SYNTHETIC ROUTES TO AZASTEROIDS AND CYCLIC AMIDINES USING AZA DIELS-ALDER REACTIONS

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ABSTRACT

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by Helen Rataj

Azasteroids exhibit a wide range of biological activity and hence the search for successful synthetic routes and novel azasteroid structures is of considerable scientific interest. The first section of this thesis deals with the formation of azasteroids using total synthesis *via* aza Diels-Alder reactions or a complementary approach based on the degradation of lanosterol. The second is concerned with the aza Diels-Alder reactions of a variety of aminoheterocycles leading to novel cyclic amidines along with a number of related structures. The total synthesis approach involved cycloaddition reactions of aromatic iminium ions with electron rich alkenes. Generated from bicyclic amines, the iminium ions behaved as 2-azadiene equivalents in the reactions with methylcyclopentadiene and cyclohexadiene to yield a selection of monoazasteroids. Furthermore, cyclohexadiene was found to act as both diene and dienophile to yield both azabicyclo compounds and azasteroids; we believe that the formation of two separate products in this case suggests a stepwise mechanism is in operation. Also, the results of biological testing of some of these novel azasteroids acting as antifungal agents is presented. The degradative route designed to give azasteroids was based on lanosterol since this steroid is rarely found in plants, but occurs in fungi. Nitrogen was successfully introduced into the molecule in the form of an oxime following a series of reactions and Beckmann rearrangements of the oximes gave a series of B-homo azasteroids. The aza Diels-Alder reactions of 2-aminopyridines, behaving as 1,3-diazadienes, with electron rich alkenes including indene and styrene gave rise to a variety of pyrido[1,2-*a*]pyrimidine derivatives. The structure of the cyclic amidine products is confirmed by single crystal X-ray analysis of a neutral amidine and of a trifluoroacetate salt. Consequently, these structural studies permit the regio- and stereochemical outcome of these additions to be defined and compared with related processes. Several aminoheterocycles were used to synthesise a variety of cyclic amidines and cyclic isothioureas in good yields, including in the case of 1-aminoisoquinoline, diazasteroids. Finally, the relationship of the diverse series of skeletons synthesised to compounds of known biological activity is emphasised.

ACKNOWLEDGEMENTS

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3.0 EXPERIMENTAL

INTRODUCTION

1.0 INTRODUCTION

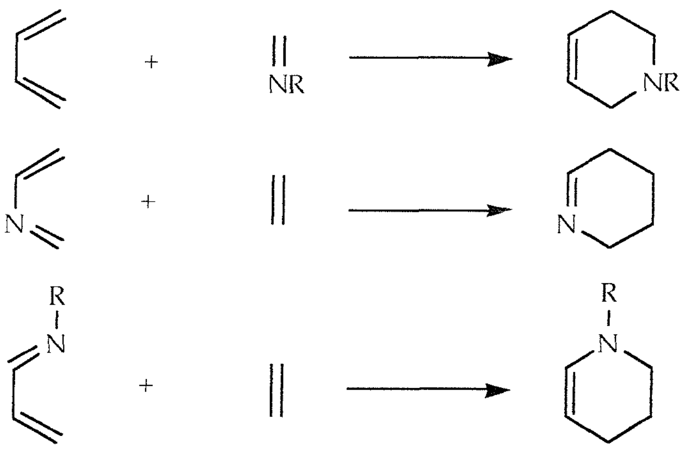
1.1 GENERAL INTRODUCTION AND BACKGROUND

The work undertaken in this thesis is a study of synthetic routes towards azasteroids and cyclic amidines. Azasteroids contain at least one nitrogen atom in the basic steroid skeleton and they attract attention for two main reasons: their biological activity has been observed in many pharmacological areas; also, the synthesis of azasteroids represents the development of new and useful reactions. There have been many different synthetic routes developed towards azasteroids; one of the most important is the Diels-Alder approach. The Diels-Alder reaction[1] consists of a 1,4-addition of a conjugated diene with a dienophile which may be a double or triple bond. It is usually a stereospecific *cis* addition to form a carbocyclic adduct with a six membered ring. The most common and successful Diels-Alder reactions occur between an electron rich diene and electon poor dienophile, although inverse electron demand reactions between an electron rich dienophile and electron deficient diene also have their uses in synthesis.[2]

Cycloaddition of reactive species containing a heteroatom can yield a variety of six membered heterocyclic compounds.[3-5] Hetero Diels-Alder reactions (Scheme 1) have generally attracted less attention than the "normal" all-carbon Diels-Alder reaction[6], despite their significant preparative value, for example, in the synthesis of complex molecules such as natural products. The presence of a heteroatom is a distinct difference from the all-carbon Diels-Alder; because of the very nature and position of the heteroatom, and any substituents present, every hetero Diels-Alder reaction may occur in a particular way. The paucity of substantial mechanistic information hinders logical synthetic planning. Furthermore, there are the possible differences of the observed regio- or stereospecificity of the reactions, and a general lack of information regarding dependable procedures, which complicates incorporation of such cycloadditions into sophisticated synthetic strategies. Nevertheless, the continuous accumulation of knowledge enables and encourages the exploitation of the hetero Diels-Alder reaction to its full potential.

The cycloaddition approach toward azasteroids can be an aza Diels-Alder reaction with several different possible positions of the nitrogen atom in the final structure.

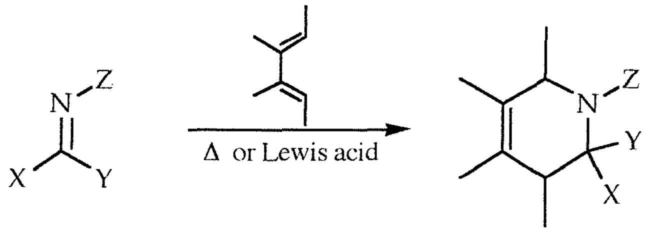
The next two sections (1.2 and 1.3) briefly introduce and give examples of azadienophiles and azadienes in Diels-Alder reactions. Also discussed is an introduction to 2-azadiene equivalents and their participation in reactions which form the origin of the work carried out in this thesis.



Scheme 1

1.2 AZADIENOPHILES IN DIELS-ALDER CYCLOADDITIONS

Diels-Alder cycloadditions with imines as the azadienophiles are generally the most popular reactions.[4,7,8] Imines and iminium ions are usually electron deficient dienophiles and hence are suitable species to take part in "normal" Diels-Alder reactions. Not all imino compounds however are suitable; simple Schiff bases have been shown to be unreactive in [4+2] cycloadditions unless particularly reactive dienes are employed.[9,10] Substitution of the imines with electron withdrawing groups improves their reactivity with electron rich dienes; therefore azadienophiles such as N-sulfonylimines and N-acylimines[11] can add to many 1,3-dienes in good yields to produce tetrahydropyridines (Scheme 2).



Z = SO_2Ar, COR
X,Y = H, CO_2R, Ar, CCl_3

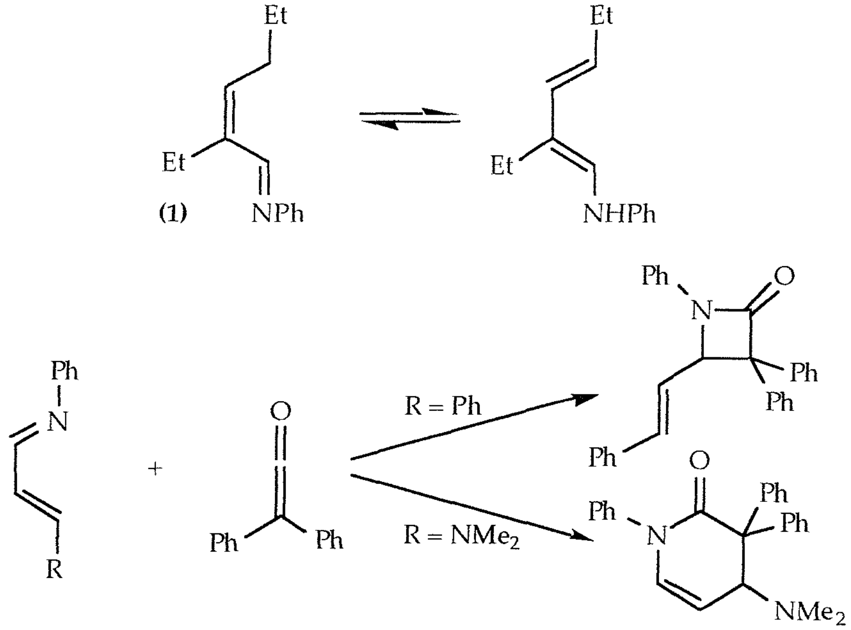
Scheme 2

1.3 AZADIENES IN DIELS-ALDER CYCLOADDITIONS

The reaction of azadienes can be divided into two types. The first is the "normal" Diels-Alder reaction[6] in which the azadiene usually contains electron donating groups and reacts with electron deficient dienophiles. In the second, the azadiene is usually electron deficient and reacts with electron rich dienophiles in inverse electron demand Diels-Alder reactions.

1.3.1 1-AZADIENES

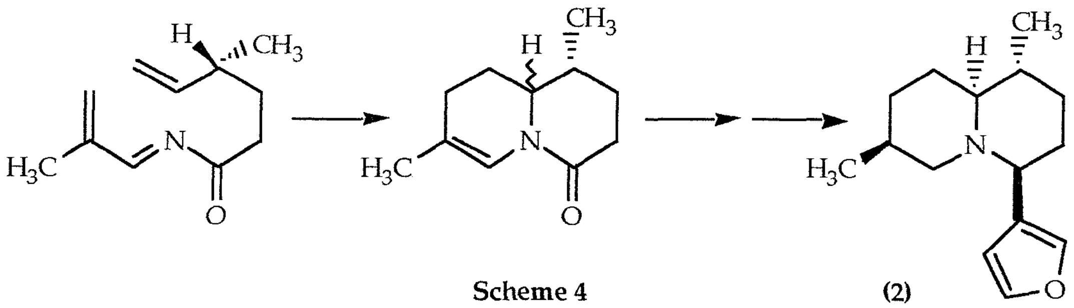
Considering the normal Diels-Alder reaction, early general observations indicated that 1-azabutadienes fail to undergo [4+2] cycloadditions[3,12] although exceptions to the rule included the reactions of benzoisoxazole[13] and unsaturated 3,4-dihydroisoquinolines.[14] Unsaturated imines such as (1) may take part in Diels-Alder reactions as the enamine; where tautomerism is impeded, [2+2] cycloadditions commonly occur (Scheme 3).[15,16]



(1)

Scheme 3

In the case of inverse electron demand Diels-Alder reactions, N-acyl-1-azabutadienes have been shown to undergo intramolecular [4+2] cycloadditions[17] in the synthesis of an intermediate amide in the total synthesis of deoxynupharidine (2)[18] (Scheme 4).



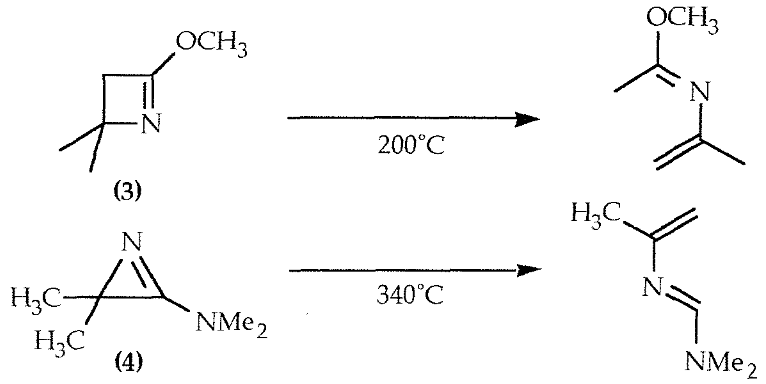
Scheme 4

(2)

1.3.2 2-AZADIENES

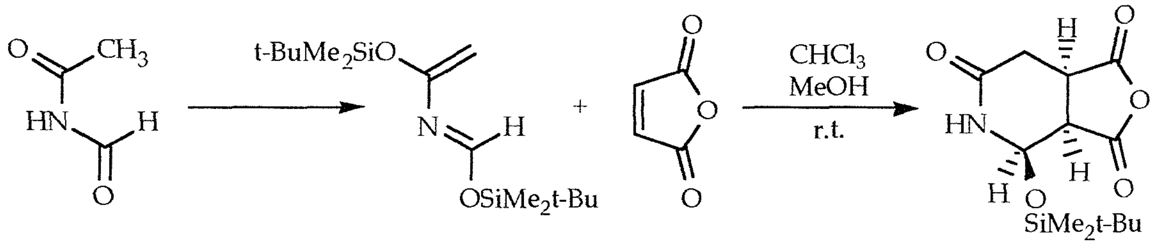
2-Azadienes which undergo normal Diels-Alder reactions have, in most cases, been substituted with strong electron donating groups in order to improve their reactivity in cycloadditions with electron deficient dienophiles.

Thermolysis of azetines (3)[19] and azirines (4)[20] yield 2-azadienes in excellent yields which undergo [4+2] cycloadditions with a wide range of electron deficient dienophiles (Scheme 5).



Scheme 5

1,3-Bis(*t*-butyldimethylsilyloxy)-2-azabutadienes[21] may be readily generated from imides, and they react easily with a variety of electron deficient dienophiles in high yielding cycloadditions (Scheme 6).

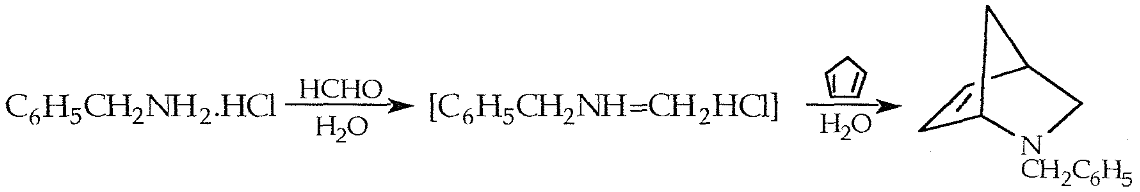


Scheme 6

Imines have previously been mentioned as potential azadienophiles. Imines or iminium ions formed from an aromatic amine and an aldehyde however may be considered as 2-azadiene equivalents. Being electron deficient species they will therefore undergo inverse electron demand Diels-Alder reactions.

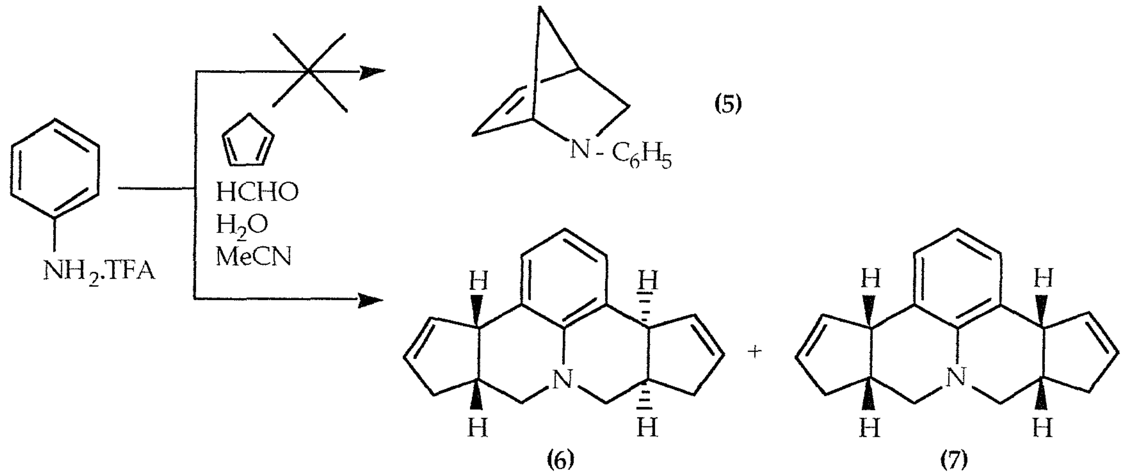
1.3.3 IMINIUM IONS IN AZA DIELS-ALDER REACTIONS

In 1988 Grieco and Bahsas[22] reported the use of iminium ions generated from aryl amines and aldehydes functioning as azadienes rather than azadienophiles, with cyclopentadiene as the dienophile, giving rise to novel tetrahydroquinolines. Previously,[23] Grieco had shown that simple immonium salts generated in situ from primary alkyl amines and formaldehyde could undergo facile condensations with cyclopentadiene to yield azanorbornenes in excellent yield (Scheme 7).



Scheme 7

In complete contrast, the use of aniline in the reaction (Scheme 8) did not yield the corresponding N-phenyl-2-azanorbornene (5), but instead gave two novel tetrahydroquinoline products (6) and (7).



Scheme 8

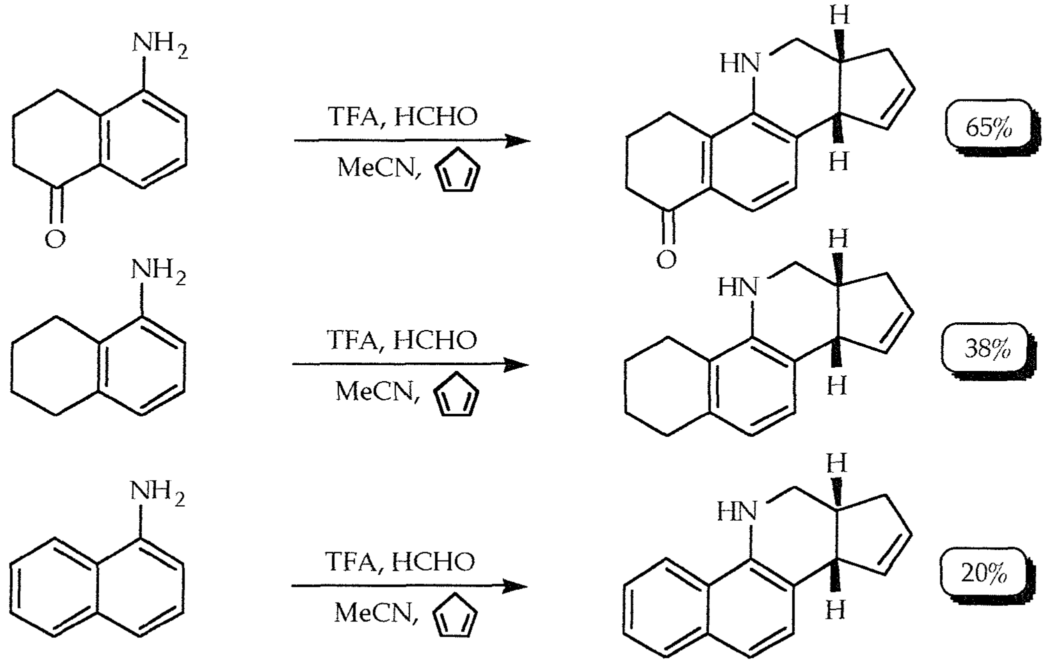
1.4 IMINIUM IONS DERIVED FROM AROMATIC AMINES AS 2-AZADIENE EQUIVALENTS

The work carried out by Grieco[22] was not only interesting, but also very useful. As a result of this research, the applications of iminium ions as azadienes under similar conditions to those of Grieco have been reported many times. A discussion of some of these results is presented in sections 1.4 and 1.5, commencing with the research carried out by Mellor *et al.* which forms the background to the subsequent studies described in this thesis.

1.4.1 OTHER STUDIES WITHIN THE GROUP

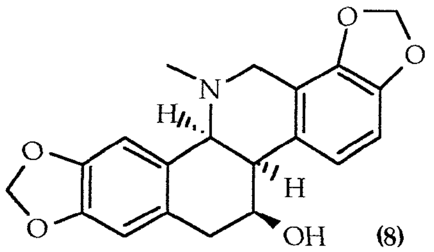
(i) Synthesis of Monoazasteroids

Following Grieco's significant new synthesis of tetrahydroquinolines, a similar procedure was developed by Mellor *et al.*[24,25,26] in the synthesis of azasteroids and related tetrahydroquinoline skeletons. In order to generate novel compounds such as azasteroids, two major amine substrates were used: bicyclic amines having the naphthalene or indane skeletons, and aminoanthraquinones. The reaction of these primary amines with formaldehyde and cyclopentadiene proved to be an efficient one pot synthesis, producing a series of monoazasteroids (Scheme 9).



Scheme 9

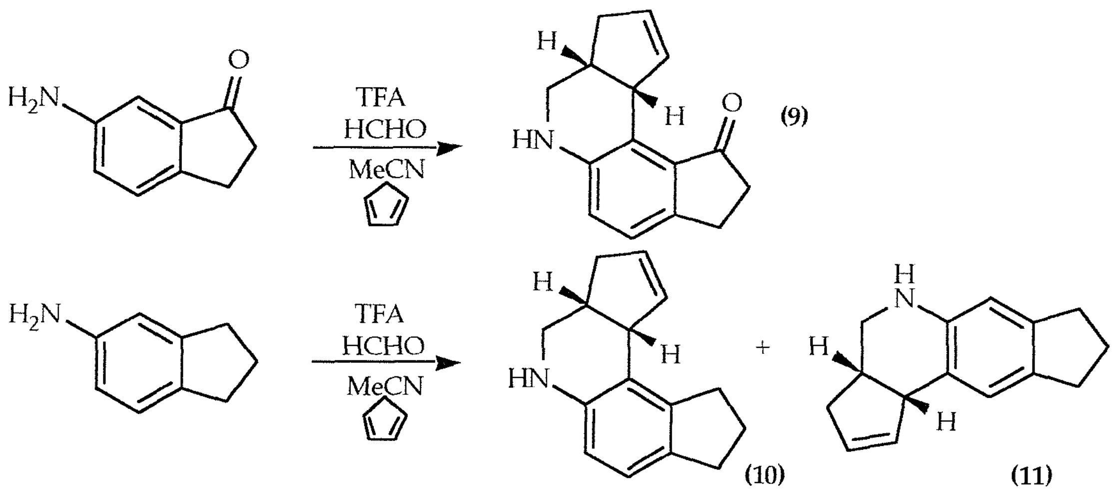
The major cycloadducts were formed regiospecifically, with a *cis* ring junction, and significant side products were only observed with an increased ratio of formaldehyde to amine. Heterocyclic steroids arouse interest due to their pharmacological properties.[27] The naturally occurring 11-azasteroid chelidonine (8) was first synthesised in 1971[28] and shows *in vivo* activity against L-1212 lymphoid leukaemia.[29]



(8)

Related azasteroids and isoquinoline skeletons have been prepared *via* cycloaddition reactions[30] and electrocyclic ring closures;[31] these will be discussed in Section 1.4.2. Many monoazasteroids occur naturally and the chemistry of such compounds has highlighted the significance of routes directed towards synthetic monoazasteroids. The application therefore of the aza Diels-Alder chemistry initiated by Grieco and Bahsas[22] to the synthesis of azasteroids is of considerable importance.

It was noticed that the yield of product from 5-amino-α-tetralone (Scheme 9) was much higher than the yields from the naphthalene derivatives lacking the carbonyl functional group. This was a general observation made throughout the studies on the bicyclic amines. However, not only did the carbonyl group affect the overall yield, but in monocyclisations where there was potential for more than one regioisomer, the regiochemical control exerted by the carbonyl group ensured that only one isomer was formed. For example, monocyclisation of 6-amino-α-indanone gave one isomer (9), whereas 5-amino-indane yielded two regioisomers, (10) and (11) (Scheme 10).

