2 mmol). To this cyanamide (2.73g, 64.8 mmol) was added and the reaction stirred for 72h. The reaction mixture was washed with water (2 × 25 ml), dried (MgSO$_4$) and concentrated. The resulting gum was dissolved in dry ethanol (20 ml) and HCl (0.59g, 16.2 mmol) added as an ethanolic solution. After 6h, triethylamine (3.28g, 32.4 mmol) was added and the reaction heated at reflux for 1h. The reaction mixture was evaporated to dryness and the residue was dissolved in water (50 ml). The resulting solution was then extracted with chloroform (3 × 25 ml), the combined extracts dried (MgSO$_4$) and concentrated. This gave a gum which crystallised on standing; recrystallisation from ("light petroleum" : CHCl$_3$) gave the title compound as a colourless solid (2.5g, 64%), m.p. 97°C.

(Found: M^+ 256.24300. $C_{13}H_{24}N_2O_3$ requires 256.24297.)

ν_{max}(CHCl$_3$) 3460, 3300, 1705, 1595, 1495 and 1300 cm^{-1};

δ_H(250 MHz; CDCl$_3$) 1.4 (10H, br s), 1.5 - 1.8 (4H, br m), 2.4 (2H, t), 3.15 (1H, t), 3.6 (1H, t), 3.7 (3H, s), 3.8 (1H, m), 4.5 (1H, br s), 4.7 (1H, br s).

m/z 256 (M^+).

Methyl-15-(imidazolin-2-on-4-yl)penta-decanoate

Methyl heptadec-16-enoate (2.82g, 10 mmol) was dissolved in dichloromethane (100 ml) containing N-bromosuccinimide (1.78g, 10 mmol). To this cyanamide (1.68g, 40 mmol) was added, and the reaction stirred for 72h. The reaction was washed with water (3 × 25 ml), dried ($MgSO_4$) and concentrated. The resulting gum was dissolved in dry ethanol (25 ml) and HCl (0.365g, 10 mmol) added as an ethanolic solution. After standing for 6h triethylamine (2.1g, 21 mmol) was added and the reaction heated at reflux for 1h. The solution was evaporated to dryness and dissolved in water (100 ml). The aqueous solution was extracted with ether (3 × 25 ml). The combined organic layers were dried ($MgSO_4$) and concentrated. This gave a gum which crystal-lised on standing. Recrystallisation from ("light petroleum" : $CHCl_3$) gave the title compound as a colourless solid (2.42g, 68%), m.p. 93°C.

(Found: C, 66.9; H, 10.8; N, 8.1. C H N_2O_3 requires C, 67.0; H, 10.6; N, 8.2%.)

ν_{max}(nujol) 3460, 3300, 1705, 1600, 1480, 1300 and 1070 cm^{-1};

δ_H(250 MHz; $CDCl_3$) 1.3 (22H, br s), 1.5 - 1.8 (4H, br m), 2.3 (2H, t), 3.15 (1H, t), 3.6 (1H, t), 3.7 (3H, s), 3.8 (1H, m), 4.55 (1H, br s), 4.7 (1H, br s).

m/z 340 (M^+).

Undec-10-en-1-ol, N-phenylcarbamate

Undec-10-en-1-oic acid (5g, 27.1 mmol) was dissolved in anhydrous ether (50 ml) and slowly added to a solution of $LiAlH_4$ (2.8g, 73 mmol) in dry ether (100 ml). The reaction mixture was stirred for 1h. The reaction was hydrolysed by the slow addition of water (5 ml) followed by aqueous sodium hydroxide (1M, 5 ml) and water (15 ml). This gave

a white precipitate which was removed by filtration. The ethereal solution was then dried (MgSO$_4$) and concentrated to give undec-10-en-1-ol as a colourless oil. This was dissolved in dry pyridine (30 ml), phenylisocyanate (2.8g, 23.6 mmol) added, and the solution stirred at room temperature for 3h. The mixture was evaporated to dryness and dissolved in chloroform (50 ml). The chloroform solution was washed with water (3 × 25 ml), dried (MgSO$_4$) and evaporated. This gave the title compound as a colourless solid (4.73g, 59.6%), m.p. 48-49°C.

(Found: C, 74.8; H, 9.4; N, 5.9. C$_{18}$H$_{27}$NO$_2$ requires C, 74.7; H, 9.3; N, 4.8%.)

v_{max}(nujol) 3300, 1680, 1600, 1530 and 1220 cm^{-1};

δ_H(250 MHz; CDCl$_3$) 1.3 (12H, br s), 1.65 (2H, m), 2.05 (2H, m), 4.15 (2H, t), 4.9 - 5.05) (2H, m), 5.7 - 5.9 (1H, m), 6.65 (1H, br s), 7.2 - 7.4 (4H, m).

m/z 289 (M^+).

[9-(*N*-Phenylcarbamoyl)hydroxynon-1-yl]-imidazolin-2-one

Undec-10-en-1-ol *N*-phenylcarbamate (1g, 3.4 mmol) was dissolved in dichloromethane (50 ml) containing *N*-bromosuccinimide (0.63g, 3.4 mmol). To this cyanamide (0.6g, 14.3 mmol) was added and the reaction was stirred for 72h. The reaction mixture was washed with water (2 × 25 ml), dried (MgSO$_4$) and concentrated. The resulting gum was dissolved in dry ethanol (25 ml) and HCl (0.124g, 3.4 mmol) was added as an ethanolic solution. After standing for 6h triethylamine (1.1g, 10.9 mmol) was added and the reaction heated at reflux for 1h. The reaction mixture was evaporated to dryness, dissolved in water (50 ml) and extracted with chloroform (3 × 20 ml). The combined organic layers were dried (MgSO$_4$) and concentrated to give a gum, which was subjected to chromatography on alumina eluting with chloroform : methanol. This gave the title compound as a colourless solid (0.63g, 54%), m.p. 144°C.

(Found: M^+ 255.25106. C$_{13}$H$_{23}$N$_2$O$_3$ requires 255.25012.)

ν_{max}(nujol) 3310, 1700, 1630, 1600, 1550, 1310 and 1220 cm^{-1};

δ_H(250 MHz; CDCl$_3$) 1.3 (12H, br s), 1.45 - 1.75 (4H, m), 3.15 (1H, t), 3.6 (1H, t), 3.7 - 3.85 (1H, m), 4.15 (2H, t), 4.6 (1H, br s), 4.9 (1H, br s), 7.00 (1H, br s), 7.2 - 7.45 (4H, m).

m/z 255, 227, 199, 85.

9-(Undec-10-en-1-amino)acridine

9-Phenoxyacridine (0.9g, 3.3 mmol) was added to a melt of phenol (30g). To this 1-amino undec-10-ene hydrochloride (0.68g, 3.3 mmol) was added. The reaction was then heated to 130°C for 3h. After cooling, the reaction mixture was then dissolved in aqueous sodium hydroxide (1M, 500 ml) and extracted with dichloromethane (3 × 50 ml). The combined organic layers were dried (Na_2SO_4) and concentrated. The residual gum was dissolved in ether (30 ml) and passed through a short alumina column. The eluant was then concentrated to give the title compound as a yellow gum, which crystallised on standing (1.12g, 97.4%), m.p. 132°C (Picrate).

(Found: C, 62.7; H, 5.8; N, 12.1. $C_{30}H_{33}N_5O_7$ requires C, 62.6; H, 5.8; N, 12.10%.)

ν_{max}(CDCl$_3$) 3290, 3050, 1625, 1555, 1520, 1430, 1260 and 770 cm^{-1};

δ_H(250 MHz; CDCl$_3$) 1.2 - 1.6 (12H, m), 1.8 (2H, m), 2.05 (2H, q), 3.8 (2H, t), 4.95 (2H, m), 5.1 (1H, br s), 5.8 (1H, m), 7.4 (2H, m), 7.7 (2H, m), 8.1 (4H, m).

m/z 346 (M^+).

9-(*N*-Acetylundec-10-en-1-amino) acridine

9-(Undec-10-en-1-amino) acridine (1g, 2.5 mmol) was added to a mixture of acetic anhydride (25 ml) and pyridine (25 ml). The reaction mixture was then heated at 100°C for 3h. After concentrating the reaction mixture, it was dissolved in aqueous sodium hydroxide (0.5M, 100 ml), and extracted with dichloromethane (3 × 30 ml). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated to give a yellow gum. This was dissolved in ether (30 ml) and passed through a short alumina column. Concentration of the eluant gave the title compound as a pale yellow gum (0.74g, 66%), m.p. 120°C (Picrate).

(Found: C, 61.95; H, 5.7; N, 11.2. C$_{32}$H$_{35}$N$_5$O$_3$ requires C, 62.2; H, 5.7; N, 11.3%.)

ν_{max}(CHCl$_3$) 3070, 1680, 1420 and 770 cm^{-1};

δ_H(250 MHz; CDCl$_3$) 1.1 - 1.4 (12H, m), 1.6 (2H, m), 1.7 (3H, s), 2.0 (2H, q), 3.9 (2H, t), 4.95 (2H, m), 5.8 (s1H, m), 7.65 (2H, m), 7.85 (2H, m), 8.05 (2H, d), 8.3 (2H, d).

m/z 388 (M^+).

The attempted preparation of 4-[9-(*N*-acetylnonyl-9-amino) acridine] imidazolin-2-one

9-(*N*-Acetylundec-10-en-1-amino) acridine was used in the general procedure for the preparation of 4-alkylimidazolin-2-ones previously described. This did not lead to the recovery of the title compound, and no identifiable products were recovered from the reaction.

1,2-Diamino octane dichloroplatinum(II)

Potassium tetrachloroplatinate(II) (0.2g, 0.47 mmol) was dissolved in water (10 ml) and a saturated aqueous solution of potassium iodide (1 ml) added. The resulting solution was heated on a steam bath for 5 min and then cooled with ice. A solution of 1,2-diamino octane (0.07g, 0.47 mmol) in water (10 ml) was then added. This resulted in the formation of a yellow precipitate, which was removed by filtration and air dried. The resulting yellow powder was added to a solution of silver nitrate (0.14g, 0.84 mmol) in water (20 ml) and the mixture stirred for 1h. The reaction mixture was then filtered and to the aqueous filtrate a solution of potassium chloride (0.07g, 0.94 mmol) in water (5 ml) added. The resulting solution was heated on a steam bath for 15 min, during which a yellow precipitate formed. The cooled suspension was filtered to give the title compound as a yellow solid (0.18g, 93%).

(Found: C, 23.1; H, 4.7; N, 6.6. $C_8H_{20}N_2Cl_2Pt$ requires C, 23.0; H, 4.9; N, 6.8%.)

N-Allyl benzamidine

Into an autoclave was placed aluminium chloride (13g, 100 mmol), dichloromethane (40 ml) and benzonitrile (10.3g, 100 mmol). To this allylamine (5.7g, 100 mmol) was carefully added. The autoclave was then sealed and heated at 180°C for 3h. The reaction was cooled, and carefully hydrolysed with water (200 ml). The solution was adjusted to pH 6.0 - 6.5, and extracted with dichloromethane (3 × 25 ml) to remove unreacted benzonitrile. The aqueous solution was basified, and extracted with dichloromethane (3 × 50 ml). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated to give an oil. This was distilled under vacuum to give the title compound as a colourless oil (10.4g, 65%), b.p. 105°C at 0.1 mmHg (lit.,[58] 108-111°C).

ν_{max}(film) 3200, 1640, 1600, 1570, 1200, 920, 780 and 700 cm^{-1};

δ_H(250 MHz; CDCl$_3$) 4.95 (2H, m), 5.1 - 5.3 (2H, m), 5.85 - 6.05 (1H, m), 7.35 (3H, m), 7.55 (2H, m).

m/z 160 (*M*$^+$).