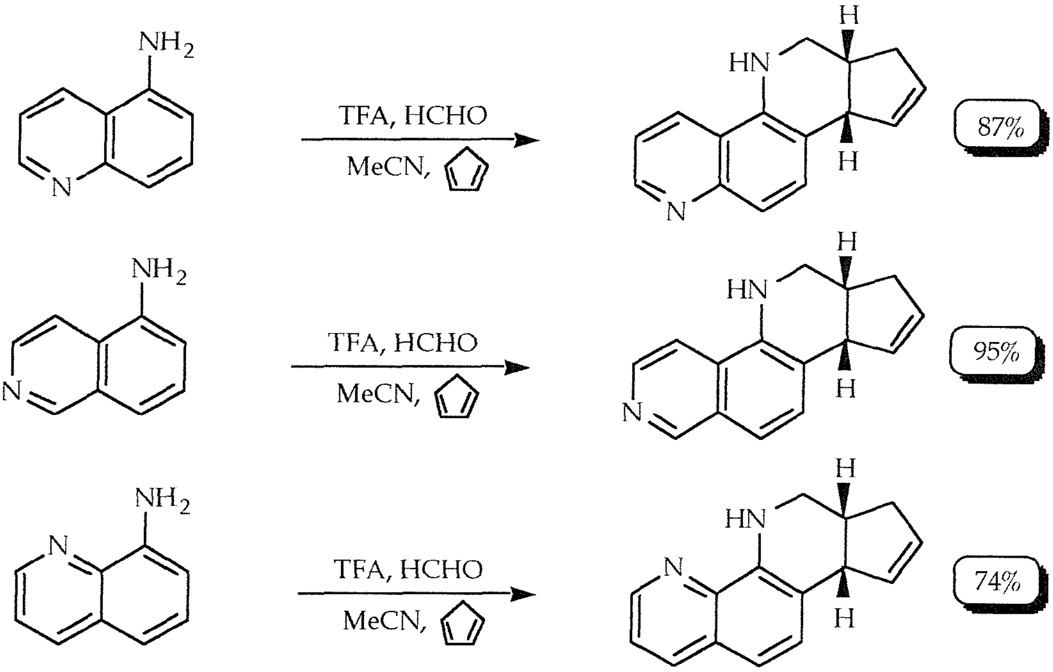


Scheme 10

The efficiency and control exerted by the carbonyl group may be attributed to its strongly electron withdrawing nature; increased electron deficiency in the azadiene moiety facilitates reaction.

(ii) Synthesis of Diazasteroids

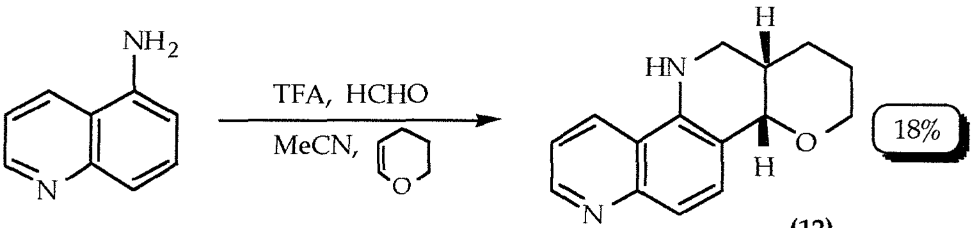
The syntheses of many categories of monoazasteroid have been developed;[32-36] however, far fewer strategies have been developed for the synthesis of diazasteroids. Although there are no naturally occurring intranuclear diazasteroids (where the nitrogen functionality is part of the steroid skeleton), there has been evidence of some biological activity associated with diazasteroids.[37-39] However, a general lack of developed synthetic chemistry has prevented thorough biological studies on diazasteroids. By the use of the aza-Diels-Alder reaction, a series of aminoquinolines and aminoisoquinolines were used[40] to provide an effective synthesis of diazasteroids (Scheme 11).



Scheme 11

Again, as with the monoazasteroids, the addition of cyclopentadiene was regiospecific; no other regioisomers were observed, although minor side products were observed in most cases. Interestingly though, 5-aminoisoquinoline afforded a single product only, the desired diazasteroid, in 95% yield.

As an extension to the synthesis of diazasteroids, the reaction of dihydropyran with formaldehyde and 5-aminoquinoline was studied.[40] This permitted the generation of diazasteroids by using a vinyl ether in the cyclocondensation reaction. The desired diazasteroid (12), a novel 4,11-diaza-15-oxa-D-homosteroid was obtained (Scheme 12).



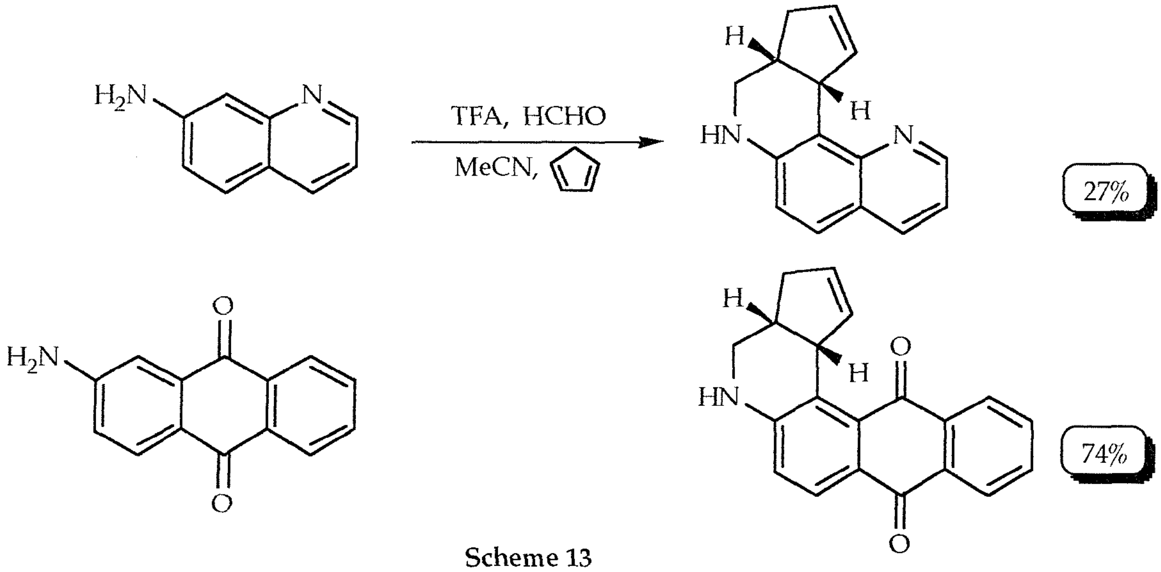
Scheme 12

(12)

These results established that access to mono and diazasteroids using the Diels-Alder reaction was easy. With the possibilities that other primary amines might react similarly, and that cyclopentadiene could be replaced in these reactions by other dienophiles, it was clear that a wide range of azasteroids might be made through this strategy.

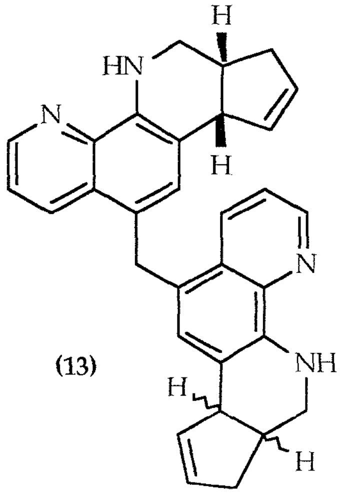
(iii) General Related Cycloadditions

Further novel skeletons were generated from amines having two potential sites for cyclisation.[24] Careful control of the reagent quantities permitted the isolation of tetrahydroquinolines with no isomeric products (Scheme 13).



Scheme 13

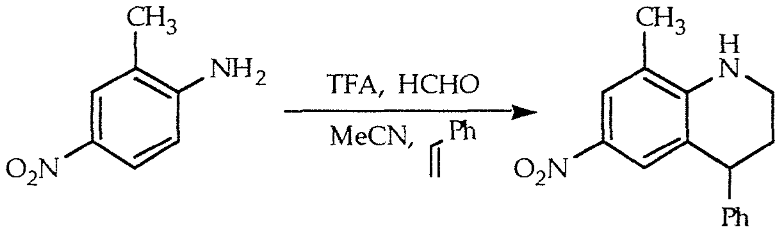
A difficulty observed in studies of cyclocondensations of cyclopentadiene with formaldehyde and anilines was the tendency for initially formed products to undergo a second condensation. Thus although 8-aminoquinoline gave a 74% yield of the desired cycloadduct (Scheme 11) using the reactant ratio 1:1 of aniline to formaldehyde, when the ratio was changed to 1:5 the diastereoisomeric products (13) were isolated in 71% yield.



(13)

Nevertheless, the isolation of the isomers was an unexpected bonus, since models suggest that the four nitrogen atoms are situated so that they might interact in formation of metal-ion complexes. No such complexes based on diazasteroids have previously been prepared.[40]

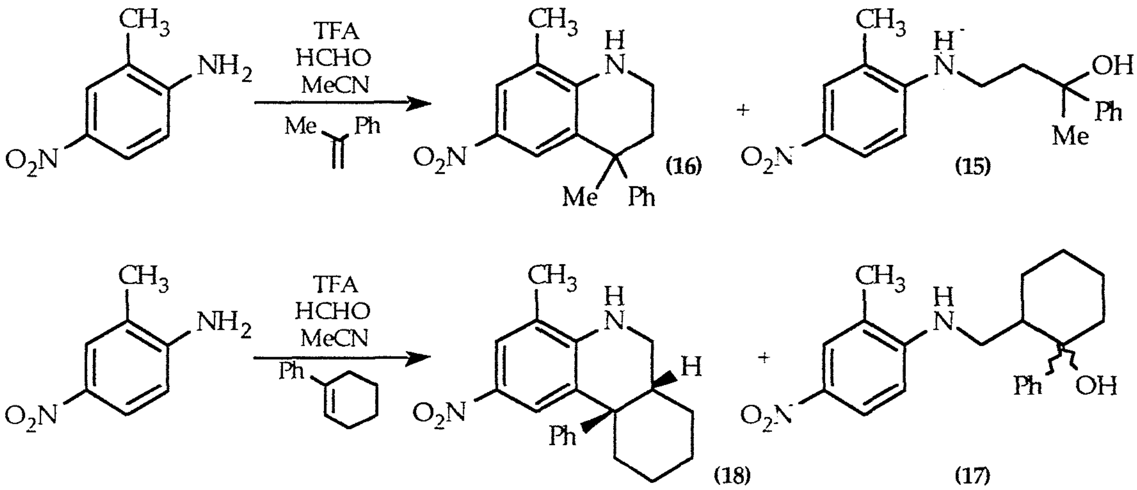
Methyl-4-nitroaniline was used as a model[42] to study the problem of second cycloadditions; this amine was a good model to test possible reactions and had two advantages: the second potential condensation was blocked by the methyl group and an iminium ion derived from this amine could be further activated by the nitro group. Hence 2-methyl-4-nitroaniline was used to introduce styrene as an electron rich partner. The reaction carried out at reflux yielded the desired cyclocondensation product (14) in excellent yield (90%) with no significant side products formed (Scheme 14).



(14)

Scheme 14

The expected major products were also formed in reactions of the amine with α-methylstyrene and 1-phenylcyclohexene, although when milder conditions were employed, the reactions gave a different result. Reaction with α-methylstyrene gave the amino alcohol (15) in addition to the cycloadduct (16). Similarly, an amino alcohol (17) was a minor product in the reaction of 1-phenylcyclohexene giving the expected cycloadduct (18) (Scheme 15).

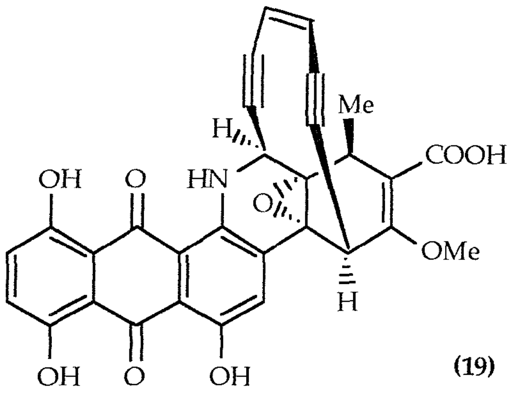


Scheme 15

The isolation of these alcohols was an interesting and important result since it gave an indication of the possible mechanism of the Diels-Alder cycloadditions, which will be discussed in section (v). The successful introduction of a variety of electron rich alkenes also emphasised the synthetic potential of these reactions since it was now clear that a wide range of products was readily accessible from the possible combinations of various amines and alkenes.

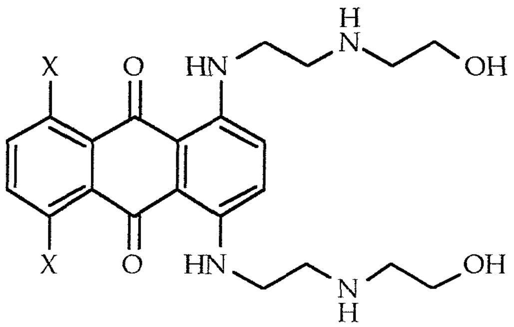
(iv) Reactions with Aminoanthraquinones

Aminoanthraquinones have long been of value in the dyestuffs industry and more recently have attracted interest in the area of medicinal chemistry. The anthraquinone dynemicin A (19) was found in 1990 as a potent enediyne class of antitumour antibiotics having DNA cleavage activity.[43-45] The role of this and other anthraquinones in the cleavage of DNA has been reviewed;[46] in some cases, antitumour activity can be observed.[47] Related tetracycles[48] and pentacycles[49] have been synthesised following the biological interest in dynemicin A.



(19)

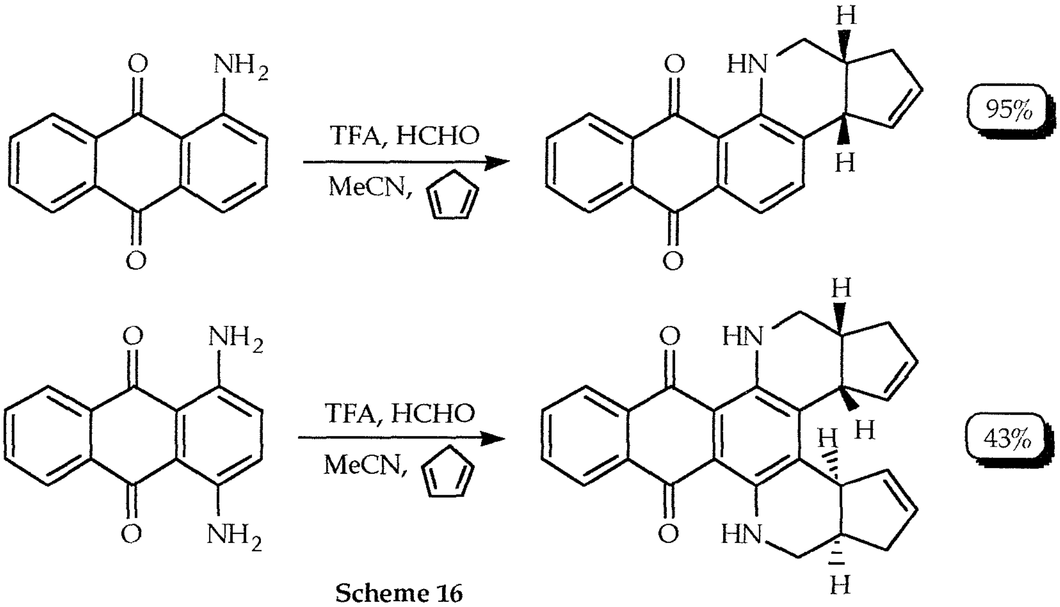
Other aminoanthraquinones such as mitoxantrone (20) and ametantrone (21) are used clinically. These anticancer agents are the most representative examples of the 1,4-bis[(aminoalkyl)amino]-9,10-diones recently developed as antitumour agents.[50]



(20) X = OH
(21) X = H

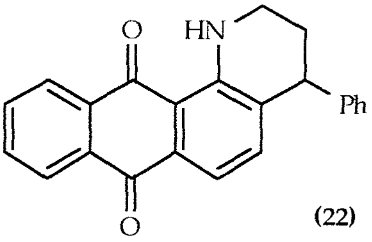
Mitoxantrone in particular is gaining an increasingly important place in the clinical treatment of human malignancies.[51] However, the drug is known to have significant toxic side effects[51] and therefore the development of related compounds having reduced side effects is an attractive area of investigation.[50,52]
A second area of interest is the interaction of aminoanthraquinones with metal ions; these complexes form a different class of anticancer agent.[53] The success of these compounds in medicinal chemistry therefore emphasises and encourages the need to establish efficient routes to a variety of aminoanthraquinones.

As a result of the renewed interest in aminoanthraquinones, the Diels-Alder chemistry of Grieco and Bahsas[22] used in the synthesis of tetrahydroquinolines was extended by Merriman *et al.*[54] to the synthesis of aminoanthraquinone derivatives. Reactions of various mono- and di-aminoanthraquinones with cyclopentadiene produced cycloadducts in moderate to excellent yields (Scheme 16).

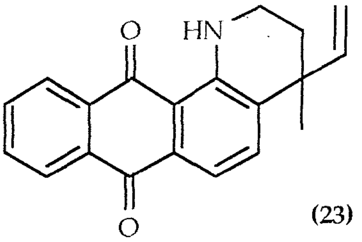


Scheme 16

Minor products were observed in some cases where further reaction with excess reagent was possible, such as with 2-aminoanthraquinone. The yields of minor and major products could be controlled by varying the number of equivalents of formaldehyde and cyclopentadiene used. Further cycloadducts were synthesised using a variety of alkenes. Although the product (22) from the reaction of styrene with 1-aminoanthraquinone was obtained in 86% yield, the inefficient reaction of isoprene with 1-aminoanthraquinone to give the quinone (23) in 15% yield suggested that the satisfactory cyclocondensations are only observed with aminoanthraquinones and relatively electron rich alkenes.

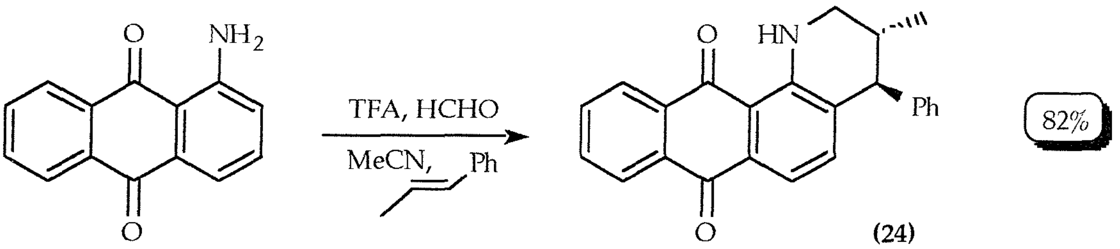


(22)



(23)

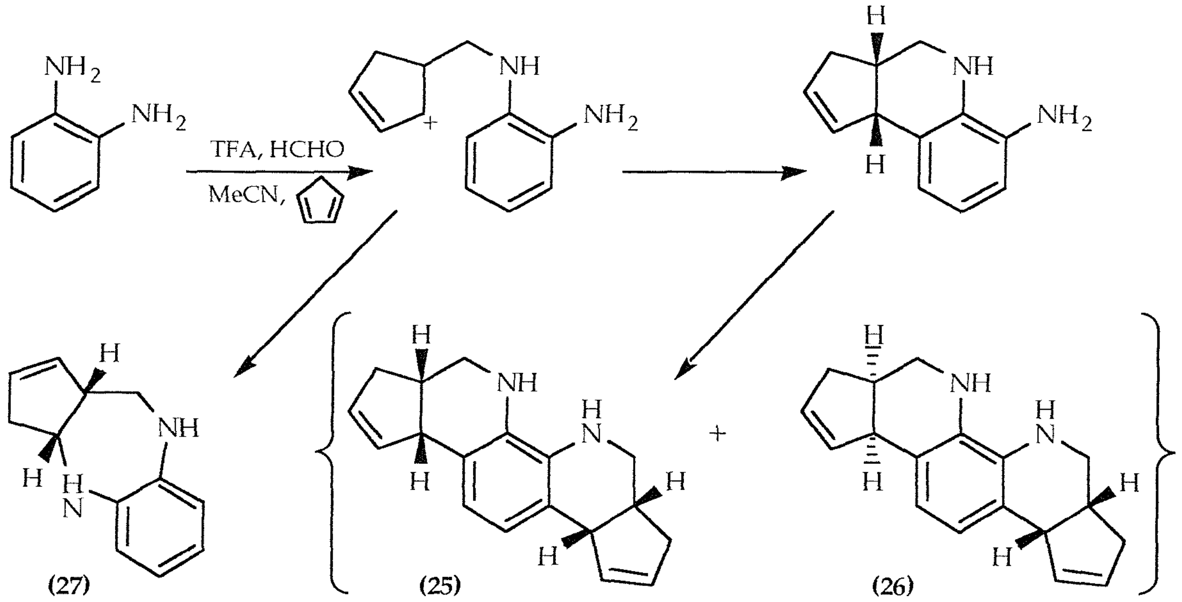
A noteworthy point in these results was the reaction of 1-aminoanthraquinone with *trans*-β-methylstyrene (Scheme 17) to produce the adduct as a single major product (24). The absence of any minor product is in contrast with the results obtained when the alkene used was α-methylstyrene,[41,42] where intermediate products isolated were of considerable importance in establishing the mechanism of the reactions; this is discussed in the next section (v). In the case of *trans*-β-methylstyrene the efficient outcome is attributed to the formation of an intermediate secondary carbocation which is more easily cyclised than the corresponding tertiary carbocation from α-methystyrene.



Scheme 17

These examples of diverse mono- and di-aminoanthraquinones generated simply from readily available starting materials and their potential use in medicinal chemistry again demonstrated the synthetic value of this aza Diels-Alder chemistry.

An interesting and unusual result in this field of aza Diels-Alder rections arose from the use of *o*-phenylenediamines resulting in two series of products.[55] Reaction of *o*-phenylenediamine with formaldehyde and cyclopentadiene in acetonitrile (Scheme 18) afforded the pentacyclic products (25) and (26), which correspond to the tetrahydroquinoline adducts previously observed with other aromatic amines.[24-26,40-42,54] However in this case, a further major product was observed and identified as the benzodiazepine (27). Benzodiazepines are of interest in medicinal chemistry and recent aspects of these compounds have been reviewed.[56] The benzodiazepine (27) was formed *via* an iminium ion reacting with cyclopentadiene to give an allylic cation. Attack by the primary amine resulted in cyclisation of the cation leading to formation of the tricyclic benzodiazepine. The isomers (25) and (26) were products of two Diels-Alder reactions between first one and then a second iminium ion with cyclopentadiene.

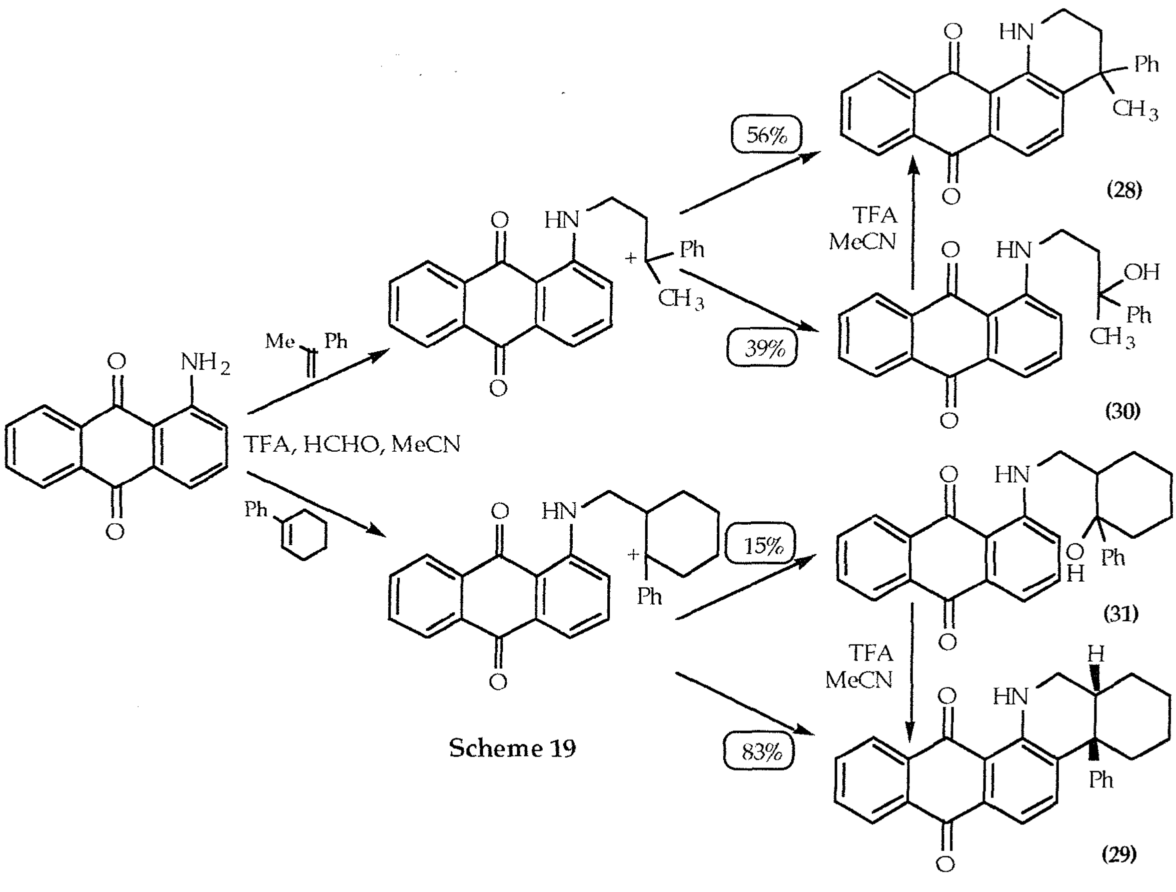


Scheme 18

Isolation of the benzodiazepine therefore suggested a non-concerted pathway for formation of the tetrahydroquinolines. The mechanism of the Diels-Alder reactions will now be discussed in the next section.

(v) Observations on Mechanism

The unresolved question regarding mechanism in the synthesis of tetrahydroquinolines was apparent; there was no firm indication that a distinct assignment of mechanism in the synthesis of diverse tetrahydroquinolines was feasible. The choice between a possible concerted mechanism, ie. a Diels-Alder reaction characterised by inverse electron demand, and the alternative stepwise mechanism, was in part settled following a study employing various electron rich alkenes.[41,42] Detailed studies were made using 1-aminoanthraquinone in reaction with α-methylstyrene and 1-phenylcyclohexene. In both cases the major products were amines, for example (28) and (29) respectively, in addition to the intermediate alcohols, (30) and (31) respectively (Scheme 19). Similar intermediate alcohols ((15) and (17)) had been isolated in the reactions of 2-methyl-4-nitroaniline with α-methylstyrene and 1-phenylcyclohexene as previously mentioned (Scheme 15). The alcohols (30) and (31) could be isolated and subsequently cyclised quantitatively in acetonitrile containing TFA to yield the amines (28) and (29) respectively.



Scheme 19

Hence the acquisition of these alcohols and their successful cyclisation implied that formation of tetrahydroquinolines from styrenes was a non-concerted process. Nevertheless, this inference was not an indication that the mechanism of these reactions with all electron rich alkenes was identical; indeed, considering particularly the reactions of cyclopentadiene, no evidence for a multi-step process was found despite the various reactions with monoamines which had already been studied.[22,25]

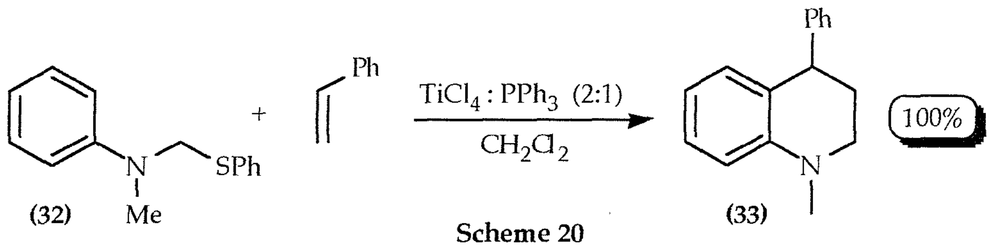
Interestingly though, it was found that cyclopentadiene reacted with *o*-phenylenediamine to give a tricyclic amine (discussed in the last section) along with the expected cycloadducts, which suggested that this cyclisation was possibly non-concerted (see Scheme 18).

The results which had by now been achieved indicated that the reaction conditions reported by Grieco and Bahsas[22] could be used for the efficient synthesis of a variety of tetrahydroquinolines, polycyclic systems and possibly more complex molecules. The success and simplicity of the reactions between diverse electron rich alkenes and aromatic amines accentuated their synthetic potential.

1.4.2 RELATED STUDIES INVOLVING 2-AZADIENE EQUIVALENTS IN AZA DIELS-ALDER REACTIONS

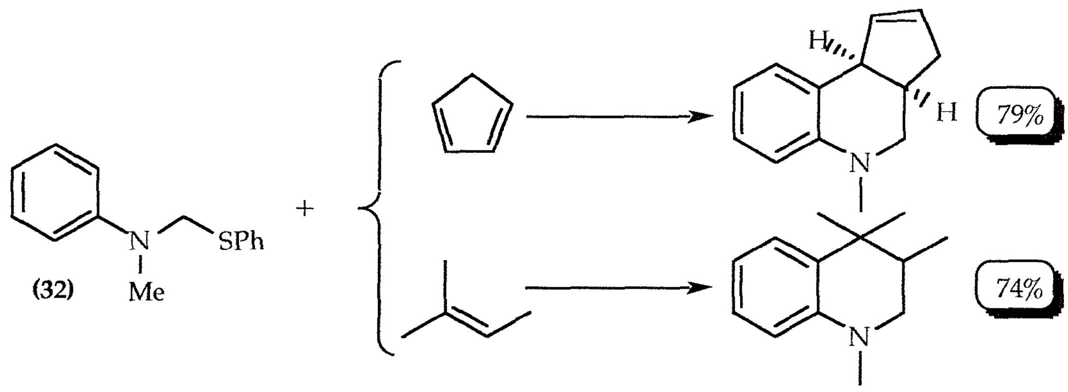
(i) Synthesis of Tetrahydroquinolines from Thiomethylamines

Following the success of Grieco's work, a similar strategy has been applied to the synthesis of substituted 1,2,3,4-tetrahydroquinolines. Beifuss *et al.*[57] have carried out cycloadditions of 2-azabutadienes and various dienophiles. The cationic 2-azabutadienes were generated *in situ* from thiomethylamines easily available from reactions of anilines with formaldehyde and thiols. Cleavage of the thiomethylamine (32) to generate the 2-azabutadiene and its subsequent reaction with various dienophiles was achieved when a 2:1 mixture of $TiCl_4$ and PPh_3 in dichloromethane was used as a Lewis acid. In this way, reaction with styrene afforded the tetrahydroquinoline (33) in 100% yield (Scheme 20).



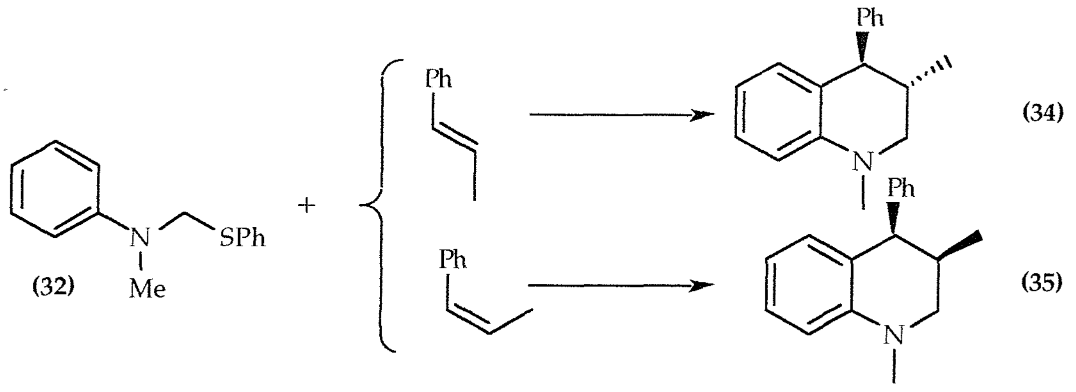
Scheme 20

Further compounds were generated in good yields by the reaction of (32) with other dienophiles (Scheme 21).



Scheme 21

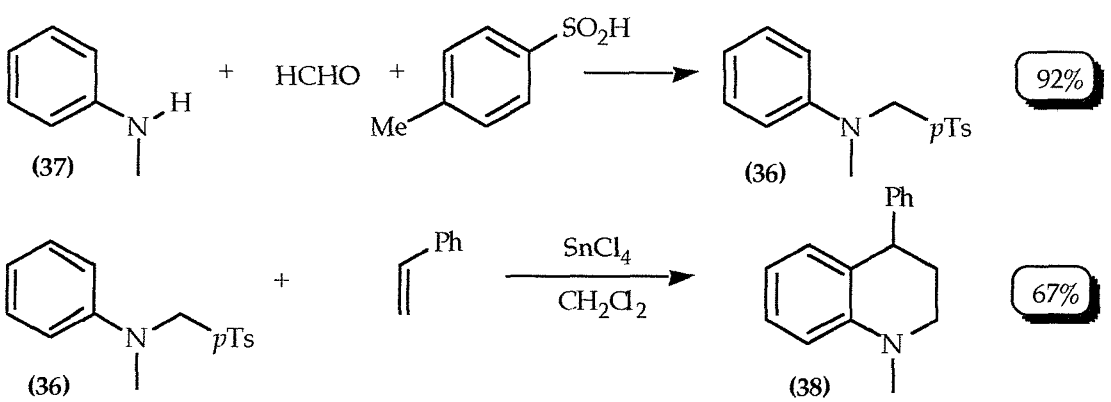
The cycloadducts were all obtained regiospecifically and diastereomerically pure. From a mechanistic point of view, the results obtained from the reactions of the thiomethylamine (32) with (*E*)- and (*Z*)- methylstyrene were particularly interesting. In each case one product was observed: the *trans* product (34) from (*E*)-methylstyrene, and the *cis* product (35) from (*Z*)-methylstyrene (Scheme 22).



Scheme 22

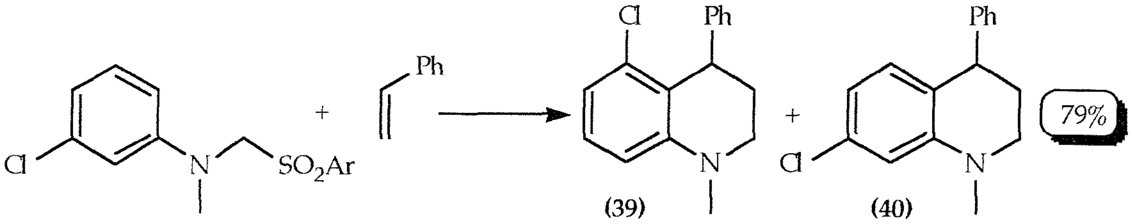
The stereochemistry of the dienophiles was therefore retained during the reactions. The results were rationalised in terms of a one step concerted $[4\pi+2\pi]$ cycloaddition, a view further supported by the fact that no side products were isolated in any of the reactions that might have originated from possible cationic intermediates. This is in contrast to the non-concerted mechanism proposed, although for different reaction conditions, by Merriman *et al.*[41,42]

This work was subsequently extended to the cycloaddition, with various dienophiles, of 2-azabutadienes generated *in situ* from α-arylaminosulfones and α-aminonitriles.[58] The α-arylaminosulfones were obtained from the reaction of anilines with aqueous formaldehyde and *p*-toluenesulfinic acid. In a similar procedure to that used previously (Scheme 20), cleavage of the α-arylaminosulfones and cyclisation of the 2-azabutadiene with dienophiles was achieved using $SnCl_4$ in dichloromethane as the Lewis acid. Synthesis of the unsubstituted α-arylaminosulfone (36) from the aniline (37) and the cycloaddition of the resulting 2-azabutadiene with styrene gave the tetrahydroquinoline (38) in good yield (Scheme 23).



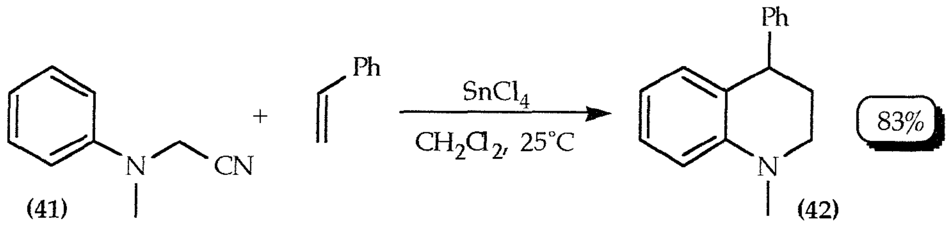
Scheme 23

The procedure was repeated with various substituted anilines to give the corresponding substituted tetrahydroquinolines. A single product was isolated in each case, except in the transformation with the *meta*-chloro substituted α-arylaminosulfone where the two possible isomers (39) and (40) were formed as a 1:2 mixture (Scheme 24).



Scheme 24

In addressing the question of mechanism, the reactions between the α-arylaminosulfone (36) and (*E*)- and (*Z*)- methylstyrene were carried out as before (Scheme 22). The consistent results obtained confirmed a concerted mechanism for the cycloadditions studied. In addition to α-arylaminosulfones, a brief study of α-arylaminonitriles was also completed, one example being the treatment of the N-methyl derivative (41) with styrene which gave the tetrahydroquinoline (42) in 83% yield (Scheme 25).

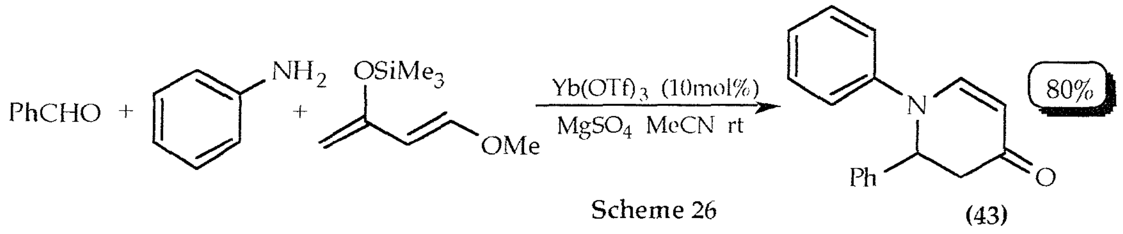


Scheme 25

In summary, the work of Grieco[22] has been extended to give new and efficient methods for the regio and diastereoselective synthesis of substituted 1,2,3,4-tetrahydroquinolines which rely on the unprecedented *in situ* generation of 2-azabutadienes from thiomethylamines, α-arylaminosulfones and α-arylaminonitriles.

(ii) Amines Acting as Azadienes and Azadienophiles under Different Conditions

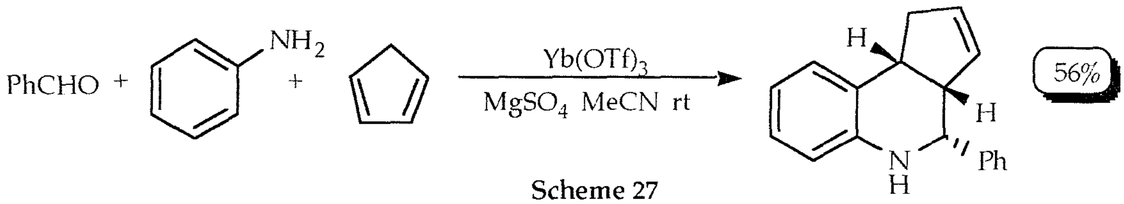
Kobayashi *et al.*[59] have carried out aza Diels-Alder reactions in which imines act as both dienophiles and azadienes under certain conditions. The reactions were catalysed by lanthanide or scandium triflates to afford pyridine and quinoline derivatives. The Lewis acid catalysts were stable and kept their activity even in the presence of water and amines. In the presence of 10mol% of ytterbium triflate and magnesium sulfate, benzaldehyde was treated successively with aniline and Danishefsky's diene in acetonitrile at room temperature (Scheme 26). The reaction proceeded smoothly to give the corresponding tetrahydropyridine (43) in 80% yield.



Scheme 26

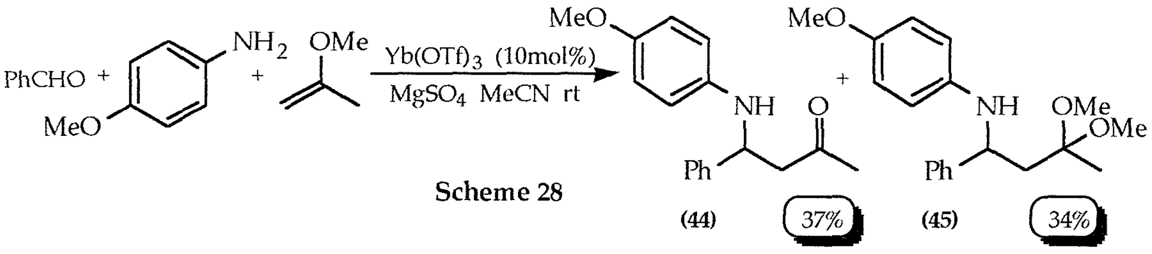
(43)

Other examples using different starting materials also produced tetrahydropyridines in high yields. The imine derived in each case was acting as a dienophile. When the original reaction (Scheme 26) was repeated using cyclopentadiene in place of 2-trimethylsilyloxy-4-methoxy-1,3-butadiene, the reaction course changed and a tetrahydroquinoline derivative was obtained in 56% yield (Scheme 27).



Scheme 27

The imine produced *in situ* acted as an azadiene, as had been found by Grieco and Bahsas.[22] Other examples using cyclopentadiene, vinyl ethers and vinyl sulfides as the dienophiles also created various tetrahydroquinolines in good yields. However, the reaction between benzaldehyde, anisidine and 2-methoxypropene did not give a tetrahydroquinoline derivative, but a β-aminoketone (44) and its dimethylacetal (45) (Scheme 28).

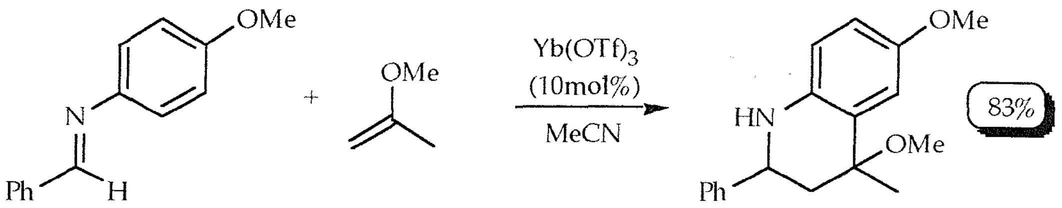


Scheme 28

(44)

(45)

The different products obtained therefore prompted interest in the mechanism. The proposed mechanism for the formation of (44) and (45) involved the quenching of an intermediate ionic species by water and methanol generated *in situ*. It was very interesting therefore to observe the reaction of the same imine with 2-methoxypropene under anhydrous conditions (Scheme 29) which produced the tetrahydroquinoline (46) originally expected. Consequently, these results indicated a stepwise mechanism in these types of imino Diels-Alder reactions.

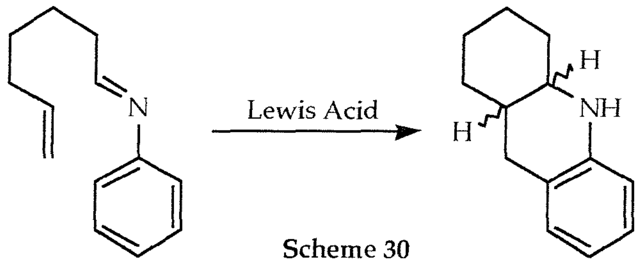


Scheme 29

(46)

(iii) Intramolecular Reactions of Azadienes - Synthesis of Octahydroacridines

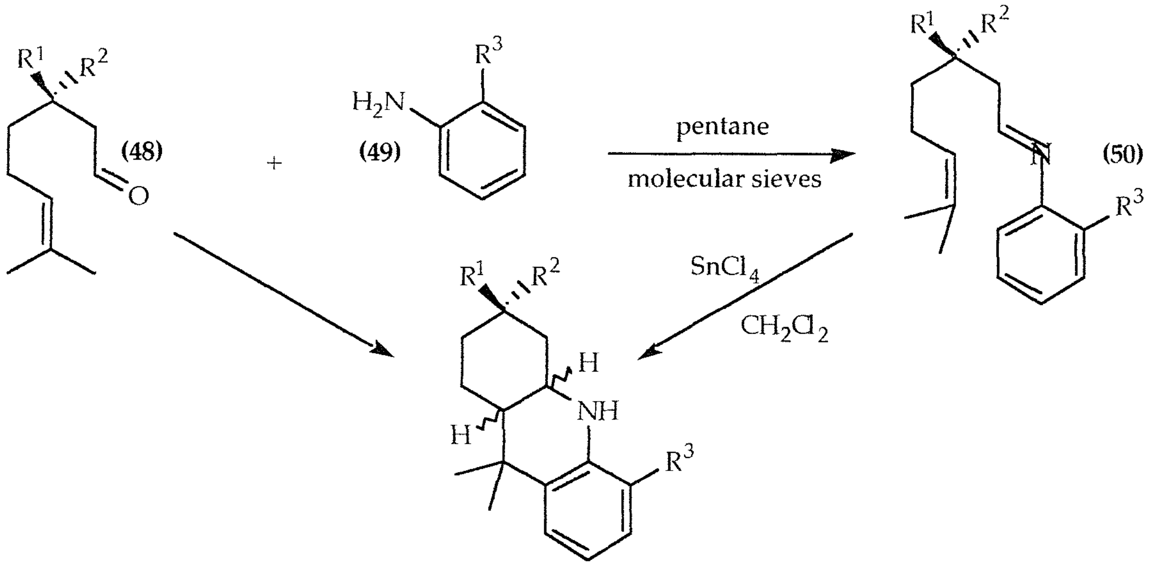
The aza Diels-Alder reactions of N-arylimines have also been developed by Laschat and Lauterwein.[60] In contrast to the approach by Grieco[22] and Mellor[24,38,40,41,42,55] in which N-arylimines have been employed in intermolecular reactions with electron rich dienophiles, the intramolecular aza Diels-Alder reaction of N-arylimines was applied to the synthesis of octahydroacridine derivatives. The Lewis acid catalysed reaction of the 2-azadiene system with monoactivated olefins tethered to it resulted in the easy and convenient formation of 1,2,3,4,4a,9,9a,10-octahydroacridines (47) (Scheme 30), a class of pharmacologically interesting compounds.[61]



Scheme 30

(47)

Several syntheses of the octahydroacridine skeleton have previously been reported,[62-64] however they were of limited synthetic value due to the lack of stereochemical control of the ring fusion, whereas an intramolecular Diels-Alder reaction was expected to give the ring system in a stereocontrolled manner. It was found that treatment of N-arylimines (50) in dichloromethane with catalytic amounts of $SnCl_4$ for several hours at -78°C followed by basic hydrolysis resulted in the formation of octahydroacridines (51) in high yields.
The synthetic utility of this cyclisation was enhanced by performing it as a one pot reaction by successive addition of the Lewis acid and the aldehyde (48) to a precooled solution of the amine (49) in dichloromethane (Scheme 31).