4,5-Dihydro-4-iodomethyl-2-phenylimidazole

(a)

N-Allyl benzamidine (1.6g, 10 mmol) was dissolved in THF (40 ml).

This was added to a solution of pyridine (1g, 12.6 mmol) and iodine

(2.54g, 10 mmol) in THF (20 ml). This solution was stirred for 24h.

The reaction mixture was treated with aqueous sodium thiosulphate

(20%, 100 ml) and extracted with chloroform (3 × 25 ml). The com-

bined organic layers were dried (MgSO$_4$) and concentrated. The

residual gum was subjected to column chromatography (silica), the

product being eluted with chloroform. Concentration of the eluant

gave the title compound as a colourless solid (0.74g, 26%), m.p. 212°C

(Hydroiodide).

(Found: C, 29.1; H, 2.8; N, 6.7. C$_{10}$H$_{12}$I$_2$N$_2$ requires C, 29.0;

H, 2.9; N, 6.7%.)

ν_{max}(CHCl$_3$) 3080, 1705, 1620, 1580, 1520 and 750 cm^{-1};

δ_H(250 MHz; CDCl$_3$) 3.3 (2H, d), 3.55 (1.5H, m), 4.05 (1.5H, m), 4.4

(1H, m), 7.35 (2H, m), 7.45 (1H, m), 7.8 (2H, m).

m/z 286 (M^+).

(b)

N-Allyl benzamidine (0.5g, 3.1 mmol) was dissolved in THF (20 ml),

and to this N-iodosuccinimide (1.4g, 6.2 mmol) was added. The reac-

tion mixture was then stirred for 17h, water (100 ml) added and the

solution extracted with chloroform (3 × 25 ml). The combined organic

layers were dried (MgSO$_4$), and concentrated. The residual solid was

then recrystallised (chloroform : methanol) to give the title compound

as a colourless solid (0.65g, 73%).

4-Methyl-2-phenylimidazole

4,5-Dihydro-4-iodomethyl-2-phenylimidazole (0.37g, 1.3 mmol) was dissolved in THF and DBU (0.25g, 1.3 mmol) added. The solution was then heated at reflux for 2h. After allowing the reaction to cool, water (100 ml) was added and the solution was extracted with dichloro-methane (3 × 25 ml). The combined organic layers were dried (MgSO$_4$) and concentrated, to give the title compound as a colourless solid (0.2g, 86%), m.p. 183°C (lit.,[103] 184°C).

δ_H(.90 MHz; CDCl$_3$) 2.3 (3H, s), 6.85 (1H, s), 7.2 - 7.6 (3H, m), 7.8 - 8.05 (2H, m).

5-Bromo-2-phenyl-3,4,5,6-tetrahydropyrimidine

N-Allylbenzamidine (1.6g, 10 mmol) was dissolved in THF (30 ml) and N-bromosuccinimide (3.56g, 20 mmol) added. The reaction was then stirred for 17h, water (200 ml) added and the resulting solution extracted with dichloromethane (3 × 25 ml). The combined organic layers were dried (MgSO$_4$) and concentrated. The resulting solid was recrystallised from dichloromethane to give the title compound as a colourless solid (2.2g, 88%), m.p. 207°C.

(Found: C, 50.0; H, 4.4; N, 11.6. $C_{10}H_{11}BrN_2$ requires C, 50.2; H, 4.6; N, 11.7%.)

ν_{max}(nujol) 3200, 3080, 1640, 1600, 1550, 1350 and 820 cm^{-1};

δ_H(250 MHz; CDCl$_3$) 3.5 (1H, br s), 3.7 (2H, m), 3.9 (2H, m), 4.35 (1H, m), 7.4 (3H, m), 7.55 (2H, m).

m/z 240 (M^+).

The reaction of N-allyl benzamidine with N-chlorosuccinimide

N-Allylbenzamidine (1.6g, 10 mmol) was dissolved in THF (50 ml) and N-chlorosuccinimide (1.96, 20 mmol) added. The reaction mixture was stirred for 17h and then added to water (200 ml). The resulting solution was extracted with chloroform (3 × 25 ml), and the combined organic layers were dried (MgSO$_4$) and concentrated. The resulting gum was dissolved in dichloromethane (50 ml) and passed through a short silica column. The eluant was concentrated to give the product as a viscous oil (1.2g, 64%).

ν_{max}(film) 3380, 3060, 3000, 1740, 1720, 1640, 1600, 1400, 1150, 780 and 700 cm^{-1};

δ_H(250 MHz; CDCl$_3$) 3.75 (2H, m), 5.2 (2H, m), 5.7 - 5.85 (1H, m), 5.9 (1H, br s), 7.45 (5H, m).

m/z 194 (M^+), 159 ($M-Cl$)$^+$, 145 and 104.

N-Methallylbenzamidine

Methallylamine hydrochloride (1.8g, 1.7 mmol) was mixed with ether (25 ml) and triethylamine (1.8g, 1.1 mmol) added. The reaction mixture was shaken for 4h and then filtered to remove triethylamine hydrochloride. The ethereal solution of methallylamine was then placed in an autoclave, containing aluminium chloride (2.2g, 1.7 mmol). To this was added benzonitrile (1.76g, 1.1 mmol) and the autoclave was sealed and heated at 180°C for 3h. After cooling to room temperature the reaction mixture was added to water (200 ml) and the resulting solution neutralised (pH = 6.0 - 6.5). The reaction was then extracted with dichloromethane (3 × 25 ml) to remove unreacted benzonitrile. The solution was made basic and again extracted with dichloromethane (3 × 25 ml). The combined organic layers were dried (Na_2SO_4) and concentrated. The residual oil was distilled under vacuum to give the title compound as a colourless oil which crystallised on standing (1.1g, 57%), m.p. 97°C.