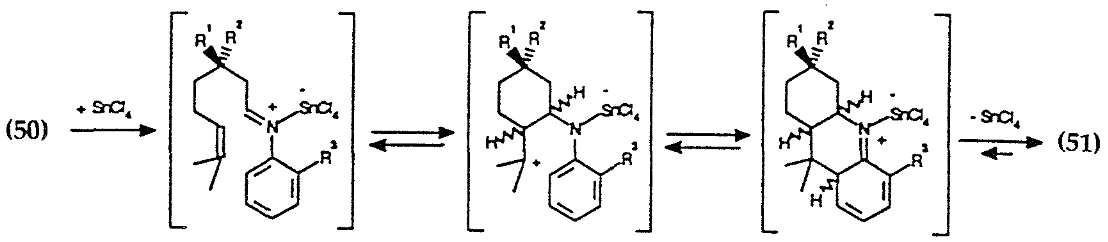


(51a) $R^1 = R^2 = R^3 = Me$ 91%
(51b) $R^1 = R^2 = Me$, $R^3 = H$ 86%

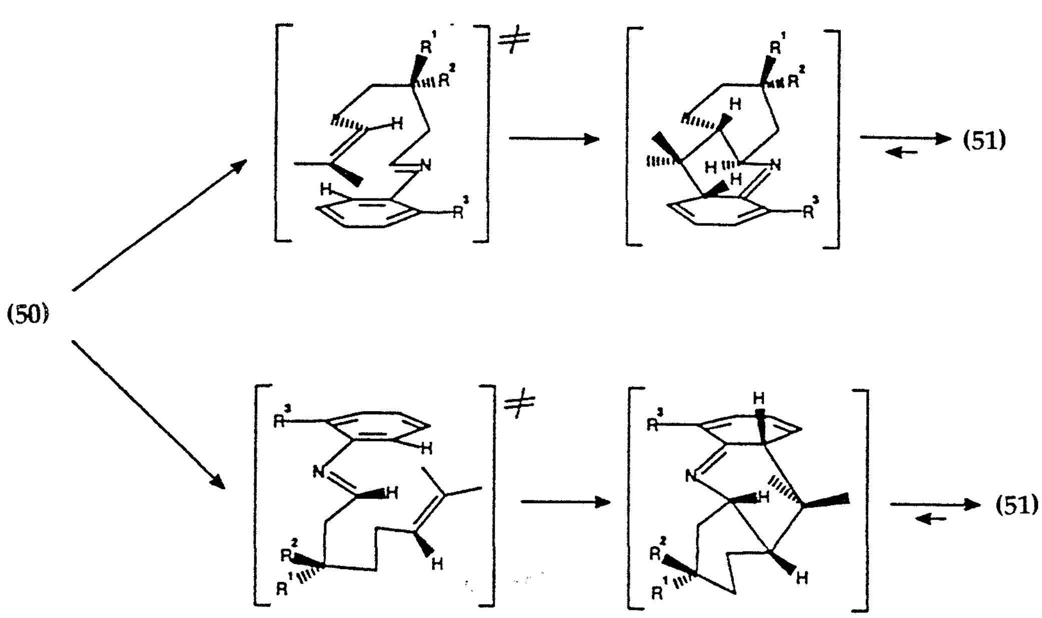
Scheme 31

The preparation of several octahydroacridines with a wide variety of substituents on the ring system was accomplished simply by choosing suitable aldehyde and aniline derivatives. In some cases the products were formed with extremely high *trans* selectivity (*trans/cis* = 99:1), and these ratios, along with the high yields were similar for the two different procedures followed, although the one pot procedure had the advantage of not requiring the isolation of the moisture and oxygen sensitive imines. Concerning the chemistry of the ring fusion, the substituents R^1 and R^2 were found to have a significant influence on the *cis/trans* ratio, and the selectivity could also be adjusted to some extent by the choice of Lewis acid and solvent.

To explain the stereochemical outcome of the cyclisation, either a multistep reaction *via* ionic intermediates (Scheme 32) or a concerted [4+2]-cycloaddition (Scheme 33) was proposed. The cycloaddition mechanism was favoured because it explained both the formation of the *trans* product (51) via the endocyclic transition state, and the formation of the *cis* product (51) *via* the exocyclic transition state. However, the stepwise mechanism could not be completely ruled out.

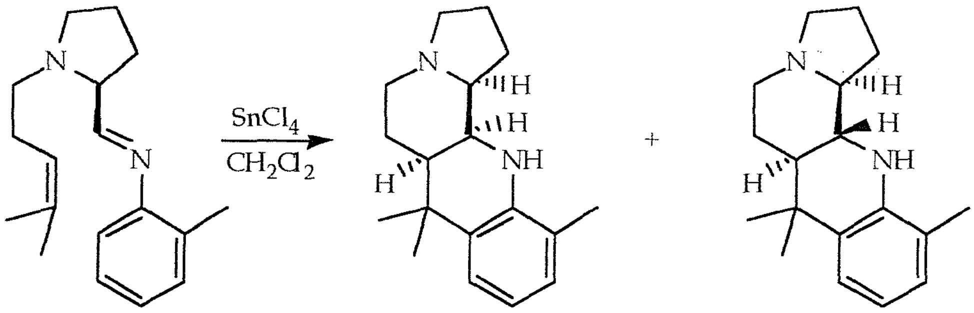


Scheme 32



Scheme 33

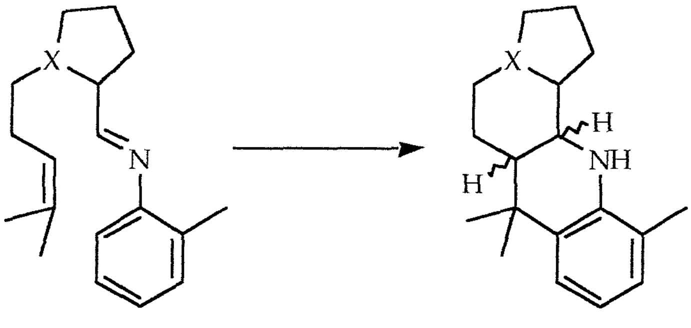
The related intramolecular aza Diels-Alder reaction of the prolinal-derived N-arylimine (52) was also studied,^{65} although in contrast to the synthesis of octahydroacridines, the diastereoselectivity in the cyclisation of (52) could be completely controlled by the choice of the Lewis acid. In a typical experiment, a solution of the N-arylimine in dichloromethane was treated with $SnCl_4$ and the resulting diazacyclopenta[a]anthracene derivative was isolated as a mixture of the *cis-cis* isomer (53) and the *trans-trans* isomer (54) (*cis:trans* = 1:99) in 82% yield (Scheme 34).



(52) Scheme 34 (53) (54)

When the reaction was repeated using different Lewis acids, the remarkable dependency of the *cis/trans* ratio on the type of Lewis acid was observed. Whereas some Lewis acids such as $SnCl_4$ yielded almost exclusively the *trans* product, the ratio was completely reversed in favour of the *cis* product when others, such as $EtAlCl_2$, were used. The diastereoselectivity in this case was explained by consideration of the possible transition state geometries which are favoured by different Lewis acids, mainly because of the different distances and dihedral angles displayedby the N-arylimine.

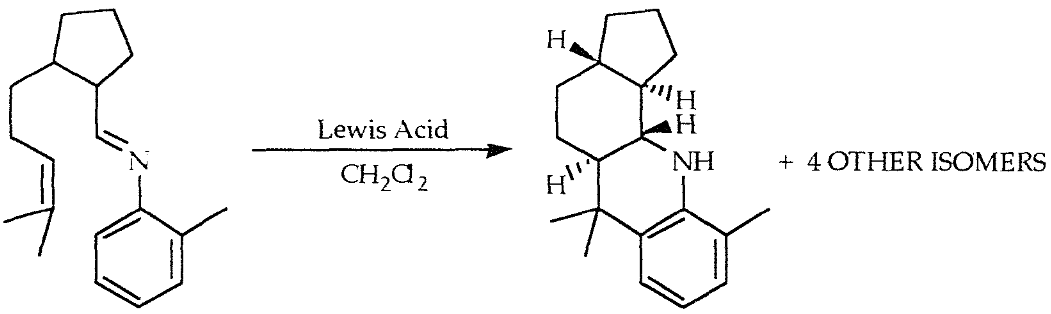
Since the stereoselectivity in the formation of the octahydroacridine derivatives was not dependent on the type of Lewis acid used, it was likely that the presence of a second nitrogen atom in the N-arylimine (52) played a part in the control of selectivity, as this was the most significant difference in the two N-arylimines ((50) and (52)). Indeed, when the Diels-Alder reactions of the corresponding carbocyclic imine (55) were studied (Scheme 35) it became apparent that this was the case.[66]



(52) X = N
(55) X = CH

Scheme 35

When the mixture of *cis* and *trans* cyclopentane derived N-arylimines (55) was treated with different Lewis acids, only five of the possible eight isomers were obtained. All the Lewis acids reacted gave the *all-trans* product (56) as the major isomer (Scheme 36).

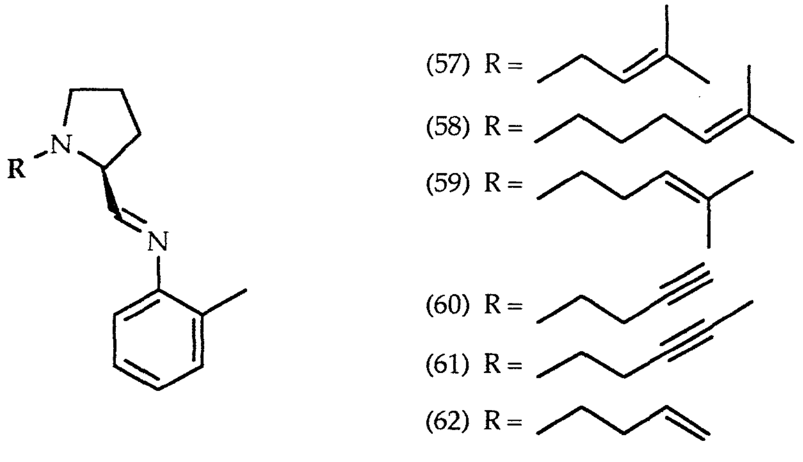


Scheme 36

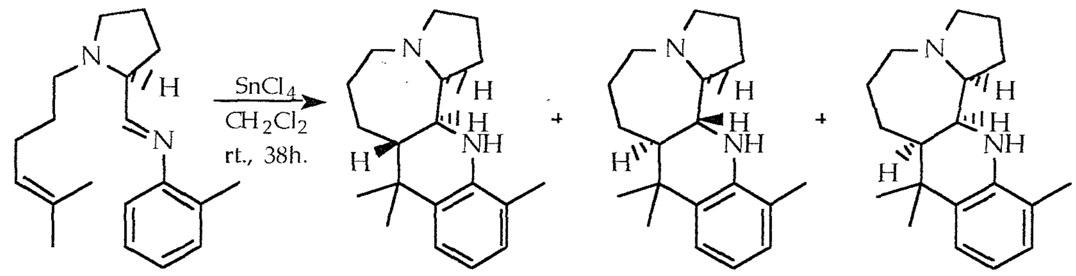
(55) (56)

The relative ratio of the five products seemed to be independent of the acidic catalyst and could not be changed from a *trans* to a *cis* selectivity as was observed in the above mentioned proline case (Scheme 34). The formal hetero Diels-Alder reaction of the prolinal derived N-arylimine (52) is therefore one of the few examples of imino cyclisation reactions where a complete reversal of diastereoselectivity is possible by the presence of an additional nitrogen atom. Force field calculations showed that the two isomers obtained in the proline case ((53) and (54)) and the major product (56) from the cyclisation of the cyclopentane imine, were in both cases more stable than the remaining isomers. These calculations and results obtained from the cyclisations supported the theory that these reactions proceed *via* a stepwise mechanism which is mainly governed by thermodynamic control, ie. the stability of the cyclisation products. However, the thermodynamic control can be overruled by chelation effects as was observed with the prolinal imine (52).

In order to investigate further the mechanism of the cyclisations, various other prolinal derived N-arylimines (57) - (62) were synthesised and treated with Lewis acids.[67]

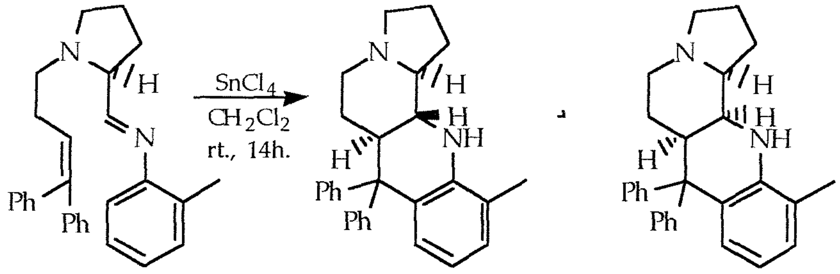


When N-arylimines (57), (60) and (62) were treated with various Lewis acids, no traces of the desired cyclisation products could be observed. Imine (58) cyclised cleanly in the presence of $SnCl_4$ to give a mixture of three diastereomeric quinolines (63), (64), (65) in a ratio of 75:23:2 (Scheme 37). No other Lewis acids could promote the reaction.



(58) **Scheme 37** (63) (64) (65)

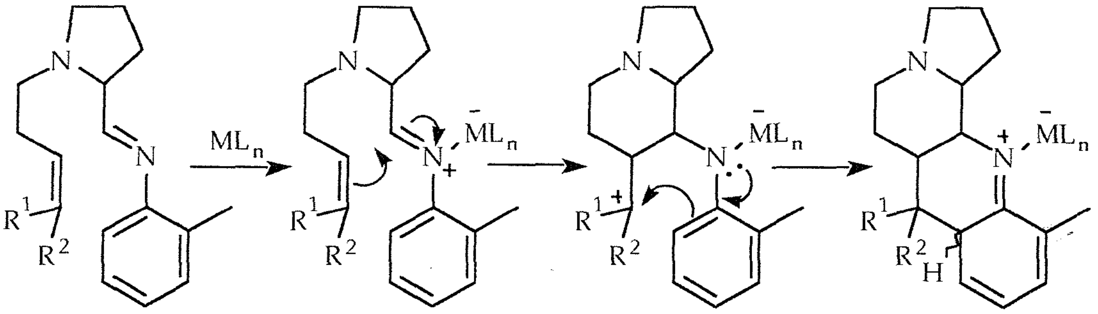
Cyclisation of imine (59) yielded mainly the *all-trans* isomer (66), similar to the earlier reaction of (52); however, in contrast to the earlier reaction, no Lewis acid induced reversal of the product ratio was observed (Scheme 38). Treatment of (61) with BF$_3$.OEt$_2$ resulted in a high yield (92%) of the cyclised product.



(59) **Scheme 38** (66) (67)

(66) : (67)
99 : 1

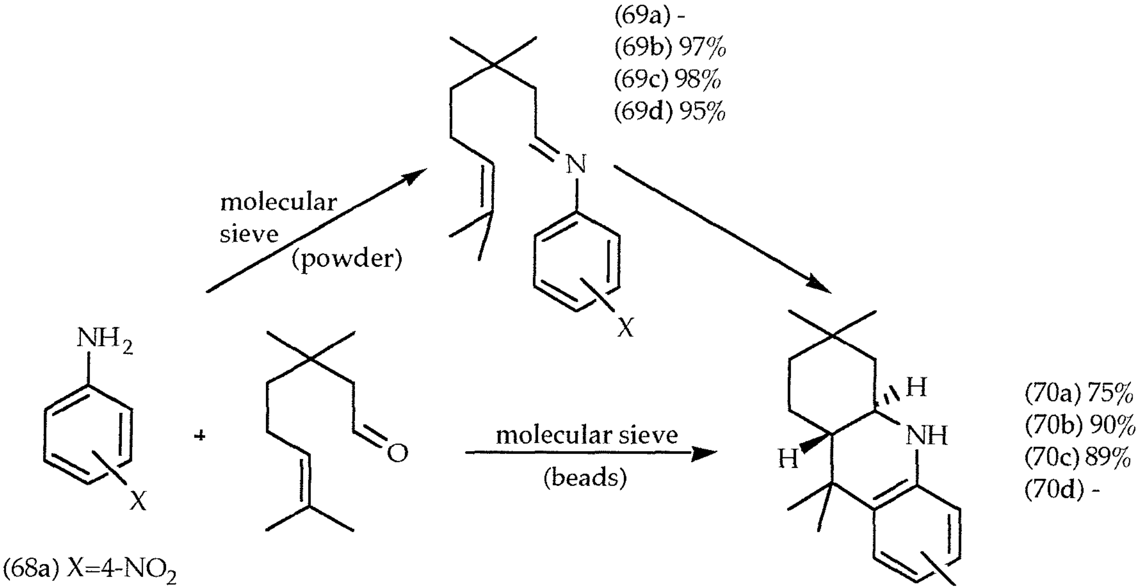
A stepwise mechanism was again concluded from these results. The absence of any cyclisation product in the case of imines (60) and (62) with terminal alkene or alkyne moieties suggested an initial iminium ion cyclisation to give a carbenium ion requiring a stabilising group. The second step involving a Friedel-Crafts type alkylation of the carbenium ion would account for the failure of (57) to form the expected tetracyclic product due to the steric constraints of the central five membered ring, and would agree with the formation of (63) - (65) bearing a seven membered ring. In a Diels-Alder mechanism the bond forming and breaking steps would also be asynchronous due to the polarisation by the imino nitrogen and therefore similar cation stabilising effects might be operative. Under thermal conditions without any Lewis acid, no cyclisation of the N-arylimines was observed, further confirming the stepwise mechanism (Scheme 39).



Scheme 39

(iv) Synthesis of Diverse Substituted Octahydroacridines

The synthetic potential of the aza Diels-Alder reaction can be further illustrated by the formation of a variety of polycyclic ring systems. Following the earlier successful syntheses of octahydroacridines[60] (Scheme 31), the scope of the reaction was extended to the synthesis of diverse substituted octahydroacridines, permitting investigation into the effects of a variety of parameters, such as substituents on the aromatic ring and molecular sieve catalysts.[68] According to previous investigations on Lewis acid catalysed cyclisations of N-arylimines,[60] it seemed reasonable that electron withdrawing substituents on the aromatic ring should favour cyclisation most, since the electrophilicity of the imine is increased. Treatment of substituted anilines (68(a) - (d)) with 3-methyl-citronellal in the presence of molecular sieves gave results which were strongly dependent on the type of molecular sieve used (Scheme 40).

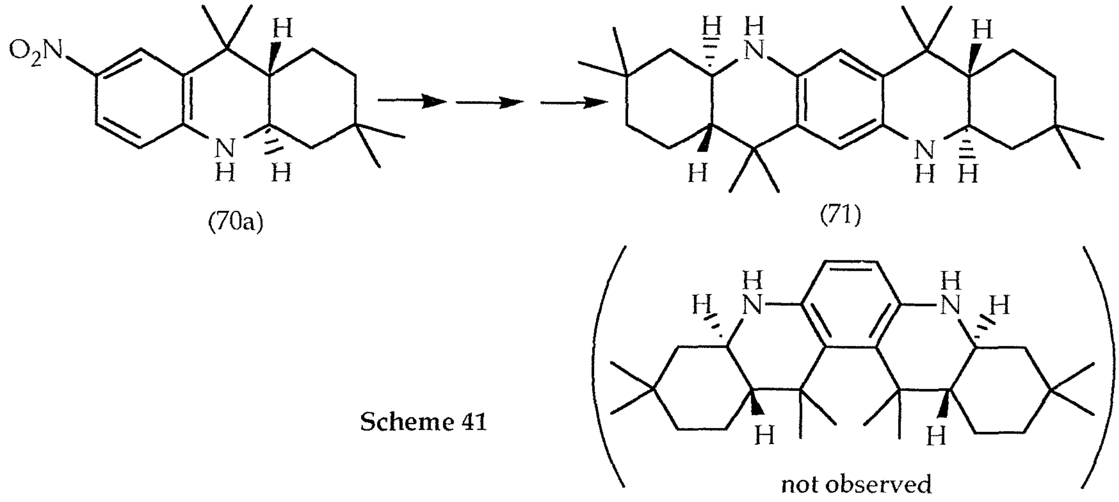


(68a) X=4-NO_2
(68b) X=4-CO_2Me
(68c) X=4-CF_3
(68d) X=2-CF_3

Scheme 40

When powdered molecular sieves were used, the anilines (68b) - (68d) gave very pure imines (69b) - (69d) in almost quantitative yield, although 4-nitroaniline (68a) could not be converted into the desired imine (69a). However, in the presence of molecular sieve beads, reaction of 4-nitroaniline resulted in the formation of the *trans*-configured cyclisation product, together with a minor by-product. When the remaining three amines (68b) - (68d) were treated with molecular sieve beads, two, (68b) and (68c), gave the cyclisation products (70b) and (70c) in very good yields. In contrast, *ortho*-trifluoromethylaniline (68d) gave a mixture of the imine (69d) and only a small amount of cyclised product (70d). The low tendency for this compound to cyclise was attributed to the steric hindrance of the ortho substituent.

The nitro-substituted product (70a) was of particular interest since it was subsequently employed in a second cyclisation *via* a reduction and imine formation sequence in the same aromatic system. Out of the two possible regioisomers, only the less sterically hindered compound (71) was observed (Scheme 41).



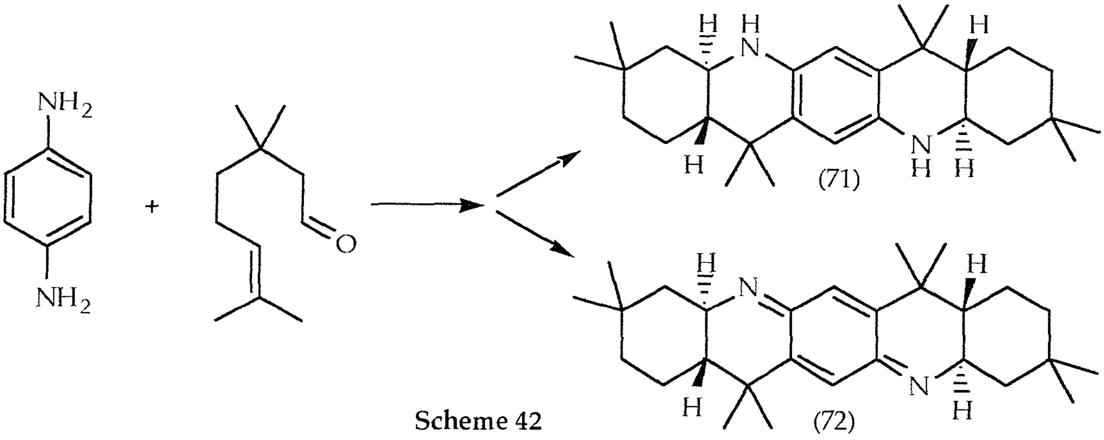
(70a)

(71)

Scheme 41

Another simpler route towards the synthesis of (71) was established using a starting amine having two amino groups on the same aromatic system. Conversion of the *para*-substituted phenylenediamine into the corresponding diimine followed by cyclisation in the presence of Lewis acid yielded not only the expected *trans* biscyclisation product (71) however, but also a novel quinone diimine (72) (ratio 53:47) (Scheme 42).