(Found: C, 75.9; H, 8.1; N, 16.2. $C_{11}H_{14}N_2$ requires C, 75.8; H, 8.1; N, 16.0%.)

v_{max}(nujol) 3120, 3060, 1620, 1600, 1360, 1205, 995 and 700 cm^{-1};

δ_H(250 MHz; $CDCl_3$) 1.8 (3H, s), 3.9 (2H, s), 4.9 (2H, d), 7.4 (3H, m), 7.6 (2H, m).

m/z 174 (M^+).

4,5-Dihydro-4,4-dimethyl-2-phenylimidazole

Methallylamine hydrochloride (1.8g, 1.7 mmol) was dissolved in dichloromethane (50 ml) and triethylamine (1.8g, 1.8 mmol) added. The solution was stirred for 3h and then placed in an autoclave containing aluminium chloride (2.2g, 1.7 mmol). Benzonitrile (1.76g, 1.1 mmol) was added, the autoclave sealed and heated at 180°C for 3h. After

cooling the reaction to room temperature, it was added to water (200 ml). The resulting solution was neutralised (pH = 6.0 - 6.5) and extracted with dichloromethane (3 × 25 ml) to remove unreacted benzonitrile. The solution was then made basic and again extracted with dichloromethane (3 × 25 ml). The combined organic layers were dried (Na_2SO_4) and concentrated. This gave a gum which crystallised on standing, and after recrystallisation (petrol : chloroform) gave the title compound as a colourless solid (1.3g, 68%), m.p. 81°C.

(Found: C, 75.7; H, 8.1; N, 16.1. $C_{11}H_{14}N_2$ requires C, 75.8; H, 8.1; N, 16.0%.)

ν_{max}(nujol) 3180, 1600, 1360, 1220, 1040, 780 and 720 cm^{-1};

δ_H(60 MHz; $CDCl_3$) 1.35 (6H, s), 3.55 (2H, br s), 7.4 (3H, m), 7.75 (2H, m).

m/z 174 (M^+), 159 and 104.

4,5-Dihydro-4-iodomethyl-4-methyl-2-phenylimidazole

N-Methallylbenzamidine (1.7g, 10 mmol) was dissolved in THF (50 ml), and N-iodosuccinimide (4.5g, 20 mmol) added. The reaction mixture was then stirred for 17h, and added to water (200 ml). The resulting solution was extracted with chloroform (3 × 25 ml), the combined organic layers dried and concentrated. The residual gum was dissolved in dichloromethane (100 ml) and passed through a short silica column. The eluant was concentrated and the resulting gum triturated with ether (100 ml) to give the title compound as a colourless solid (2.3g, 76%), m.p. 106°C.

(Found: M^+ 300.01240; $C_{11}H_{13}IN_2$ requires 300.01235.)

ν_{max}(CHCl$_3$) 3080, 2920, 1700, 1620, 1540, 750 and 700 cm^{-1};

δ_H(250 MHz; CDCl$_3$) 1.55 (3H, s), 3.4 - 3.9 (4H, m), 5.0 (1H, br s), 7.3 - 7.65 (3H, m), 7.95 (2H, d).

m/z 300 (M^+), 173 $(M-I)^+$, 159 and 104.

N-Allyl-2,2,2-trichloroacetamidine

Trichloroacetonitrile (5.4g, 3.7 mmol) was dissolved in benzene (25 ml) and cooled to 10°C. To this allylamine (2.25g, 3.9 mmol) was slowly added as a solution in benzene (20 ml). The resulting solution was allowed to rise to room temperature and then stirred for 17h. The solution was concentrated and the residual oil distilled under vacuum. This gave the title compound as a colourless oil (6.1g, 80.1%), b.p. 110°C at 1 mmHg.

ν_{max}(film) 3460, 3340, 3080, 2980, 2900, 1640, 1520 and 830 cm^{-1};

δ_H(250 MHz; CDCl$_3$) 3.95 (2H, m), 5.15 - 5.35 (2H, m), 5.85 - 6.05 (1H, m).

m/z 201 (M^+).

4,5-Dihydro-4-iodomethyl-2-trichloromethylimidazole

N-Allyl-2,2,2-trichloroacetamidine (2g, 10 mmol) was dissolved in THF (50 ml). This was added to a solution of pyridine (1.58g, 20 mmol) and iodine (2.5g, 20 mmol) in THF (50 ml). The solution was stirred for 17h and then added to aqueous sodium thiosulphate (20%, 200 ml). The resulting solution was extracted with dichloromethane (3 × 25 ml), the combined organic layers were dried (MgSO$_4$) and concentrated. The residual gum was dissolved in dichloromethane (20 ml) and passed through a short silica column. The eluant was then evaporated to give the title compound as a colourless solid (2.87g, 88%), m.p. 106°C.

(Found: C, 18.5; H, 1.8; N, 8.3. C$_5$H$_6$Cl$_3$IN$_2$ requires C, 18.3; H, 1.8; N, 8.5%.)

ν_{max}(nujol) 3120, 1605, 1280, 820 and 800 cm^{-1};

δ_H(250 MHz; CDCl$_3$) 3.3 (2H, m), 3.65 (1H, m), 4.0 (1H, m), 4.35 (1H, m), 4.9, (H, br s).

m/z 327 (M^+).

5-Bromo-3,4,5,6-tetrahydro-2-trichloromethylpyrimidine

N-Allyl-2,2,2-trichloroacetamidine (2g, 10 mmol) was dissolved in THF (50 ml). This was added to a solution of pyridine (1.58g, 20 mmol) and bromine (1.6g, 20 mmol) in THF (50 ml). The reaction mixture was stirred for 17h and then treated with aqueous sodium thiosulphate (20%, 200 ml). The resulting solution was extracted with dichloromethane (3 × 25 ml), the combined organic layers dried (MgSO$_4$) and concentrated. The residual gum was dissolved in dichloromethane (20 ml) and passed through a short silica column. The eluant was then concentrated to give the title compound as a colourless solid (2.1g, 74%), m.p. 171°C.

(Found: C, 21.4; H, 2.09; N, 9.8. C$_5$H$_6$Cl$_3$N$_2$ requires C, 21.4; H, 2.15; N, 9.9%).