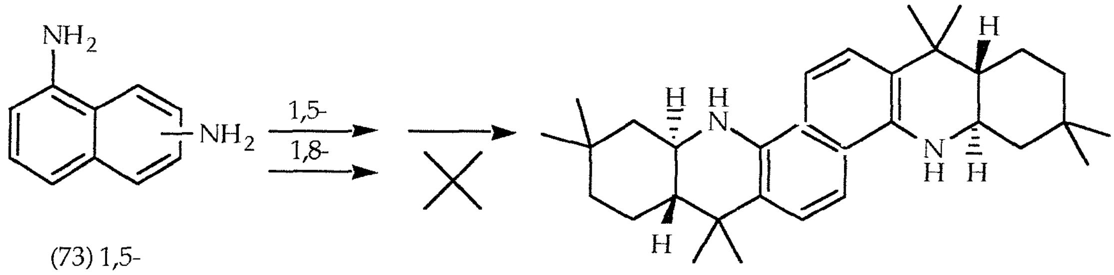
Interestingly, the *meta*-substituted phenylenediamine could only be converted into the corresponding diimine, and could not be cyclised further.


(71)

(72)

Scheme 42

Different behaviour of *meta* and *para* substituted systems was also observed in the case of naphthalenediamines (73) and (74). While the 1,5-disubstituted naphthalenediamine (73) reacted cleanly to give the diimine which could be further converted into the biscyclisation product (75) in the presence of $MeAlCl_2$; the diimine of the corresponding 1,8-disubstituted substrate could not be obtained under these conditions (Scheme 43).

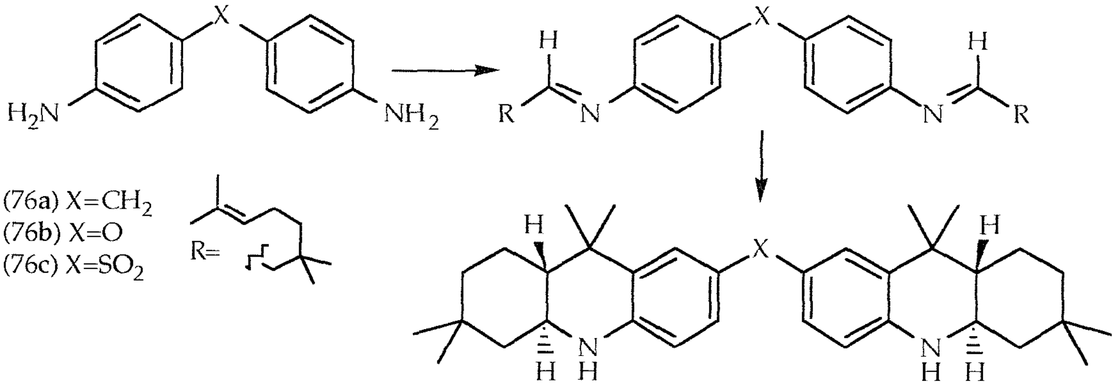


(73) 1,5-
(74) 1,8-

Scheme 43

(75)

Although the diimino compounds of these diamines with two amino functions on the same aromatic system were accessible by using powdered molecular sieves, it was not possible to convert the diimines into the biscyclisation products in a single step using molecular sieve beads. This led to the conclusion that the presence of a second imino function decreases the reactivity of the first, so that stronger activation, eg. by Lewis acids, was required to obtain the products. However, this novel reaction was used very successfully for diamines with separated aromatic systems, yielding biscyclisation products from aryldiamines. The reaction between 4,4'-diaminophenylmethane (76a) and 3-methyl-citronellal in the presence of molecular sieve beads gave the biscyclisation product (77a) in 57% yield. The one pot biscyclisation worked equally well for both electron donating and withdrawing groups (X) in the tether; thus the two diphenylmethyl analogues yielded the biscyclisation products in good yields (Scheme 44).



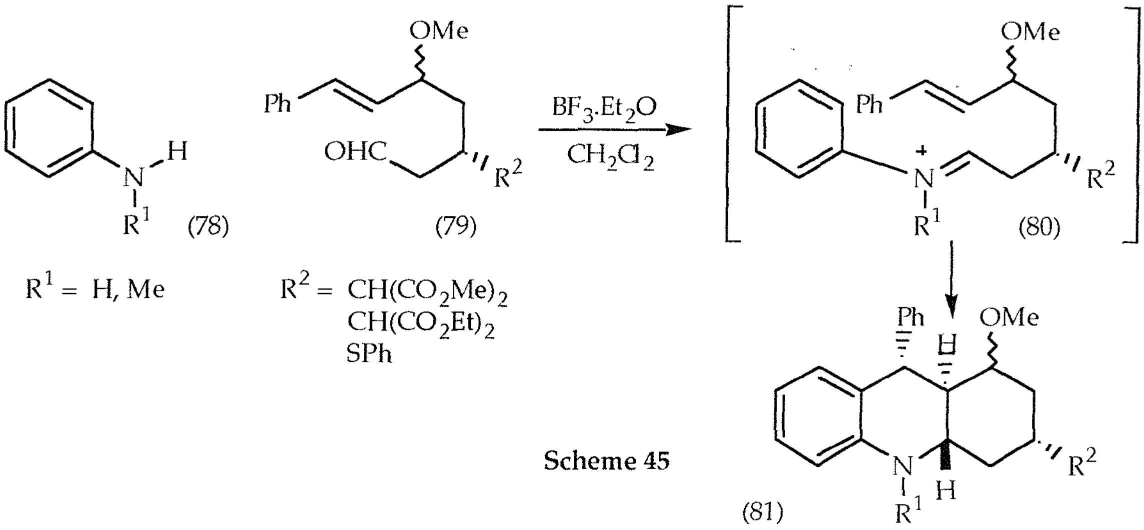
(76a) $X=CH_2$
(76b) $X=O$
(76c) $X=SO_2$

Scheme 44

(77a) 57%
(77b) 68%
(77c) 58%

The difference in reactivity of molecular sieve beads and powder in the cyclisations of these N-arylimines can be explained in terms of the acidic properties of the catalyst.[69] Since formation of the imine requires only catalytic amounts of acid, the trace amounts in powdered sieves should be sufficient for the reaction. In contrast, the cyclisation requires stronger acidic conditions since the product amines are more basic than the starting imines, thus the Bronsted acidic properties of molecular sieve beads are needed for successful cyclisation.

Octahydroacridines are also featured in the work of Beifuss *et al.*[70] who have extended their work on tetrahydroquinolines[57] (see earlier section, 1.4.2 (i)) to the synthesis of substituted 1,2,3,4,4a,9,9a,10-octahydroacridines. Having shown that 1,2,3,4-tetrahydroquinolines can be prepared by intermolecular polar [4π+2π]-cycloadditions of cationic 2-azabutadienes generated from thiomethylamines,[57] α-arylaminosulfones and α-arylaminonitriles,[58] a similar strategy was applied to the diastereoselective synthesis of octahydroacridines.
The intramolecular polar [4π+2π]-cycloaddition of substituted α-aryliminium ions (80) generated *in situ* by condensation of anilines (78) and ω-unsaturated aldehydes (79) gave a range of octahydroacridines (81) in yields of 63 - 76% (Scheme 45).
The ω-unsaturated aldehydes were obtained as mixtures of diastereoisomers, with respect to the methoxy group, by addition of nucleophiles $(R^2)^-$ to the α,β-unsaturated aldehydes.
The Lewis acid catalysed reactions of the anilines and aldehydes gave exclusively the *trans*-annulated diastereoisomeric octahydroacridines (81), with the best yields being observed when the transformations were performed with $BF_3.Et_2O$ as the Lewis acid in dichloromethane.



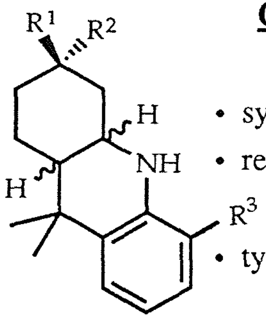
Scheme 45

A domino imine condensation - intramolecular polar $[4\pi+2\pi]$-cycloaddition process was thought to be responsible for the formation of the products. An (*E*)-configuration was assumed for the $C=N^+$ bond of the iminium ions (80) formed in the first step, since calculations showed that both di- and tri-substituted iminium ions with an (*E*)-configuration were considerably more stable than the corresponding (Z)-isomers.

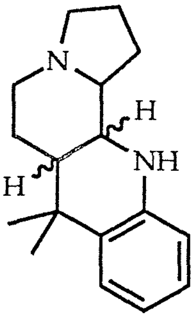
The second step, an intramolecular cyclisation, was assigned a concerted $[4\pi+2\pi]$ cycloaddition mechanism, rather than a two step process, consistent with the results from the group's earlier studies on tetrahydroquinolines.[57,58] The mechanism was rationalised by the fact that only two out of 16 possible diastereoisomers are formed in the reaction, which is best explained by assuming that both (*E*)-iminium ions undergo kinetically controlled cycloadditions. Furthermore, calculations suggested that the diastereoisomeric products (81), which were also shown not to undergo isomerisation under reaction conditions, were not the most thermodynamically stable of the 16 possible diastereoisomers; this was consistent with a kinetically controlled process.

The main points associated with the syntheses of a variety of octahydroacridines described in the last two sections ((iii) and (iv)) have been summarised overleaf in order to facilitate comparison.

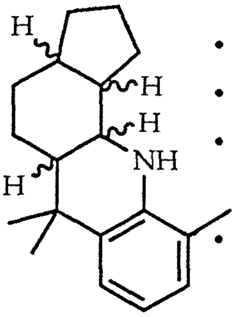
Octahydroacridines - Summary



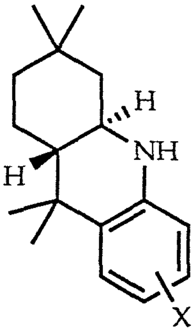
- synthesis of novel octahydroacridines
- reactivity and *cis/trans* selectivity mainly dependent on substitution pattern in 3-position of cyclic precursor
- type of Lewis acid plays minor role in determination of *cis/trans* ratio



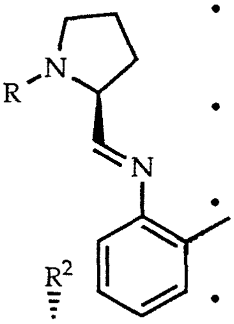
- aza Diels-Alder reactions of prolinal-derived N-arylimines
- diastereoselectivity completely controlled by choice of Lewis acid (eg. $SnCl_4$ => *trans*; $MeAlCl_2$ => *cis*)



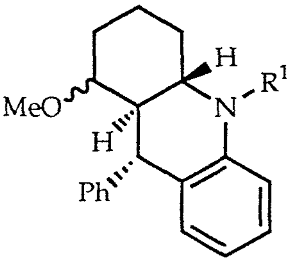
- aza Diels-Alder reactions of cyclopentane derived N-arylimines
- mixtures of *cis/trans* derivatives isolated irrespective of Lewis acid
- results establish evidence for chelation control by second nitrogen in cyclisation reactions of N-arylimines
- force field calculations support a stepwise iminium ion cyclisation under thermodynamic control



- synthesis of octahydroacridines with electron withdrawing substituents on the aromatic ring
- Lewis acid catalysis could be avoided if molecular sieve beads used instead of powder
- cyclisation extended to a novel one pot biscyclisation of aryldiamines with separated aromatic systems.



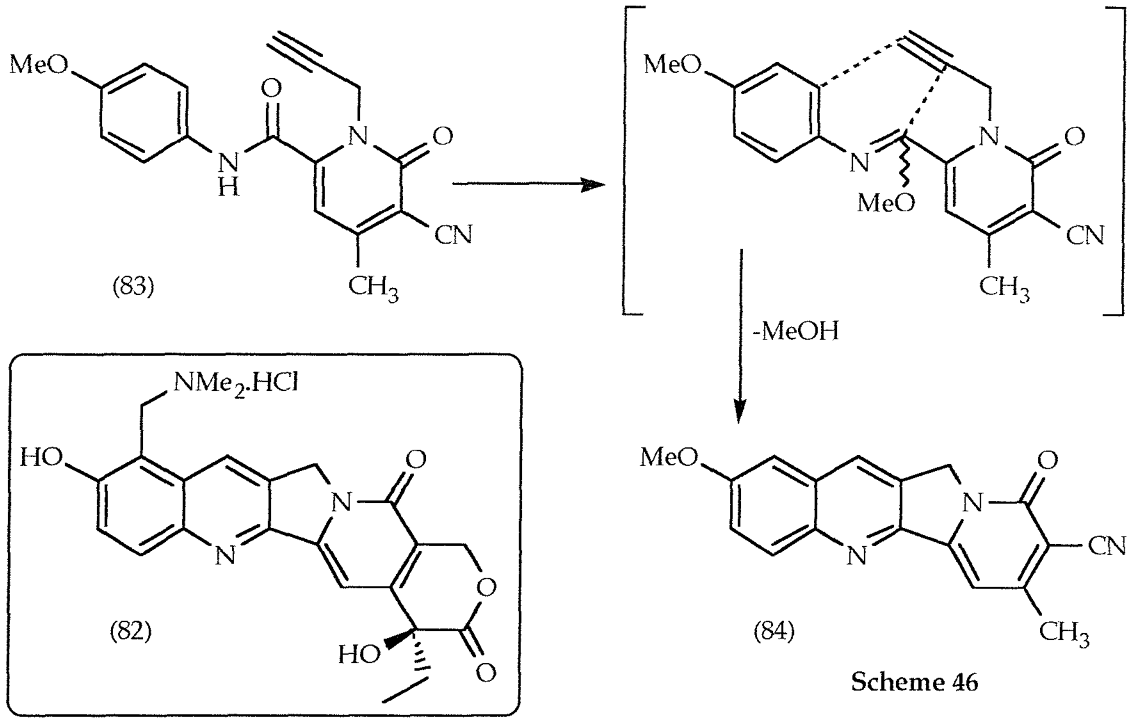
- cyclisation of various prolinal-derived N-arylimines bearing different tethers
- variation of the dienophile and length of the tether strongly influenced reactivity and diastereoselectivity
- chelation control reversal of product ratio was sensitive towards changes of ring size and steric effects
- stepwise mechanism concluded



- synthesis of substituted octahydroacridines
- highly diastereoselective (only *trans* isomers observed)
- one step mechanism proposed

(v) Related Applications of [4+2]-Cycloadditions

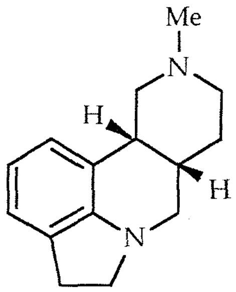
In addition to the aza Diels-Alder reactions of N-arylimines discussed in the previous sections, the intramolecular [4+2]-cycloadditions of N-arylimidates have also been reported[71] in the synthesis of camptothecin alkaloids (Scheme 46). Camptothecin (82) is a selective inhibitor of mammalian topoisomerase I[72] and a number of analogues are being developed as anticancer agents.[71,73]



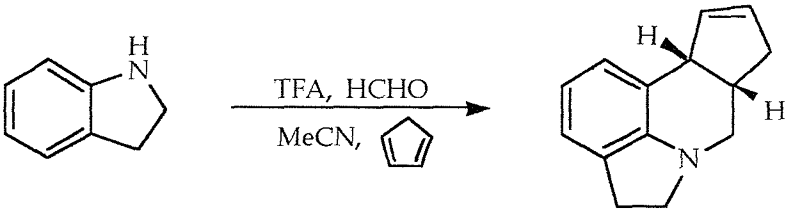
Scheme 46

Stirring (83) with trimethyloxonium fluoroborate in dichloromethane and then acetonitrile gave the O-methylimidate, with cycloaddition and subsequent elimination of methanol yielding the tetracyclic quinoline (84) in 82% yield. The formation of the product was effectively the intramolecular cycloaddition of an "electron neutral" alkyne with a 2-azadiene, and thought to be the first reported use of N-arylimidates serving as 4π components in a Diels-Alder reaction.

The discovery of Grieco and Bahsas[22] has also been applied to the attempted synthesis of a 5-HT receptor antagonist, SDZ SER-082 (85).[74] One of the three proposed routes involved the aza Diels-Alder reaction of indoline with formaldehyde and cyclopentadiene in acetonitrile containing trifluoroacetic acid, which gave the hexahydroquinoline (86) in 63% yield (Scheme 47).



(85)



(86)

Scheme 47

The product was formed regio- and stereospecifically, its structure being determined by nmr experiments which established the regiochemistry and showed a typical *cis* coupling of 6.5Hz associated with the ring junction proton at 3.74ppm.

The route was not subsequently advanced to the synthesis of the desired naphthyridine (85) due to further chemistry proving unsuccessful, but nevertheless, it illustrated the synthetic importance of Grieco's work since the Diels-Alder procedure had ultimately been a successful and potentially useful reaction.

1.5 SUMMARY

The initial work of Grieco[22] has given rise to an expanding area of research involving aza Diels-Alder reactions. Grieco found that immonium ions derived from aryl amines and aldehydes functioned not as heterodienophiles but rather as electron deficient 2-azadiene equivalents in a 1,4-cycloaddition reaction with cyclopentadiene, giving rise to novel tetrahydroquinolines. Earlier reports had concluded that simple immonium salts would undergo cyclocondensations with cyclopentadiene to yield azanorbornenes.[23] In sharp contrast however, the use of aniline in the reaction yielded tetrahydroquinolines, prompting interest in this new role reversal cyclocondensation.

Mellor *et al.*[24-26,40-42,54,55] have undertaken extensive research in this area. Efficient one pot syntheses of azasteroids and related tetrahydroquinoline skeletons were initially developed by the reaction of aromatic primary amines with formaldehyde and cyclopentadiene.[24,41] The success of these reactions led to further studies involving a variety of amines such as *ortho*-phenylenediamines,[55] mono- and di-aminoanthraquinones,[54] and their reactions with diverse electron rich alkenes including styrenes, enol ethers and pyrans.[42] The isolation of intermediate products such as alcohols which could be further cyclised to give tetrahydroquinolines provided evidence of the non-concerted nature of the reaction. Furthermore, observations have been made regarding the potential clinical importance of cycloadducts such as anthraquinones and benzodiazepines.[54,55]

Ledderhose *et al.*[57,58] have synthesised 1,2,3,4-tetrahydroquinolines from cycloadditions of thiomethylamines, α-arylaminosulfones and α-arylaminonitriles with various dienophiles. In contrast to results from Mellor *et al.*,[42] no intermediate or side products were isolated, supporting the view that the results could best be rationalised in terms of a one step concerted cycloaddition. Tetrahydroquinoline derivatives have been obtained, in addition to pyridine and quinoline derivatives, by Kobayashi *et al.*[52] The reactions, which were catalysed by lanthanide triflates, involved amines acting as both dienophiles and azadienes under different conditions. The use of cyclopentadiene in place of Danishefsky's diene in the reaction produced tetrahydroquinolines rather than tetrahydropyridines. The proposed mechanism involving an intermediate indicated a stepwise reaction.

The aza Diels-Alder reaction has also been applied to the synthesis of octahydroacridines. A new intramolecular Lewis acid catalysed reaction of N-arylimines with nonactivated olefins tethered to the 2-azadiene system was developed in order to prepare octahydroacridine derivatives,[60] a class of pharmacologically interesting compounds. The reactivity and selectivity was mainly dependent on the substitution in the precursor, whereas the type of Lewis acid played only a minor role in determining the selectivity. A concerted cycloaddition mechanism was proposed, although a stepwise mechanism could not be ruled out. With further work, involving the effect of molecular sieves,[68] on the synthesis of substituted octahydroacridines, it was found that isolation of the imines and Lewis acid catalysis could be avoided if molecular sieve beads were used instead of powder. In contrast to these results, it was shown that diastereoselectivity in the aza Diels-Alder reaction of prolinal derived N-arylimines could be completely controlled by the choice of Lewis acid.[65] Subsequent studies on the reactions of corresponding cyclopentane derived N-arylimines established that chelation control by a second nitrogen atom was possible in the reactions of these imines.[66] Force field calculations supported a stepwise iminium ion cyclisation under thermodynamic control rather than a concerted mechanism. An extension of the work on proline derived N-arylimines showed that reactivity and selectivity in the cyclisations of compounds bearing different tethers was strongly influenced by the modification of the dienophile, and confirmed earlier reports which had concluded a stepwise mechanism.[67]

In contrast, Ledderhose *et al.*[70] proposed a concerted mechanism for their synthesis of octahydroacridines. The products were formed with high diastereoselectivity from the intramolecular cycloaddition of the imines generated from condensation of amines and aldehydes. The isolation of only two diastereoisomers which did not isomerize indicated a one step cycloaddition.

The studies of Grieco[22] have also been extended to the intramolecular cycloadditions of N-arylimidates in the novel syntheses of camptothecin alkaloids,[71] which were thought to be the first reported reactions of this kind. Finally, a hexahydroquinoline derivative was synthesised using the method of Grieco and Bahsas in the attempted synthesis of a 5-HT receptor antagonist,[74] further emphasising the synthetic importance of the procedure.

DISCUSSION

2.0 DISCUSSION

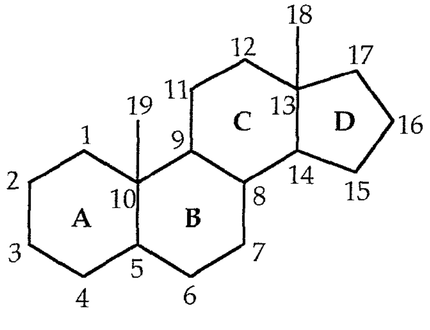
2.1 SYNTHESIS OF MONOAZASTEROIDS: Part 1

This chapter begins with a brief outline of the importance of azasteroids, the synthesis of which is the focus of the studies described in the subsequent sections. The work described later in this chapter is a discussion of the results obtained from the cyclocondensations of two bicyclic aromatic amines with aqueous formaldehyde and a number of electron rich alkenes, performed with trifluoroacetic acid catalysis in acetonitrile. The aim of this section of work was to create an azasteroid skeleton in a one step reaction following the procedure established by Grieco[22] and developed by Merriman[26] and Gregoire.[25]

The work has focused on the reactions of two amines which were chosen for their potential to produce a particular product in the Diels-Alder reactions undertaken. Their use was briefly examined by Gregoire, hence creating the opportunity to extend and improve upon those studies in order to meet the aim of azasteroid synthesis. The presentation of the results follows the synthesis of the starting materials and their reactions, initially with cyclopentadiene, and subsequently with the introduction of other electron rich alkenes. The suitability of methylcyclopentadiene as an electron rich partner is examined initially in the reaction with a basic aniline derivative known to give good results in similar reactions.

2.1.1 THE STRUCTURE AND IMPORTANCE OF AZASTEROIDS

Steroids with a nitrogen atom replacing one or more carbon atoms in the basic steroidal framework (87) are known as intranuclear azasteroids. These are the focus of this section.



(87)

The position of the nitrogen atom within the skeleton can be varied, and the azasteroid may be classified according to the numbered position, eg. 11-azasteroid.

The importance of azasteroids can be attributed to two main factors: their bioactivity and the challenge of their synthesis. The replacement of a carbon of a steroid molecule by a nitrogen affects the chemical properties of the steroid and often results in useful and important alterations to its biological activity. A wide range of activity has been observed in many pharmacological areas[75] including anabolic, cardiovascular, anti-fungal, anti-microbial, anti-cancer and CNS acting agents.