ν_{max}(CHCl$_3$) 3200, 1640, 1500, 1460, 1320, 820 and 800 cm^{-1};

δ_H(250 MHz; CDCl$_3$) 3.75 (2H, m), 3.95 (2H, m), 4.3 (1H, m), 5.0 (1H, br s).

m/z 280 (M^+).

N-Methallyl-2,2,2-trichloroacetamidine

Methylallylamine hydrochloride (1.07g, 10 mmol) was mixed with benzene (50 ml) and triethylamine (1.21g, 12 mmol) added. The resulting suspension was stirred for 17h and then trichloroacetonitrile (1.325, 10 mmol) added. The reaction mixture was then stirred for 24h, filtered and concentrated. The residual oil was then distilled under vacuum to give the title compound as a colourless oil (1.7g, 80%), b.p. 112°C at 1 mmHg.

(Found: 213.98210. $C_6H_9{}^{35}Cl_3N_2$ requires 213.98313.)

ν_{max}(film) 3460, 3340, 3100, 2980, 2920, 1730, 1640, 1525, 1330, 1265, 900, and 840 cm^{-1};

δ_H(250 MHz; CDCl$_3$) 1.8 (3H, s), 3.9 (2H, s), 4.95 (2H, m), 5.35 (1H, br s).

m/z 214 (M^+), 179, 143 and 97.

4,5-Dihydro-4-iodomethyl-4-methyl-2-trichloromethylimidazole

N-Methallyl-2,2,2-trichloroethamidine (2g, 9.3 mmol) was dissolved in THF (100 ml). The resulting solution was added to a mixture of pyridine (1.5g, 18 mmol) and iodine (2.35g, 18 mmol) in THF (50 ml). The reaction mixture was stirred for 17h and then added to aqueous sodium thiosulphate (20%, 200 ml). The resulting solution was extracted with dichloromethane (3 × 25 ml), the combined organic layers dried and concentrated. The residual gum was dissolved in ether (100 ml) and passed through a short silica column. The eluant was then concentrated to give the title compound as a colourless solid (2.7g, 86%), m.p. 105°C.

(Found: C, 21.2;   H, 2.2;   N, 8.1. $C_6H_8Cl_3IN_2$ requires C, 21.1;

H, 2.3;   N, 8.2%).

ν_{max}(CHCl$_3$)   3160, 1610, 1460, 1200, 1040 and 795 cm^{-1};

δ_H(250 MHz; CDCl$_3$)   1.5 (3H, s), 3.35 (2H, q), 3.7 (2H, q), 5.1 (1H,

br s).

m/z   341 (M^+), 305, 213 $(M-I)^+$, 199.

PART B

EXPERIMENTAL FOR CHAPTER IV

General procedure for the preparation of triazenes

3-(3,3-Dimethyltriazen-1-yl)pyridine-4-carboxylic acid

3-Aminopyridine-4-carboxylic acid (1.36g, 9.85 mmol) was suspended in ethanol (20 ml) added. This mixture was cooled in ice, and treated dropwise with an ice cold solution of sodium nitrite (1.77g, 25 mmol) in water (25 ml). After the addition, the mixture was stirred at 0°C for a further 20 min. The cold diazotisation solution was then added dropwise to an ice cold mixture of sodium carbonate (3.44g, 32 mmol) and dimethyl-amine (26% aqueous solution, 1.73g, 10 mmol) in water (20 ml). The resulting mixture was stirred for a further 30 min at 0°C, acidified to pH = 5-6 with concentrated hydrochloric acid, and extracted with chloroform (5 × 25 ml). The combined organic layers were dried (Na_2SO_4), and concentrated to give the title compound as a pale yellow solid (1.4g, 72%), m.p. 134°C.

(Found: C, 49.15; H, 5.1; N, 28.5. $C_8H_{10}N_4O_2$ requires C, 49.5; H, 5.2; N, 28.85%.)

ν_{max}(nujol) 3400, 2600, 1700, 1520, 1320, 1260, 1120 and 700 cm^{-1};

δ_H(250 MHz; $CDCl_3$) 3.4 (3H, s), 3.8 (3H, s), 7.95 (1H, d), 8.5 (1H, d), and (1H, s).

m/z 194 (M^+), 150, 123, 94 and 78.

3-(3,3-Pentamethylenetriazen-1-yl)pyridine-4-carboxylic acid

3-Aminopyridine-4-carboxylic acid (1.4g, 10 mmol) was coupled to piperidine (0.85g, 10 mmol) using the general procedure for the preparation of triazenes. Recrystallisation from ether gave the title compound as a pale yellow solid (1.1g, 47%), m.p. 110°C.

(Found: C, 56.4; H, 6.0; N, 24.1. $C_{11}H_{14}N_4O_2$ requires C, 56.40; H, 6.0; N, 23.90%.)

ν_{max}(nujol) 3080, 1730, 1560, 1320 and 820 cm^{-1};

δ_H(250 MHz; CDCl$_3$) 1.8 - 2.0 (6H, br m), 3.85 (2H, br t), 4.0 (2H, t), 8.0 (1H, d), 8.55 (1H, d), 9.05 (1H, s).

m/z 234 (M^+), 190, 150, 121, 94 and 84.

3-(3,3-Diisopropyltriazen-1-yl)pyridine-4-carboxylic acid

3-Aminopyridine-4-carboxylic acid (1.4g, 10 mmol) was coupled to diisopropylamine (1g, 10 mmol) using the general procedure for the preparation of triazenes. Recrystallisation from ether gave the title compound as pale yellow needles (0.87g, 35%), m.p. 133°C.

(Found: C, 57.5; H, 7.3; N, 22.2. $C_{12}H_{18}N_4O_2$ requires C, 57.6; H, 7.2; N, 22.4%.)