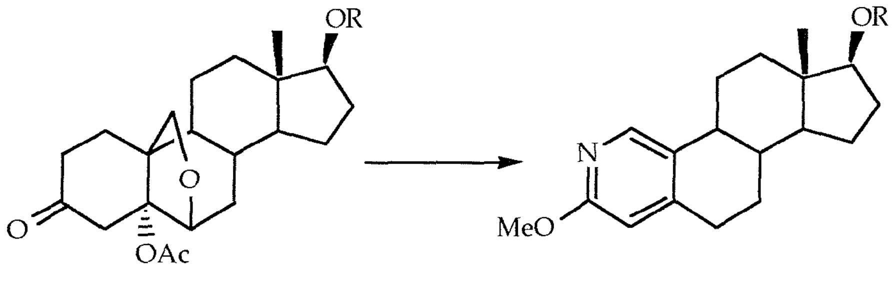
One attractive feature of azasteroids is that replacement of a CH_2 group with a similarly sized NH group does not alter the shape of the molecule to any great extent[76], but can affect its properties. Hence the azasteroid can mimic an all-carbon steroid in biological systems, and significantly change or block the biosynthetic pathway.

Azasteroids are also of interest since their synthesis represents a challenge to organic chemists often resulting in the development of useful reactions,[77,78] such as the Torgov[79] reaction in which the total synthesis of carbocyclic steroids can be readily adapted to the synthesis of azasteroids by replacement of the starting tetralone with an aza analogue. The use of Diels-Alder cyclisations also has a wide range of potential applications in azasteroid synthesis.[80]

A brief review of some naturally occurring and synthetic intranuclear azasteroids is presented in the following sections. There are few naturally occurring azasteroids, and the majority of medicinally useful azasteroids are synthetic compounds.

(i) 2-Azasteroids

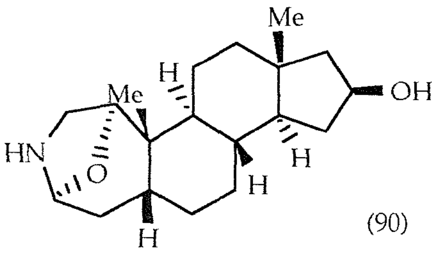
Some 2-azasteroids have been reported as anticholesterolemic, antiviral and antileukaemic agents.[81] The aromatic azasteroid, 2-aza-estradiol-3-methylether (89) has been prepared[82] in several steps from the known 6,19-ether (88) (Scheme 48).



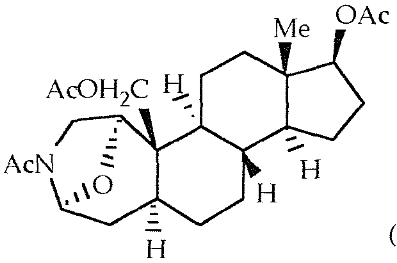
(88) Scheme 48 (89)

(ii) 3-Azasteroids

A series of naturally occurring 3-azasteroids has been isolated from salamanders;[83] samandarine (90) is a central nervous system toxin. The anaesthetic agent (91) is also a seven membered ring A azasteroid.

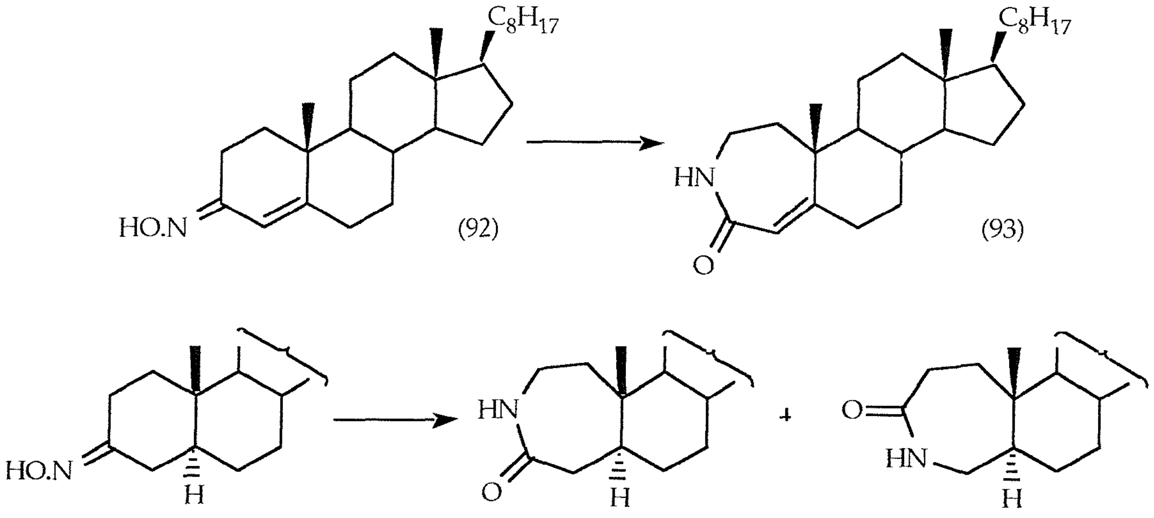


(90)



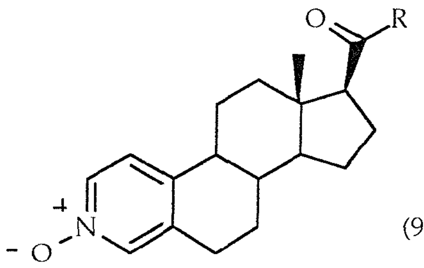
(91)

Many syntheses of 3-aza lactams start from the easily available A-ring ketones. The 4-oxo-3-aza-A-homo lactam (93) has been obtained from the Beckmann rearrangement of cholest-4-en-3-one (92)[84] oxime (*E* and *Z* isomers), although the corresponding saturated (5α) oximes give a mixture of 4-oxo-3-aza and 3-oxo-4-aza lactams[85] (Scheme 49).



Scheme 49

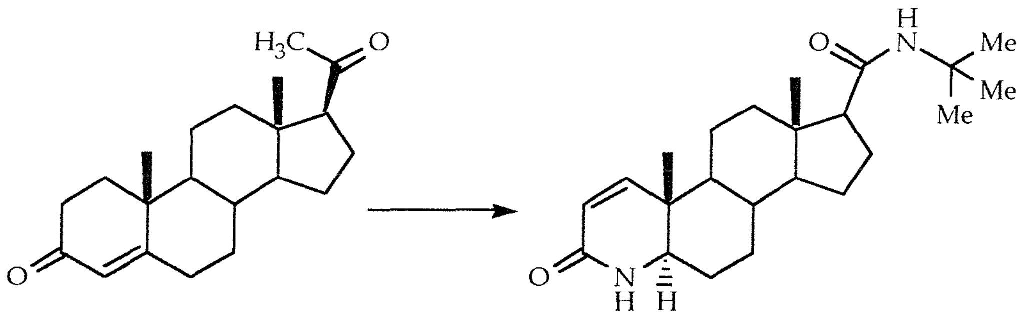
3-Pyridyl-N-oxide steroids (94) have been synthesised from nortestosterone and found to be potent inhibitors of an isozyme of 5α-reductase.[86] The enzyme catalyses the conversion of testosterone to the more potent androgen dihydrotestosterone which is believed to be involved in several androgen dependent diseases such as benign prostatic hyperplasia (BPH). Two isozymes of this enzyme have been discovered in humans.[86]



(94) R = NEt_2, NH-*t*Bu

(iii) 4-Azasteroids

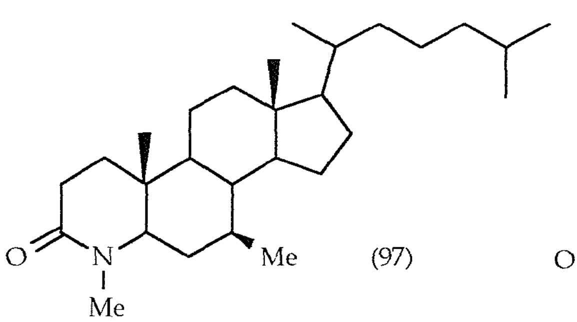
The enzyme 5α-reductase is also a main focus for studies leading to the synthesis of 4-azasteroids. Several reports have described the inhibition of 5α-reductase by a series of 4-azasteroids,[33,87-90] and the *in vitro* activity of these compounds has been demonstrated in different tissues, species and in different disease states.[33] The implications of dihydrotestosterone in the pathogenesis of conditions such as BPH have led to the development of human 5α-reductase inhibitors as potential therapeutic agents for BPH.[91] A variety of specific 4-azasteroid 5α-reductase inhibitors have been synthesised over the last few years[33,91,92] since the identification of 3-keto-4-azasteroids as potent inhibitors of the enzyme.[87] This led to the first drug therapy, Proscar,[91,93] for the treatment of BPH. The active agent in Proscar is finasteride (96) (17β-(N-*t*-butyl)carbamoyl-4-aza-5α-androst-1-en-3-one).

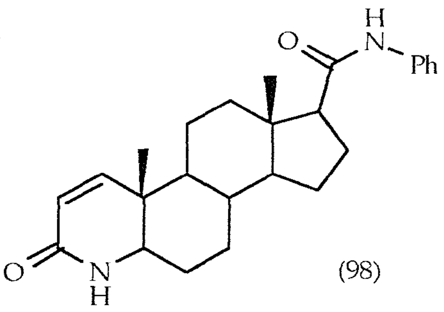


(95) **Scheme 50** (96)

Its synthesis from progesterone (95) (Scheme 50) consists of a side chain construction involving a hypobromite reaction and *t*-butyl amide formation followed by elaboration of ring A.[81]

As already mentioned there are two forms of 5α-reductase, isozymes type I and II. Finasteride is a selective inhibitor of the human type II enzyme. A series of 7β-substituted 4-azacholestan-3-ones have been developed as selective inhibitors of human type I 5α-reductase,[94] and the azasteroid 4,7β-dimethyl-4-aza-cholestan-3-one (MK-386) (97) was chosen for human clinical trials.

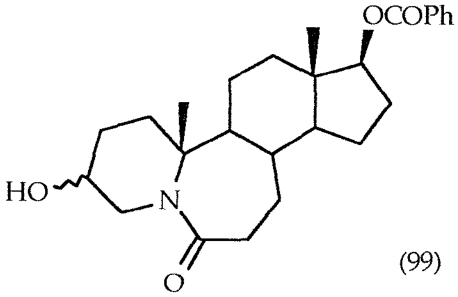

(97)


(98)

Inhibition of both enzymes by a dual inhibitor was expected to result in a more effective lowering of dihydrotestosterone compared to the use of a type I or type II inhibitor separately. Hence some 4-aza-3-oxo-5a-androst-1-ene-17β-N-arylcarboxamides[95] were synthesised; compounds such as (98) were found to be potent inhibitors of both 5α-reductase isozymes.

(iv) 5-Azasteroids

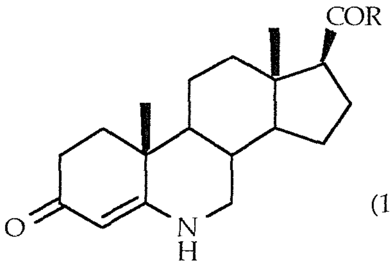
There are few reports concerning 5-azasteroids; one recent study of several 3-substituted-B-homo-5-azasteroids showed evidence supporting neighbouring group participation by the nitrogen atom in the stereospecific rearrangements of the compounds to ring contracted A-nor products.[96] Conversion of the hydroxyl group at the 3-position in (99) into a good leaving group resulted in the high yielding rearrangements, accompanied by competing substitution at C-3 with inversion of configuration.


(99)

Since substituents at C-3 are of particular importance in the recognition and binding of steroid hormones by the active sites of receptors and enzymes, these studies suggested that the nitrogen atom of 5-azasteroids could have profound effects on their biological properties by altering the reactivity at this position.

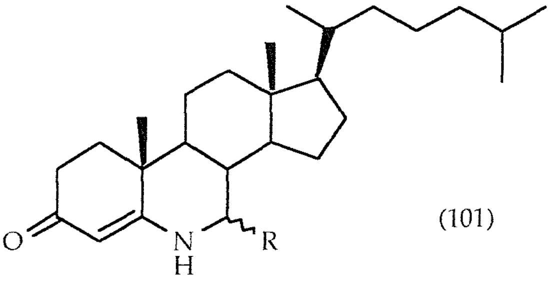
(v) 6-Azasteroids

As with 4-azasteroids, the synthesis of many 6-azasteroids has been directed towards potential inhibitors of human type I and II 5α-reductase.[97-99] The 17β-[N-(diphenylmethyl)carbamoyl]-6-aza-androst-4-en-3-ones (100) were found to be potent inhibitors of both type I and II 5α-reductase, with exceptional potency against the type II enzyme.[97] More recently, 6-azacholesten-3-ones (101) were also found to be potent inhibitors of both enzymes.[100]



(100)

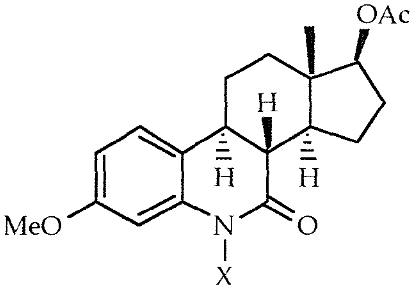
R = NHCHPh
R = NHCH(4-fluorophenyl)$_2$
R = NHCH(4-chlorophenyl)$_2$



(101)

R = H, Me

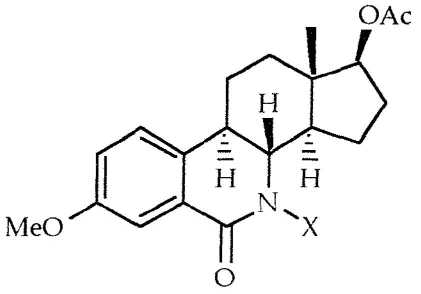
Some novel 6-aza-B-homoestranes have been synthesised as antifertility agents.[34] Aromatic 6-azasteroids (6-azaestrane derivatives) have also been reported recently.[101] Only a few examples of 6-azaestranes, generally prepared by total synthesis[102] using the Torgov[79] reaction have been reported. The 6-azaestrane lactam (102) and its N-chloro derivative (103) were prepared from 3-methoxyestrone.



(102) X = H
(103) X = Cl

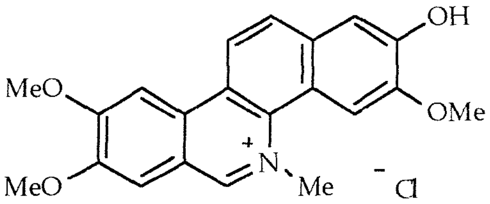
(vi) 7-Azasteroids

The 7-azaestrane lactam (104) and its N-chloro derivative (105) were also prepared alongside the 6-aza compounds mentioned above.[101]



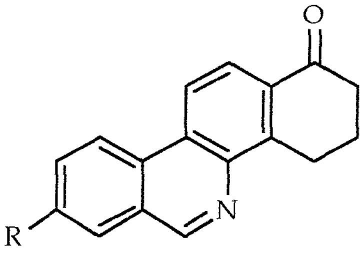
(104) X = H
(105) X = Cl

An important naturally occurring 7-azasteroid is the benzo[c]phenanthridine alkaloid fagaronine chloride (106), isolated in 1972.[103] This compound displayed significant anti-viral and anti-leukaemic activity.[104] The ring structure of (106) is similar to that of the naturally occurring 11-azasteroid chelidonine (8) described in Section 1.4.1.

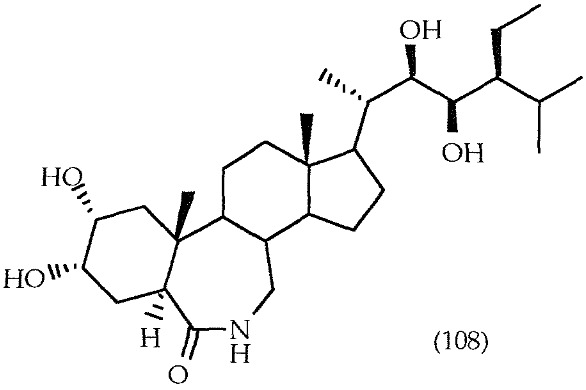


(106)

Benzo[c]phenanthridine alkaloids are a specific group of isoquinoline alkaloids which occur only in higher plants,[105] and the chemistry and synthesis of these compounds has seen a tremendous growth in interest due to their biological activity.[106] The total synthesis of fagaronine chloride has been reported.[107]



(107) R = H, OMe

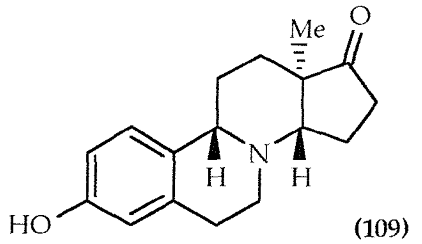


(108)

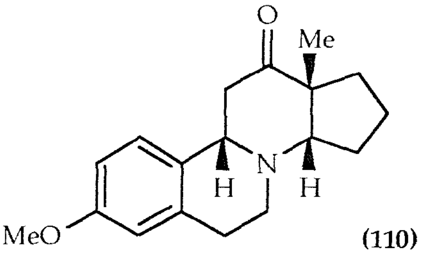
1-Oxo-1,2,3,4-tetrahydrobenzo[c]phenanthridine (107) obtained from an intramolecular benzyne electrocyclisation with a Schiff base[108] is an example of a synthetic 7-azasteroid. The brassinosteroids are a class of steroidal phytohormones found in the plant kingdom with high plant growth promoting activities.[109] Several 7-aza analogues of brassinolide, such as (108)[110] have been synthesised and evaluated for their plant regulating activity.[111]

(vii) 8-Azasteroids

8-Azaestrone was the first azasteroid to be synthesised in which the nitrogen atom is common to two rings[76] and most of the 8-azasteroids synthesised have been 8-azaestrogens.[112-114] The azasteroids (-)-8-azaestrone (109) and related (-)-8-aza-12-oxo-17-desoxoestrone (110) have recently been synthesised with high enantiomeric purity.[115]



(109)

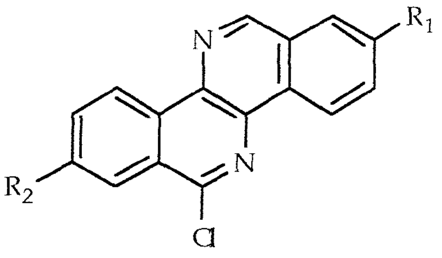


(110)

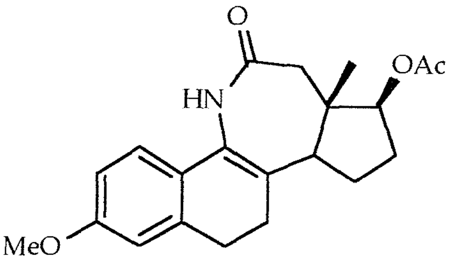
It has been observed that many 8-azasteroids possess useful therapeutic properties such as anti-inflammatory, anti-fertility, cardiovascular and hypotensive activity.[116]

(viii) 11-Azasteroids

The most well known naturally occurring 11-azasteroid is chelidonine (8) (page 6), a benzo[c]phenanthridine alkaloid. A series of related 11-aza-benzo[c]phenanthridines (111) have recently been synthesised[117] with the further aim of investigating their biological and physicochemical properties, since the area of aza-benzophenanthridines remains relatively unexplored.

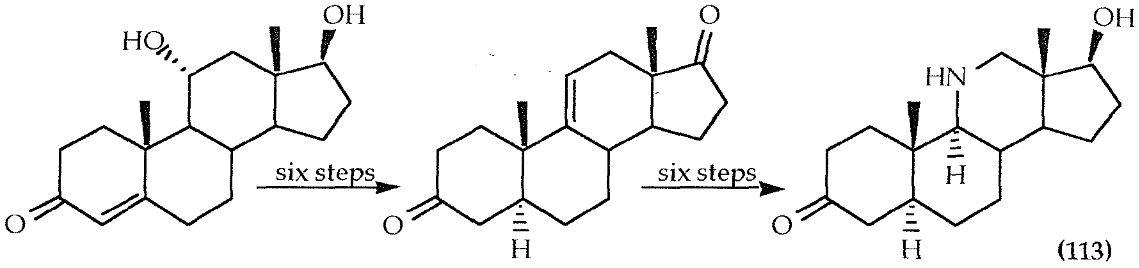


(111) $R_1, R_2 = H, OMe$



(112)

The synthesis of the 11-aza-C-homoestrane (112) has been reported[34] and the compound was found to display significant estrogenic and antifertility activity. However, a second reported synthesis of the same azasteroid by a different route[118] notes large discrepancies in the properties of the two compounds, confirming the structure of the 11-azasteroid by both spectroscopic methods and X-ray crystallography. The 11-aza analogue of 4,5α-dihydrotestosterone has been synthesised.[119] The properties of this analogue were thought to be potentially very interesting since the testosterone metabolite was regarded as being highly active.[119] 11-Aza-4,5α-dihydrotestosterone (113) was formed in twelve steps from 11α-hydroxytestosterone (Scheme 51).

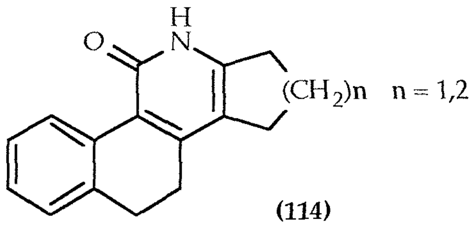


(113)

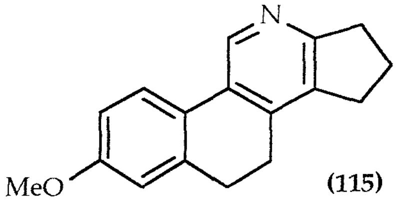
Scheme 51

(ix) 12-Azasteroids

The 12-azasteroids (114) have been prepared in a single step from a readily available enamine.[120] Enamines also yielded 12-azasteroids such as (115) from cycloaddition reactions with 1,2,4-triazines.[121]

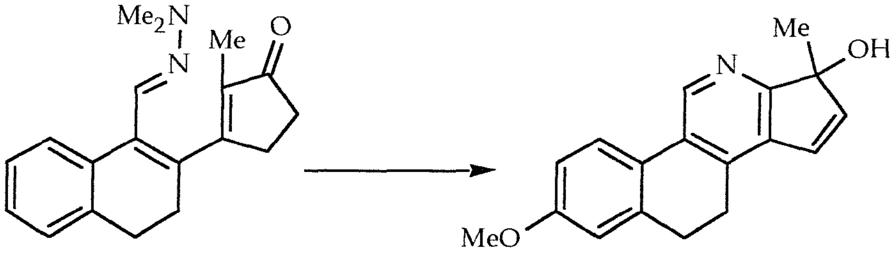


(114)



(115)

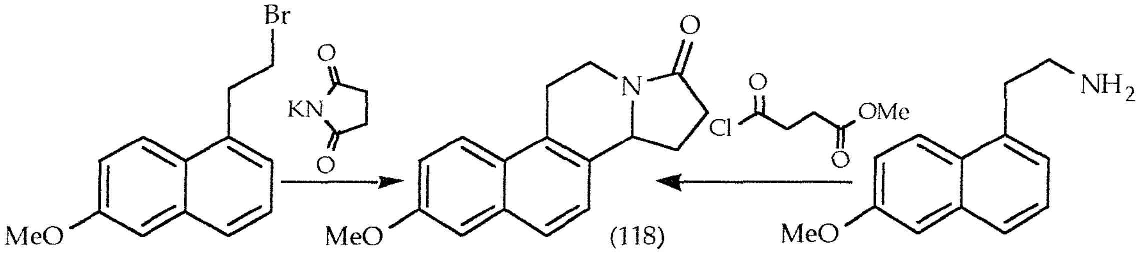
An approach to 12-aza analogues of estrone has also been reported.[36] Ring C of the azasteroid (117) was formed by electrocyclic ring closure of a dienone N,N-dimethylhydrazone (116). However, the structure of the product was not the one originally expected. The 13-methyl was not retained in the cyclisation, undergoing a thermal shift to give the pyridine structure (117) despite variations in the reaction conditions (Scheme 52).