ν_{max}(nujol) 3400, 2600, 1705, 1320 and 700 cm^{-1};

δ_H(250 MHz; CDCl$_3$) 1.35 (6H, d), 1.45 (6H, d), 4.2 (1H, m), 4.95 (1H, m), 7.95 (1H, d), 8.5 (1H, d), 9.0 (1H, s).

m/z 250 (M^+), 206, 150, 122, 100, 94, 86.

3-(3,3-Dimethyltriazen-1-yl)pyridine-2-carboxylic acid

The title compound was prepared from 3-aminopyridine-2-carboxylic acid (1.36g, 9.85 mmol) using the general procedure for the preparation of triazenes. After recrystallisation (chloroform : ether) it was obtained as a white crystalline solid (0.49g, 26%), m.p. 126°C.

(Found: C, 49.6; H, 5.1; N, 28.9. $C_8H_{10}N_4O_2$ requires C, 49.5; H, 5.2; N, 28.8%.)

ν_{max}(nujol) 3360, 3080, 2620, 1730, 1500, 1430, 1320 and 700 cm^{-1};

δ_H(250 MHz; CDCl$_3$) 3.3 (3H, s), 3.7 (3H, s), 7.4 (1H, dd), 8.0 (1H, d), 8.6 (1H, d).

m/z 194 (M^+), 150, 122 and 94.

3-Amino-2-methylpyridine-4-carboxylic acid

2-Methylpyridine-3,4-dicarboxylic acid (4g, 26.3 mmol) was sus-
pended in freshly distilled acetic anhydride (25 ml), and heated on a
water bath until complete complete dissolution had taken place. The
excess acetic anhydride was then removed *via* evaporation and
acetamide (4g, 67.8 mmol) added. The reaction mixture was then heated
on an oil bath at 130°C for 2h. After concentrating the reaction
mixture the solid residue was triturated with ethanol (20 ml), the
suspension thus produced filtered and dried. The resulting powder
was dissolved in 10% aqueous sodium hydroxide (50 ml) containing
bromine (1.9g, 23.7 mmol), and heated on a steam bath for 30 min. The
solution was cooled on an ice bath and adjusted to pH = 5 with glacial
acetic acid. The precipitated title compound was then collected and
dried as an orange solid (1.2g, 41%), m.p. 252°C (hydrochloride).

(Found: C, 55.5; H, 5.15; N, 17.9. $C_7H_8N_2O_2$ requires C, 55.3;
H, 5.3; N, 18.1%.)

ν_{max}(hexachlorobutadiene) 3400, 3280, 1620 and 1160 cm^{-1};

δ_H[250 MHz; $(CD_3)_2SO$] 2.45 (3H, s), 6.45 (1H, d), 6.45 (2H, br s),
7.75 (1H, d).

m/z 152 (M^+), 134, 106 and 79.

The attempted diazotisation and coupling of 3-amino-2-methylpyridine-4-carboxylic acid

3-Amino-2-methylpyridine-4-carboxylic acid (1.5g, 9.8 mmol) was
suspended in ethanol (25 ml) and concentrated hydrochloric acid (2.5 ml)
added. This mixture was then cooled to 0°C in ice, and treated drop-
wise with an ice cold solution of sodium nitrile (1.77g, 25 mmol) in
water (25 ml). After the addition the mixture was stirred at 0°C for

a further 20 min. The cold diazotisation solution was then added dropwise to an ice cold mixture of sodium carbonate (3.44g, 32 mmol) and dimethylamine (26% aqueous solution, 1.73g, 10 mmol) in water (20 ml). The resulting mixture was stirred for a further 30 min at 0°C, acidified to pH = 5-6 with concentrated hydrochloric acid, and extracted with chloroform (5 × 25 ml). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated to give 3-(3,3-*dimethyltriazen-1-yl*) 2-*methylpyridine-4-carboxylic acid* (0.011g, 1.1%), m.p. 123°C.

(Found: C, 52.4; H, 5.8; N, 26.3. C$_9$H$_{12}$N$_4$O$_2$ requires C, 51.9; H, 5.8; N, 26.9%.)

ν_{max}(nujol) 3400, 2600, 1700 and 700 cm^{-1};

δ_H(250 MHz; CDCl$_3$) 2.58 (3H, s), 3.25 (3H, br s), 3.55 (3H, br s), 7.55 (1H, d), 8.3 (1H, d).

m/z 208 (M^+), 164, 136, 108, 53 and 44.

The aqueous solution was then concentrated under vacuum and cooled. The resulting precipitate was then filtered, dried and recrystallised (ethanol) to give 3-*hydroxy-2-methylpyridine-4-carboxylic acid* (0.9g, 63%), as a pale brown solid, m.p. >300°C.

(Found: C, 54.95; H, 4.5; N, 9.2. C$_7$H$_7$NO$_3$ requires C, 54.9; H, 4.6; N, 9.15%).

ν_{max}(nujol) 3440, 3080, 1650, 1610, 1400 and 830 cm^{-1};

δ_H[250 MHz; (CD$_3$)$_2$SO] 2.45 (3H, s), 7.5 (1H, d), 7.7 (1H, d).

m/z 153 (M^+), 135, 107 and 79.

General procedure for the decomposition of triazenes in the presence
of tetracyclone

The triazene (0.5 mmol) and tetracyclone (2.5 mmol) were dissolved
in dry acetonitrile (20 ml).   To this mixture 1 drop of trifluoroacetic
acid was added, and the reaction heated at reflux for 6h.   The reaction
mixture was then concentrated and the residual gum subjected to column
chromatography (silica).   Elution with (petrol : ether) and evaporation
of the eluant gave 5,6,7,8-tetraphenylisoquinoline as a colourless
solid, m.p. 220°C (lit.,   221°C).

v_{max}(nujol) 3070, 1600, 1480 and 700 cm^{-1};

δ_H(250 MHz; CDCl$_3$) 6.85 (8H, m), 7.25 (12H, m), 7.45 (1H, d), 8.45
(1H, d), 9.05 (1H, s).

m/z 433 (M^+), 356 and 105.