(116) Scheme 52 (117)

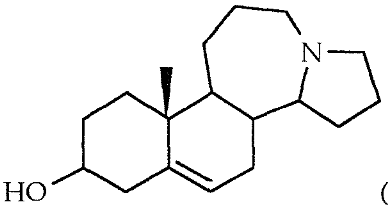
(x) **13-Azasteroids**

Two different syntheses of 13-aza-18-norequilenin (118) have been published[122,123] (Scheme 53).



Scheme 53

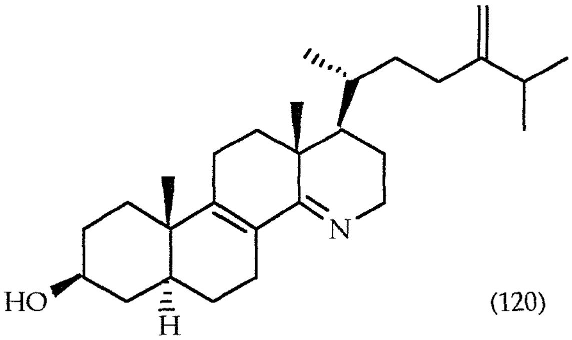
The 13-azasteroid (119) has been prepared[81] from 3β-hydroxyandrost-5-en-17-one in a route involving a 13,17-seco keto ester and Beckmann rearrangement of its oxime followed by cyclisation to give 12a-homo-18-nor-13-aza-androst-5-en-3β-ol.



(119)

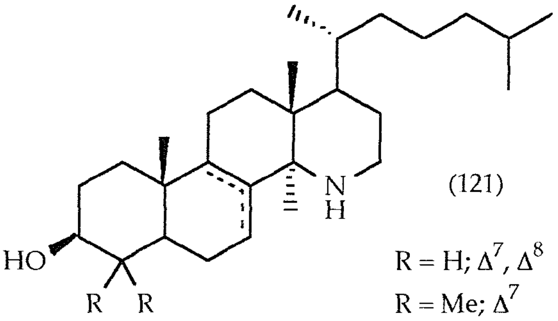
(xi) **15-Azasteroids**

The mold *Geotrichum flavo-brunneum* produces a group of 15-aza-D-homosteroids that possess powerful antimycotic activity.[124] The most potent member of this class is antibiotic A25822B (120),[125] a 15-aza-24-methylene-D-homocholestadiene.



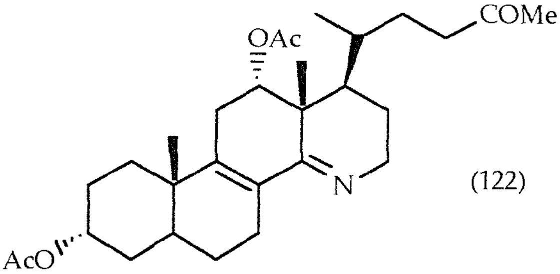
(120)

15-Aza-D-homosteroids such as (120) block the biosynthesis of ergosterol, an essential component of the cell membranes of yeasts and fungi, by inhibiting the enzyme Δ^{14}-sterol reductase.[126] The first synthesis of antibiotic A25822B was achieved from epiandrosterone.[127] A series of related 14α-methyl-15-aza-D-homosterols such as (121) has been synthesised[32] and was found to display significant antimycotic activity. Cholic and chenodeoxycholic acids have been transformed into analogues (122) of the antifungal azasteroid A25822A.[128]



(121)

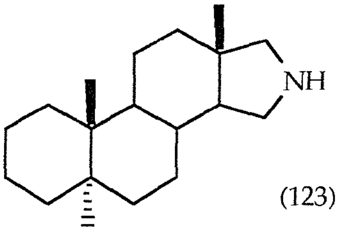
R = H; Δ^7, Δ^8
R = Me; Δ^7



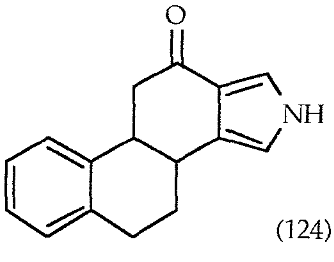
(122)

(xii) 16-Azasteroids

A versatile method for substitution of a carbonyl group of steroidal ketones by a heteroatom has been employed in the synthesis of 16-aza-5α-androstane (123).[129]



(123)



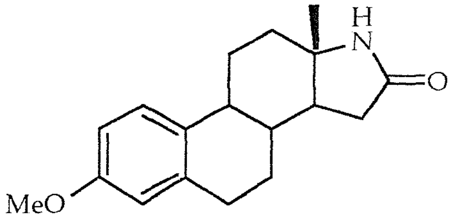
(124)

The 16-azasteroid (124) has been synthesised from tetralone using a Robinson annulation followed by olefin isomerisation and subsequent pyrrole synthesis.[130] Tetralone is a key starting material in the synthesis of monoazasteroids via Diels-Alder reactions dicussed in the next section.

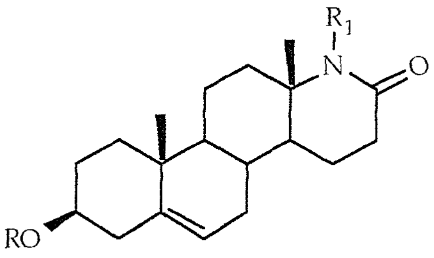
(xiii) 17-Azasteroids

The 17-position of steroid hormones is particularly important in both receptor recognition and as the site of key biosynthetic transformations, and therefore, numerous methods for the preparation of 17-azasteroids have been developed.[81] A number of azasteroids in the estrane and androstane series were synthesised from 16,17-seco 17-carboxylic acid precursors by means of a diphenylphosphoryl azide mediated Curtius rearrangement as the key step.[131] The products, such as (125), were subsequently converted into their N-chloro derivatives.

17a-Aza-D-homoandrost-5-en-17-one derivatives (126) were prepared from the corresponding androst-5-en-17-one derivatives by rearrangement of their oximes.[132]



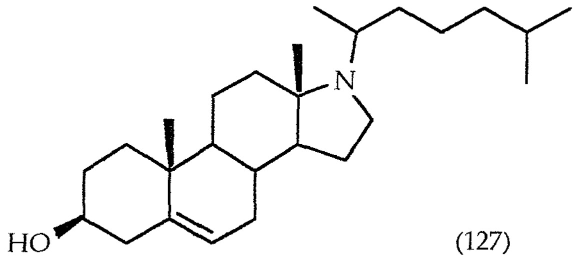
(125)



R = Ac, Me

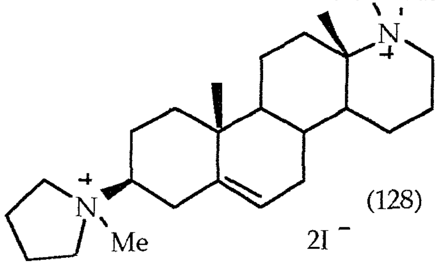
(126) R_1 = H, Me, Et, allyl

The N-alkylation of 17-azasteroid lactams has also been investigated[133] with the aim of synthesising 17-azacholesterol (127) since this previously unreported compound was of potential biological interest. The azasteroid (127) was synthsised from the N-(3-hydroxy-1-methylpropyl)-17-aza lactam,[134] and was expected to act as a hypocholesterolemic agent.

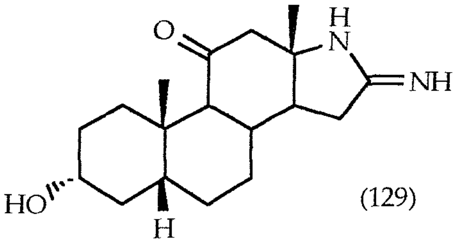


(127)

Chandonium iodide (128) is a potent neuromuscular blocking agent.[135] Several 17-azasteroid analogues of chandonium iodide have been synthesised and found to have neuromuscular blocking activity.[136] 3α-Hydroxy-16-imino-17-aza-5β-androstan-11-one (129) was reported as a potent γ-amino-butyric acid receptor antagonist.[137]



(128)

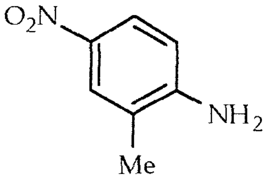


(129)

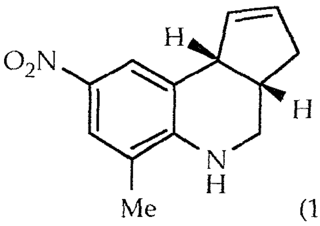
2.2 SYNTHESIS OF MONOAZASTEROIDS : Part 2

2.2.1 REACTION WITH SUBSTITUTED ANILINE AND CYCLOPENTADIENE

A difficulty observed earlier in studies of cyclocondensations of cyclopentadiene with formaldehyde and anilines was the tendency for initially formed products to undergo a second condensation. Hence in the initial study to establish an efficient procedure for future reactions with cyclopentadiene and methylcyclopentadiene it was decided that 2-methyl-4-nitroaniline (130) would be a suitable starting material. This amine had two advantages: the second potential condensation is blocked by the methyl group, and an iminium ion derived from this amine is further activated by the nitro group.



(130)



(131)

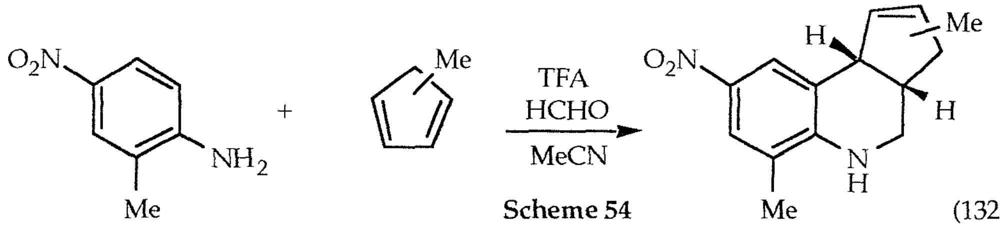
A 1.4M solution of the amine in acetonitrile containing one equivalent of trifluoroacetic acid was added to a heterogeneous mixture at 0°C of cyclopentadiene and 37% formalin solution (ratio of amine:cyclopentadiene:formalin = 1:5:5) and the mixture was stirred at room temperature under nitrogen for 1 hour. A basic work up produced a brown oil which, when purified by flash column chromatography on deactivated basic alumina gave a yellow solid in 52% yield. Subsequent recrystallisation resulted in yellow crystals and spectroscopic analysis confirmed the formation of the adduct (131).

Merriman had observed[26] that decreasing the number of equivalents of formaldehyde and cyclopentadiene in reactions favoured the production of monocyclocondensation adducts and impeded the formation of undesired over-addition products. Hence the reaction conditions were adjusted in subsequent procedures, and the yield of the adduct was optimised at 81% in a reaction performed using 1.2 equivalents of formaldehyde and cyclopentadiene.

2.2.2 REACTION WITH SUBSTITUTED ANILINE AND METHYLCYCLOPENTADIENE

Following the success of the reaction with cyclopentadiene, the cyclocondensation of 2-methyl-4-nitroaniline with methylcyclopentadiene was addressed. Not only would this serve as a suitable comparison with cyclopentadiene, it would also introduce the opportunity to examine the effect of this alkene on the outcome of the reaction. Methylcyclopentadiene had not been employed in the work of Gregoire[25] and Merriman,[26] and its incorporation into the aza Diels-Alder synthesis of azasteroids was one of the initial aims of the project. An immediate query arose concerning the position of the methyl on the cyclopentadiene ring. Clearly there would be isomers of the diene present in the reactions, leading to isomers in the products. The diene was obtained by the cracking of the commercially available dimer using a simple distillation apparatus to give a mixture of 1-methyl- and 2-methylcyclopentadienes,[138] and was freshly distilled for each reaction.

An experiment with 2-methyl-4-nitroaniline and methylcyclopentadiene under conditions similar to those previously employed with cyclopentadiene yielded a brown oil which appeared to be one major compound by TLC. However, flash chromatography on alumina followed by nmr analysis of the resulting yellow solid indicated the presence of more than one product (Scheme 54).



Scheme 54

(132)

Three distinct singlets in the ^1H nmr corresponding to the methyl from the diene suggested at least three isomers; this was further emphasised by the ^{13}C nmr where many signals were repeated, a feature often observed with mixtures of isomers. A more careful analytical examination of the products by TLC failed to separate the single spot, despite variations in the solvents and the polarity of the solutions. Repeated elutions with a low polarity solvent system which can sometimes separate what appears to be one spot also failed in this case. Nevertheless, several further attempts at flash chromatography and dry flash chromatography were carried out with little or no variation in the outcome; also the product repeatedly exhibited signs of decomposition upon standing. However, when the flash chromatography eluant containing the product was concentrated slowly under reduced pressure with no heat and the resulting solution allowed to stand, a bright yellow solid was precipitated, which did not decompose upon standing following isolation. Again the product was an isomeric mixture.

Attempts at recrystallisation were unsuccessful as the products readily decomposed with gentle heating. With the aid of Dr. John Liebeschuetz, the cycloadduct was analysed at the DowElanco laboratories. Initial results revealed that the isomers were not separable by HPLC, although GC-MS analysis was very encouraging. Four major products could be detected by gas chromatography (Figure 1, Figure 2).

Figure 1: GC Analysis of Methylcyclopentadiene Adduct (132) and MS of Fraction 2.

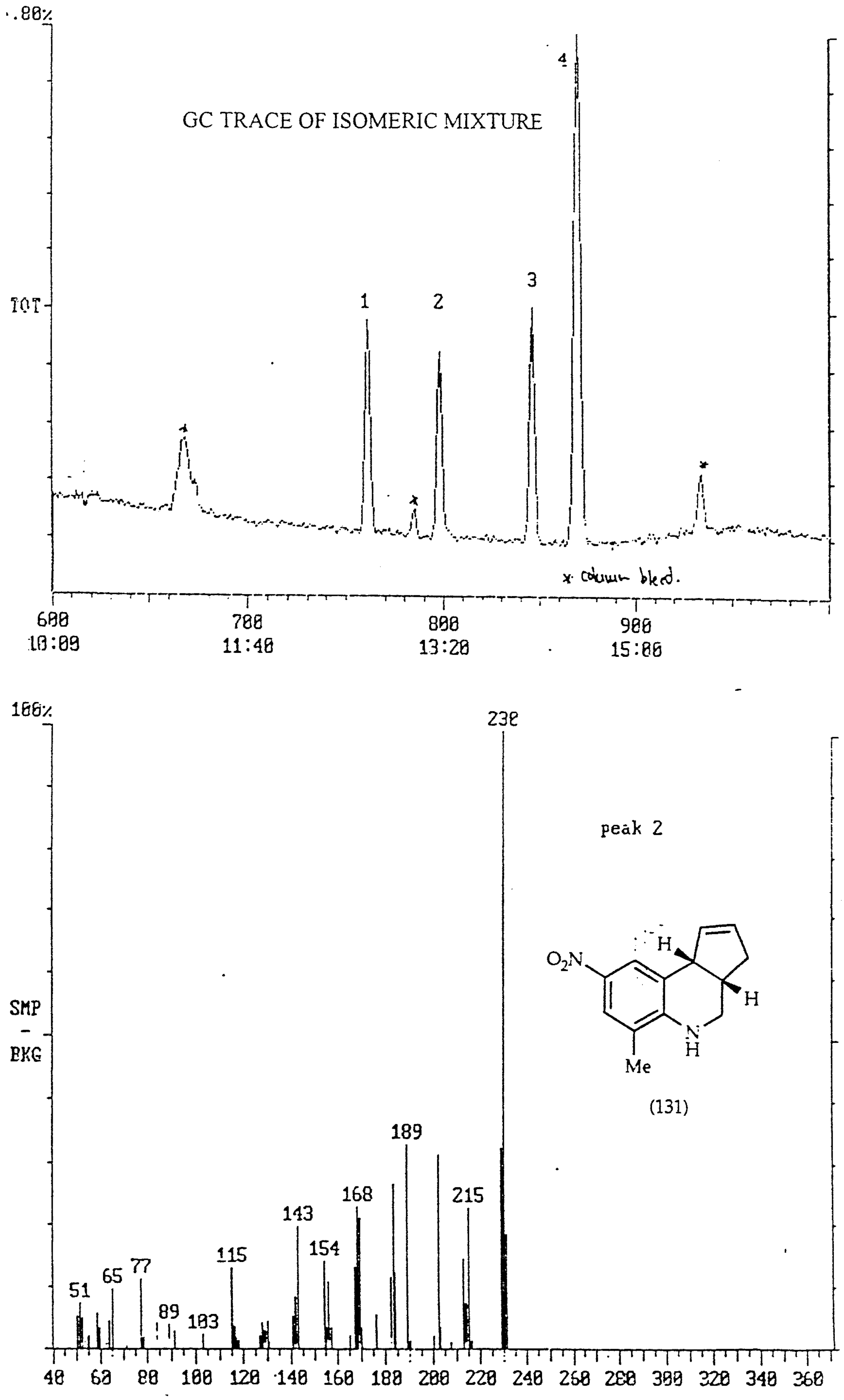
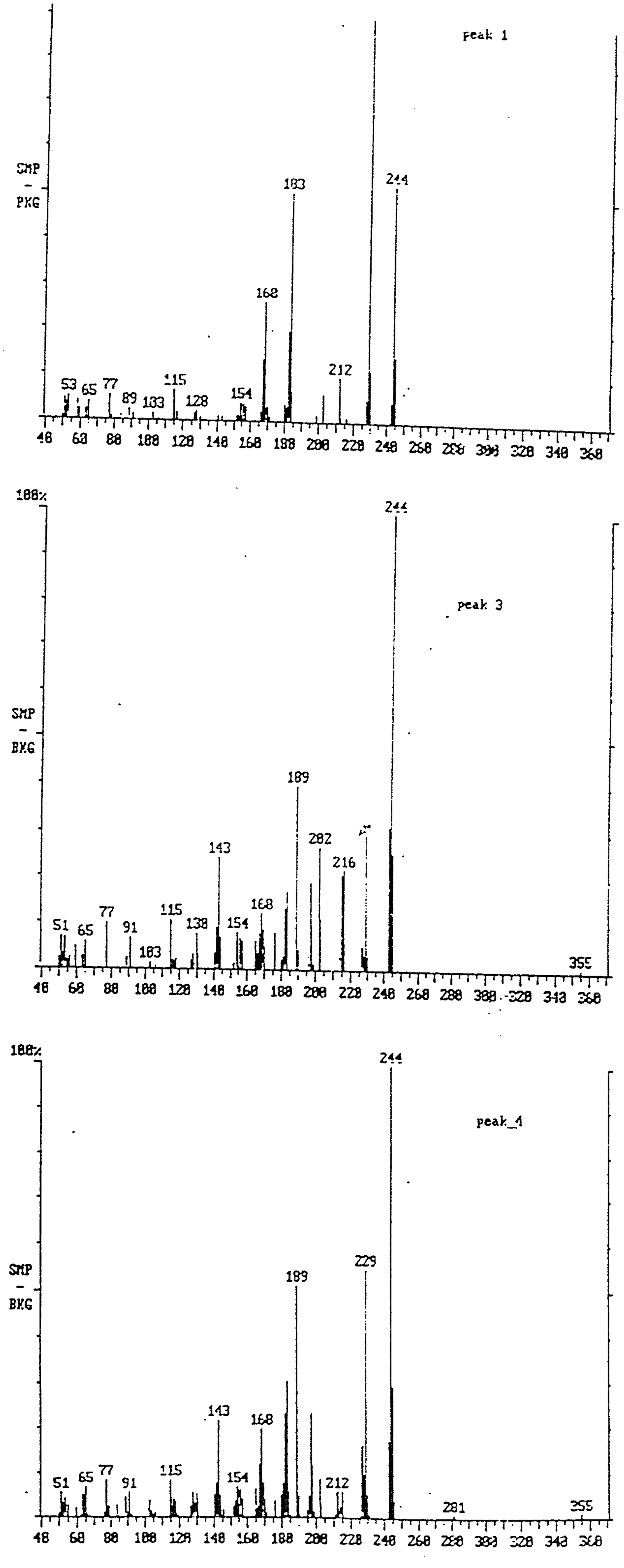
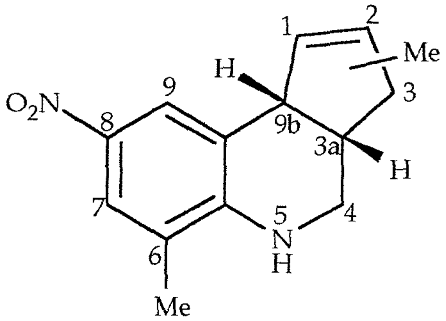


Figure 2: MS Analysis of Methylcyclopentadiene Adduct (132) Fractions 1, 3 and 4.



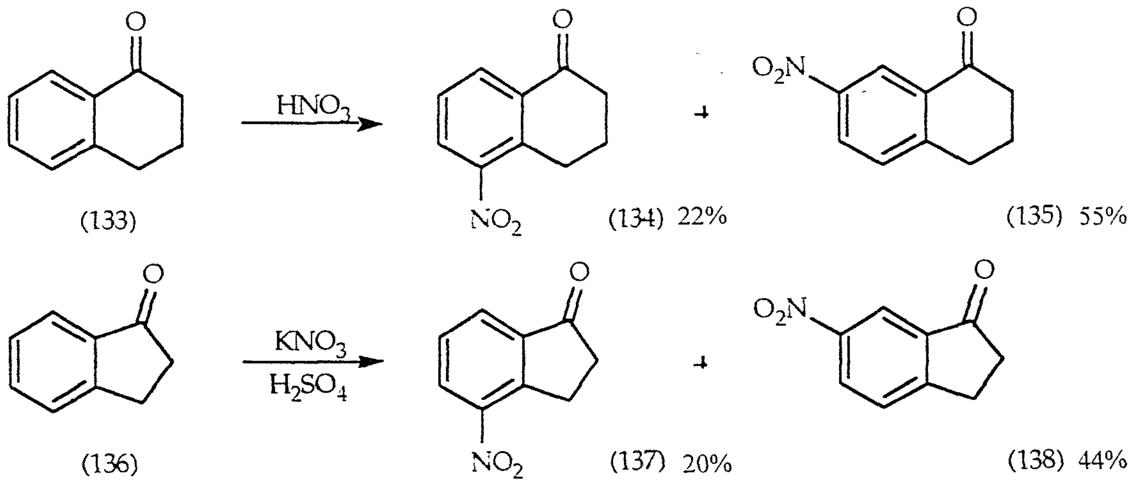
Analysis of the components by mass spectroscopy showed that the second of the four peaks could be attributed to the simple cyclopentadiene adduct (131) since the molecular ion peak was the correct value (230) for this compound. Furthermore, the fragments observed in the mass spectrum were identical to those of the cyclopentadiene (131) adduct synthesised earlier. The remaining three components all showed a molecular ion peak of 244, indicating methylcyclopentadiene adducts (132). However, whereas with the third and fourth components, 244 was also the base peak, the first isomer had a base peak of 229, corresponding to the loss of a methyl group. This would suggest that the methyl group was originally at the ring junction (C_{3a} or C_{9b}), since the resulting ion is more stable than that produced if the methyl was lost from a vinylic carbon. The last two isomers displayed similar fragments in the mass spectrum, following the initial loss of a methyl group, and were thought to have the methyl group on the double bond (C_1 or C_2). Since it was difficult to obtain sufficient quantities of each isomer for further analysis by nmr, further assignments were not possible. However, it was clear from the initial results that the cycloadditions with methylcyclopentadiene had been successful, giving adducts containing a methyl group at the ring junction and on the double bond (132). The successful separations of the isomers at the analytical level by gas chromatography suggested that initial poor results from HPLC analysis could be improved upon to enable an efficient separation of larger quantities of products via preparative methods.