The reaction of 3-(3,3-dimethyltriazen-1-yl)pyridine-4-carboxylic acid
with tetracyclone

3-(3,3-Dimethyltriazen-1-yl)pyridine-4-carboxylic acid (0.28g,
1.44 mmol) was subjected to the general procedure previously described,
yielding 5,6,7,8-tetraphenylisoquinoline as a colourless solid (0.293g,
47%).

The reaction of 3-(3,3-pentamethylenetriazen-1-yl)pyridine-4-carboxylic
acid with tetracyclone

3-(3,3-Pentamethylenetriazen-1-yl)pyridine-4-carboxylic acid (0.25g,
1.06 mmol) was used in the general procedure for the reaction of triazenes
with tetracyclone.   5,6,7,8-Tetraphenylisoquinoline was isolated as
a colourless solid (0.206g, 45%).

The reaction of 3-(3,3-diisopropyltriazen-1-yl)pyridine-4-carboxylic
acid with tetracyclone

3-(3,3-Diisopropyltriazen-1-yl)pyridine-4-carboxylic acid (0.1g,
0.5 mmol) was subjected to the general procedure for the reaction of
triazenes with tetracyclone previously described.   5,6,7,8-Tetraphenyl-
isoquinoline was isolated as a colourless solid (0.09g, 43%).

General procedure for the reaction of triazenes in the presence of
2,5-dimethylfuran

   The triazene (0.5 mmol) and 2,5-dimethylfuran (5 mmol) were dissolved
in dry acetonitrile (2 ml).   The solution was then heated at reflux
for 14h, and then concentrated.   The residual gum was subjected to
column chromatography (silica) eluting with petrol : ether.   Evaporation
of the eluant gave the Diels-Alder adduct as a viscous oil, m.p.
159 - 160°C (picrate).

(Found: C, 50.8; H, 3.5; N, 13.8. $C_{17}H_{14}N_4O_8$ requires C, 50.7;
H, 3.5; N, 13.9%.)

ν_{max}(film) 2920, 2860, 1600, 1380, 1300, 1130 and 850 cm^{-1};

δ_H(90 MHz; CDCl$_3$) 1.95 (3H, s), 2.00 (3H, s), 6.8 (2H, q), 7.15 (2H,
d), 8.3 (2H, m).

m/z 173 (M^+), 160, 147, 131 and 77.

The reaction of 3-(3,3-dimethyltriazen-1-yl)pyridine-4-carboxylic acid
with 2,5-dimethylfuran

   3-(3,3-Dimethyltriazen-1-yl)pyridine-4-carboxylic acid (0.1g, 0.5
mmol) was used in the general procedure previously described.   The
Diels-Alder adduct was recovered as a colourless gum (0.023g, 26%).

The reaction of 3-(3,3-pentamethylenetriazen-1-yl)pyridine-4-carboxylic
acid with 2,5-dimethylfuran

   3-(3,3-Pentamethylenetriazen-1-yl)pyridine-4-carboxylic (0.230g,
0.98 mmol) was used in the general procedure for the reaction of
triazenes with 2,5-dimethylfuran.   The Diels-Alder adduct was isolated
as colourless gum (0.037g, 22%).

The reaction of 3-(3,3-dimethyltriazen-1-yl)pyridine-4-carboxylic acid with furan

3-(3,3-Dimethyltriazen-1-yl)pyridine-4-carboxylic acid (0.12g, 0.62 mmol) and freshly distilled furan (2g, 29.4 mmol) were dissolved in dry acetonitrile (5 ml). The reaction mixture was then placed in an autoclave and heated at 130°C for 4 h. The reaction mixture was concentrated and subjected to chromatography (silica). Elution with (petrol : ether) and evaporation of the eluant gave the Diels-Alder adduct as a viscous oil (0.036g, 40%), m.p. 177°C picrate (lit., 178°C).

ν_{max}(film) 2950, 2860, 1600, 1450, 1380, 1350, 1140 and 870 cm^{-1};

δ_H(90 MHz; CDCl$_3$) 5.9 (1H, d), 6.0 (1H, d), 7.1 (2H, m), 7.3 (1H, d), 8.3 (1H, d), 8.5 (1H, s).

m/z 145 (M^+), 119, 103 and 77.

The photochemical decomposition of 3-(3,3-dimethyltriazen-1-yl)pyridine-4-carboxylic acid in the presence of tetracyclone

3-(3,3-Dimethyltriazen-1-yl)pyridine-4-carboxylic acid (0.2g, 1.03 mmol) and tetracyclone (1g, 2.6 mmol) were dissolved in dry aceto-nitrile (100 ml). This solution was then placed in a pyrex photolysis tube and irradiated at 300 nm for a total of 96h. The reaction mixture was then concentrated and the residual gum subjected to column chromato-graphy (silica). Elution with petrol : ether and concentration of the eluant gave 5,6,7,8-tetraphenylisoquinoline (80 mg, 18%)

The decomposition of 3-(3,3-dimethyltriazen-1-yl)pyridine-4-carboxylic acid in the presence of 1,4-dimethylpyrano[3,4-b]indol-3-one

3-(3,3-Dimethyltriazen-1-yl)pyridine-4-carboxylic acid (0.18g, 0.89 mmol) and 1,4-dimethylpyrano[3,4-b]indol-3-one (0.076g, 0.36 mmol), were dissolved in dry acetonitrile (15 ml). This solution was then treated at reflux for a total of 36 hours. The reaction mixture was then concentrated and the residual gum subjected to column chromatography (silica). Elution with chloroform : methanol (98:2) led to the sequential recovery of the two products. Concentration of the first fraction gave isoellipticine (0.018g, 20%), m.p. 245°C (lit.,[104] 243 -250 °C).

δ_H(250 MHz; CDCl$_3$) 2.9 (3H, s), 3.2 (3H, s), 7.35 (1H, m), 7.6 (2H, m), 8.05 (1H, d), 8.15 (1H, s), 8.4 (1H, d), 8.65 (1H, d), 9.7 (1H, s).

m/z 246 (M^+), 231, 123, 112 and 95.

Concentration of the second fraction gave ellipticine (0.018g, 20%), m.p. 314°C (lit.,[104] 311 - 319°C).

δ_H(250 MHz; CDCl$_3$) 2.8 (3H, s), 3.3 (3H, s), 7.35 (1H, m), 7.55 (2H, m), 7.9 (1H, d), 8.2 (1H, s), 8.4 (1H, d), 8.5 (1H, d), 9.75 (1H, s).

m/z 246 (M^+), 231, 123, 109 and 96.

APPENDIX I

X-RAY DATA

Crystal Data

$C_{10}H_{11}N_2Br$, M = 239.1, monoclinic, a = 10.126(2), b = 5.654(1), c = 17.600(3)Å, β = 100.92(2)°, U = 989Å^3, space group $P2_1/a$, Z = 4, D_c = 1.60gcm^{-3}, μ(Cu-K_α) = 53cm^{-1}, $F(000)$ = 480. 1256 independent reflections ($\theta \leqslant 58°$) were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. Of these 1141 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The structure was solved by the heavy atom method and the non-hydrogen atoms refined anisotropically. An empirical absorption correction, based on 366 azimuthal measurements, was applied. The amine proton was located from a ΔF map, and refined isotropically. The positions of the remaining hydrogen atoms were idealised, C-H = 0.96Å, assigned isotropic thermal parameters, U(H) = 1.2U_{eq}(C), and allowed to ride on their parent carbon atoms. Refinement converged to give R = 0.038, R_w = 0.044 [w^{-1} = $\sigma^2(F)$ + 0.00058F^2]. The maximum residual electron density in the final ΔF map was 0.50 eÅ^{-3} and mean and maximum shift/error in final refinement were 0.002 and 0.024 respectively.

(17)
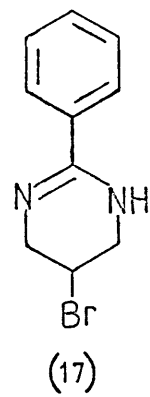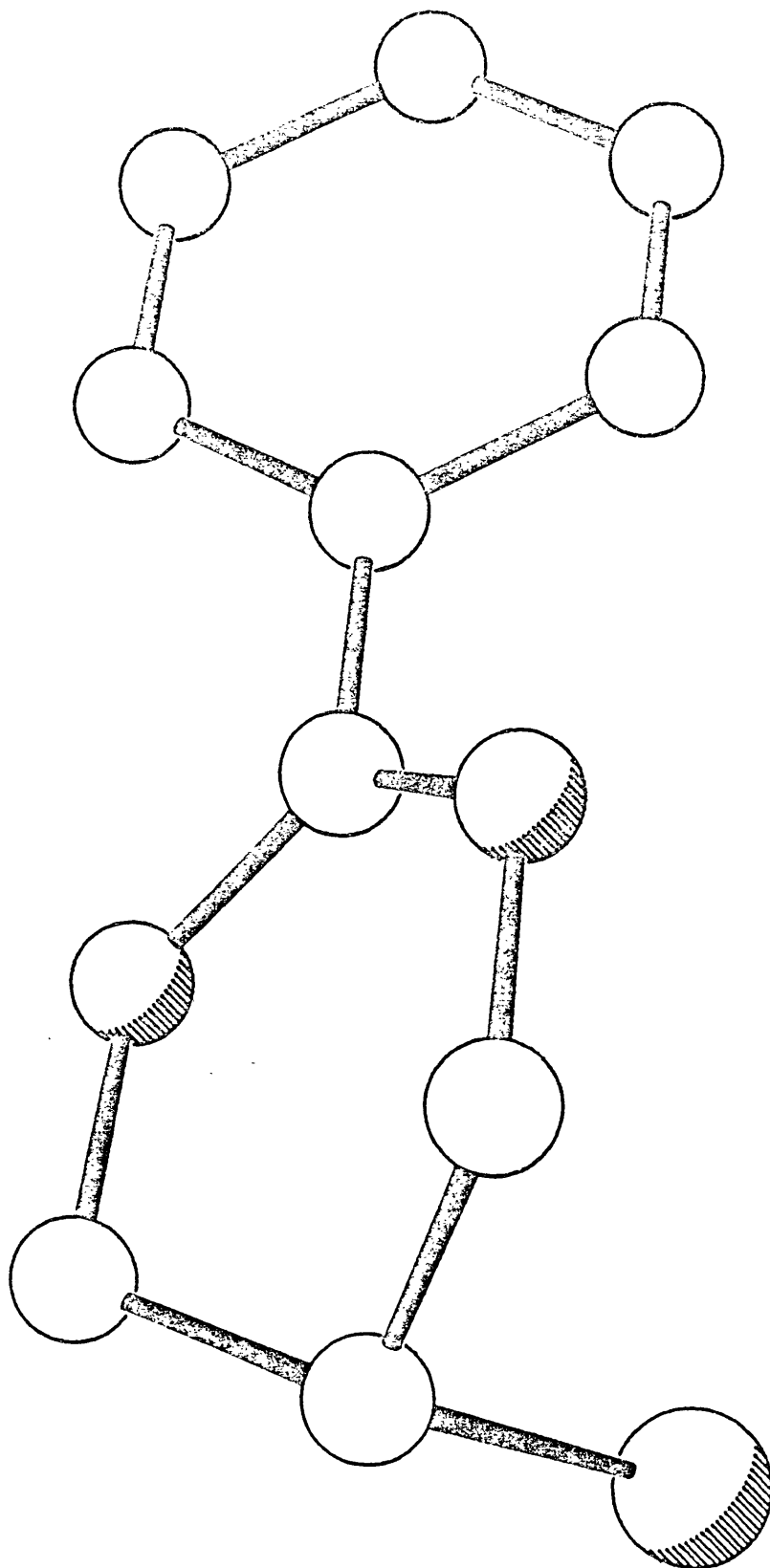
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