(132)

2.2.3 REACTION WITH AROMATIC AMINO-KETONES AND CYCLOPENTADIENE

In order to slightly broaden the starting amines studied and to move towards the aim of making azasteroids, the next class of compounds investigated were aromatic amino-ketones, in particular α-tetralone and α-indanone derivatives. The amino compounds were accessible *via* nitration (Scheme 55) of α-tetralone (133) and α-indanone (136) followed by subsequent reduction of the nitro group.



Scheme 55

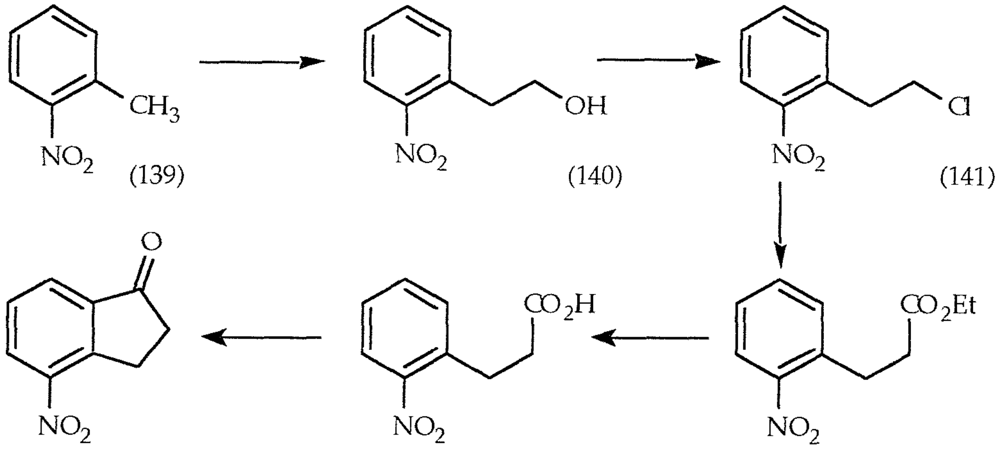
(i) Preparation of Starting Amines: Nitration

The nitration was carried out as described by Gregoire,[25] using the method of Von Braun[139] in fuming nitric acid below 0°C. This provided 5- and 7-nitro-α-tetralones (134) and (135) with the latter as the major isomer; examination of the nmr integrals of the crude reaction product indicated a ratio of 1:4. The electron withdrawing effect directs the nitration to the two meta positions, and the effect of the hydrocarbon chain favouring the para position results in the main electrophilic substitution at the 7-position. Evidently, the amino derivative of 7-nitro-α-tetralone could undergo both mono and dicyclisation processes, and therefore attention was focused only on the 5-nitro isomer. Despite the fact that the 7-nitro isomer could be partially separated by simple recrystallisation of the crude mixture, flash chromatography was required to completely isolate the desired less polar 5-nitro-α-tetralone. The total yield of both products was generally good, and only very minor quantities of starting material were ever detected. Small adjustments in the reaction procedure optimised the yield of the 5-nitro isomer at 22%.

The nitration of α-indanone (136) was carried out using the method of Ingold and Pigott[140] using concentrated sulfuric acid and potassium nitrate as described by Gregoire.[25] The nitration pattern was very similar to that observed in the tetralone series, with the 4-nitro (137) and 6-nitro (138) derivatives being formed in 1:5 ratio respectively. Surprisingly, Gregoire only observed the formation of the 6-nitro isomer. The 4-nitro isomer was found in this case to have an R_f value very close to that of the starting material and may therefore have been overlooked by Gregoire. As with the tetralone case only 4-nitro-α-indanone was of interest due to its suitability for monocyclisations.

(ii) Nitration - Alternative Route

It was accepted that the required isomer of both nitro-tetralone and nitro-indanone would not be formed in yields significantly greater than the 20 - 25% usually achieved despite various attempts at optimisation. Hence an alternative route was proposed for the formation of 4-nitro-α-indanone (Scheme 56). Paraformaldehyde was used in the first step to synthesise the alcohol (140),[141] although acrylonitrile had also been employed with the aim of synthesising the analogous tetralone derivative. Starting with *o*-nitrotoluene (139), the alcohol was synthesised in good yield (78%). The route progressed as far as the chloride (141), synthesised from the alcohol using $SOCl_2$,[142] although it was subsequently discontinued since it had become evident that the disappointing yields encountered and combined duration of the reactions would offer little or no improvement upon the usual nitration procedures.

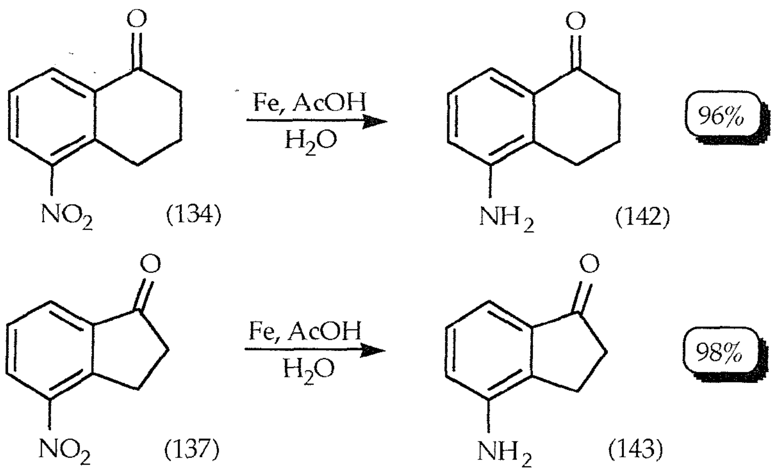


Scheme 56

Although the nature of the nitration procedures originally employed discouraged the possibility of large scale reactions and the low yields of the desired isomers prompted the investigation of alternative routes, the procedures were thought to be the optimum ones in this case.

(iii) Preparation of Starting Amines: Reduction

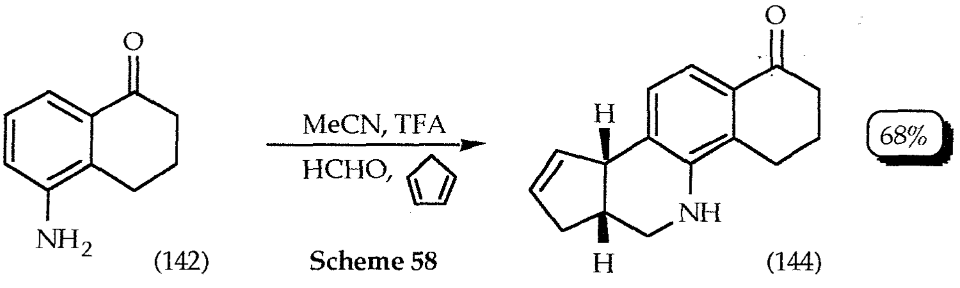
The reductions of nitro tetralone and indanone to the corresponding amines were carried out with four equivalents of iron powder in glacial acetic acid and water at approximately 80°C as described in the literature.[143] The reactions were consistently successful with excellent yields of both 5-amino-α-tetralone (142) and 4-amino-α-indanone (143) (Scheme 56). Purification by flash column chromatography was considered adequate for the next stage following examination of the nmr data.



Scheme 57

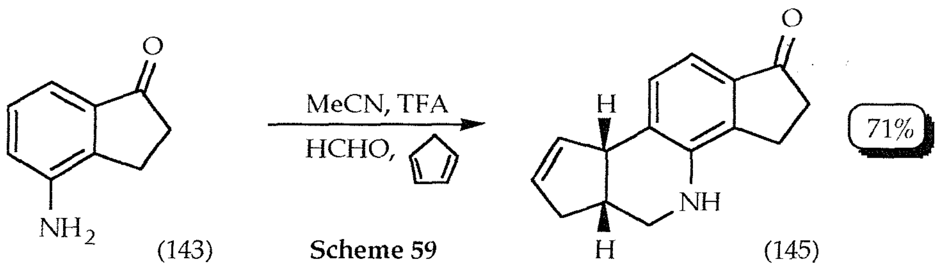
(iv) Monocyclisations with Cyclopentadiene

Cyclopentadiene was an ideal electron rich alkene with which to react the amines in order to create steroidal skeletons. The reactions would also establish a procedure which could be used to introduce methylcyclopentadiene and other alkenes as the electron rich partners. The cyclisations of the two amines (142) and (143) with cyclopentadiene were investigated under conditions already known to be successful in the reaction with 5-amino-α-tetralone (142), in order to optimise the procedure established by Gregoire.[25] A solution of the amine (142) in acetonitrile containing TFA, cyclopentadiene and formalin solution was stirred at room temperature for 35 minutes (Scheme 58). A basic work up produced a crude yellow oil which yielded a yellow crystalline material following chromatography. Spectroscopic data from the 5-amino-α-tetralone derivative agreed with that obtained by Gregiore[25] and the structure was therefore unambiguously assigned (144).



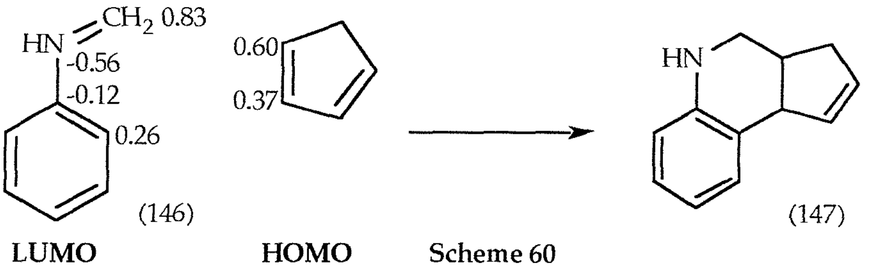
Scheme 58

The monocyclisation of 4-amino-α-indanone (143) was similarly carried out (Scheme 59), and also yielded one major compound, a yellow solid. The structure (145) was assigned following routine analysis. The ^1H nmr spectra of both cycloadducts were very similar, as expected, with one minor difference in the aromatic doublet nearest the carbonyl group, which was shifted slightly upfield in the indanone derivative. The yields of the two azasteroids were good, and handling the compounds did not prove a problem since they were relatively stable.



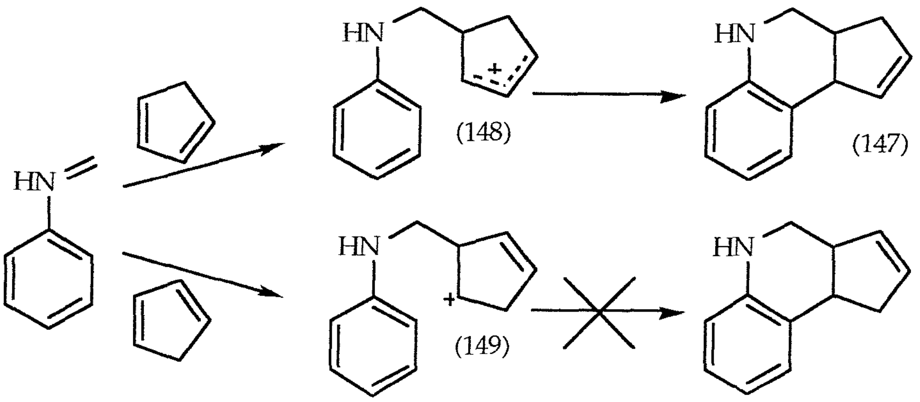
Scheme 59

The initial results from the cyclisations with cyclopentadiene agree with the findings of Merriman and Gregoire regarding the regio and stereospecific nature of the reaction, with only one product being detected and isolated. If the reactions are concerted (the mechanism will be discussed later), the observed regioselectivity can be rationalised by considering the atomic orbital coefficients of the molecular orbitals of the reactants. For an inverse electron demand case, the important reaction is that of the LUMO of the azadiene (eg. the simple imine (146)[144]) and HOMO of the dienophile (cyclopentadiene[145]). The large/large small/small selection rule can then predict the regiochemical outcome (147) of the reaction (Scheme 60).



Scheme 60

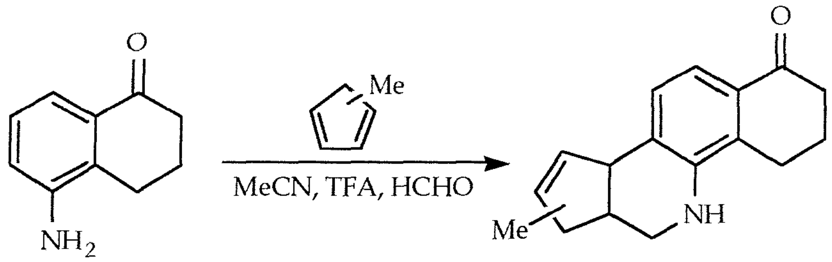
For the non-concerted case, the greater stability of the allylic cation (148) over the alternative carbocation (149) would account for the regiospecificity observed in the product (147) (Scheme 61).



Scheme 61

2.2.4 REACTION WITH AROMATIC AMINO-KETONES AND METHYLCYCLOPENTADIENE

With the initial cyclisations proving successful, the chemistry was advanced with the use of methylcyclopentadiene. The first experiment, with 5-amino-α-tetralone (142), followed the procedure established earlier in the cyclopentadiene case, hence the reaction with one equivalent of freshly distilled methylcyclopentadiene yielded a black oil which was shown by TLC to consist mainly of decomposed material, although there were traces of a new compound present. Flash chromatography provided an unstable yellow oil (the compound was observed to darken gradually upon standing). Despite initial nmr analysis indicating isomeric compounds, it also clearly showed the presence of a cycloadduct (Scheme 62).

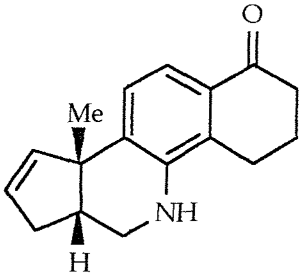


(142)

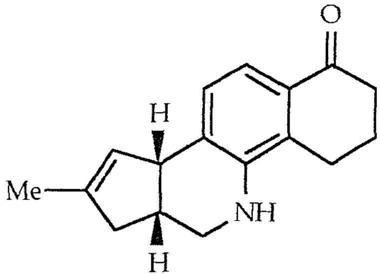
Scheme 62

Optimisation of the reaction was a challenge which was carefully approached, since there were many factors which affected the outcome. Improvement of the generally poor yield was attempted by increasing the equivalents of methylcyclopentadiene and the duration of the experiment. Due to its instability however, it was observed that these alterations were detrimental to the product. Furthermore, the fact that unreacted starting material was rarely detected in the reaction product emphasised the trivial nature of these variables, since it was clearly not a case of the poor yield being due to the reaction not having gone to completion. Ensuring that no heat was applied during the evaporation of solvents under reduced pressure was helpful in preventing decomposition. Despite its sensitive nature, it became possible to isolate relatively pure samples of the cycloadduct, which nevertheless exhibited gradual decomposition. This was overcome when the mixture of isomers was isolated as a more stable solid, although attempted recrystallisations resulted in its decomposition. The product remained a mixture of two isomers in approximately 1:1 ratio, as shown by the two methyl singlets in the ^{1}H nmr and doubling up of signals in the ^{13}C. Only when extreme care was applied to repeated separations by chromatography was it possible to isolate one of the isomers; the second isomer remained contaminated with the first.

The two compounds were ultimately separated by HPLC: analytical runs achieved base-line separation of the isomers and thereby established ideal conditions for small scale preparative work. Reverse phase HLPC using methanol and water gave two major products. Although the yields were very low, the quality of the two novel azasteroids (150) and (151) was excellent. Interestingly, a small quantity of the simple cyclopentadiene adduct (131) was also isolated.



(150)

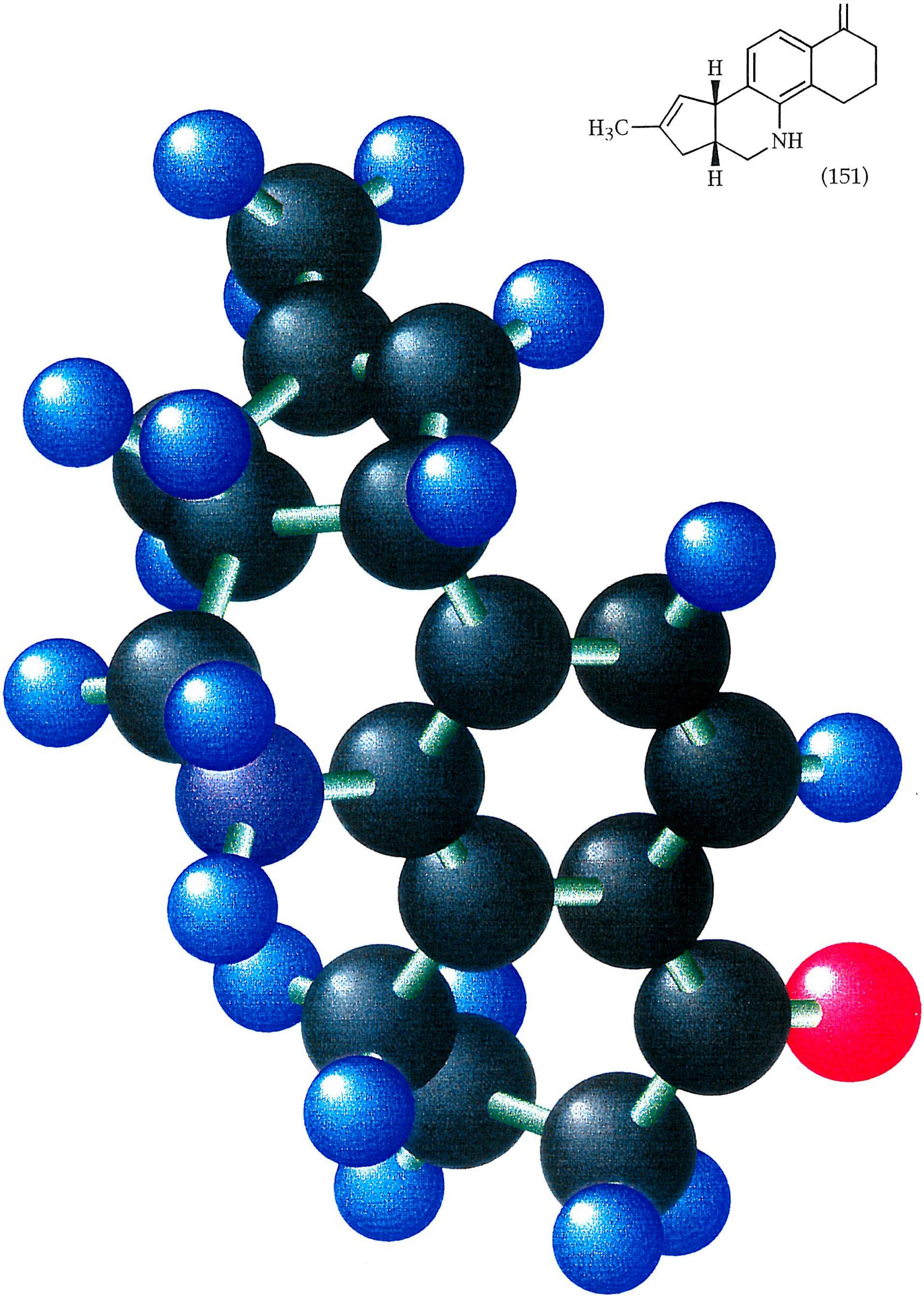


(151)

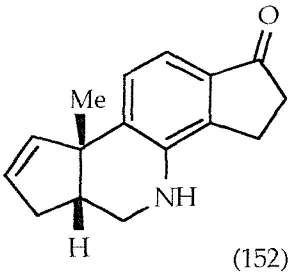
The first isomer (150) with the methyl at the ring junction was assigned its structure following examination of the ^{1}H nmr and its comparison with data from the simple cyclopentadiene adduct (131). With the signal at 3.94ppm from the ring junction proton missing, and the signals from all other protons on the five membered ring intact, the position of the methyl was clear. The chemical shift of the methyl group in the first isomer (150) was 1.45ppm and 1.72ppm in the second (151); hence the methyl group is in a field of slightly higher electron density in the first isomer which is consistent with its ring junction position. The assignment was confirmed by the ^{13}C nmr where the ring junction carbon signal had changed from that implying a methine to that implying a quaternary centre. The position of the methyl group on the double bond in the second isomer (151) was evident from the presence of only one of the CH protons as a singlet in the ^{1}H nmr. Its position was assigned on the basis of data from the ^{13}C nmr which showed the carbon bearing the methyl group had been transformed into a quaternary signal. Figure 3 overleaf shows the computer predicted 3-dimensional structure of (151) calculated using the molecular modelling program at the DowElanco laboratories.

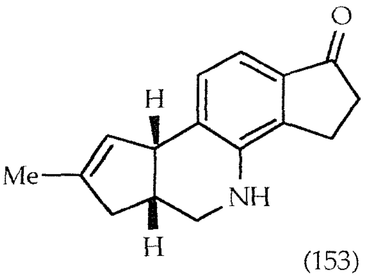
A similar situation was encountered with 4-amino-α-indanone (143). The monocyclisation with methylcyclopentadiene, carried out under conditions optimised for 5-amino-α-tetralone, initially yielded a dark yellow oil, which was shown by nmr to be a mixture of two isomers. The spectrum was almost identical to those initially obtained for the tetralone adduct, suggesting that corresponding isomers had been formed. A small sample of the first isomer could be isolated, although complete separation was only achieved with analytical and preparative HPLC, confirming the identity of the isomers as (152) and (153).

Figure 3: Molecular Modelling 3-D structure of (151).

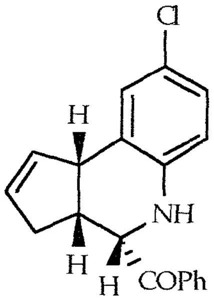


(151)


(152)

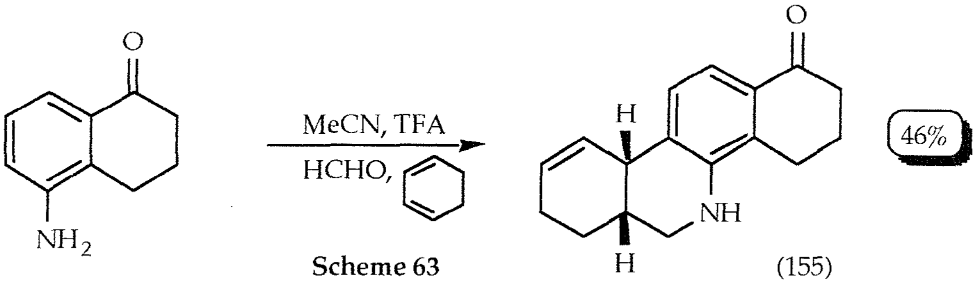

(153)

The stereochemistry of the ring junction protons in some related structures synthesised by Gregoire[25] and Merriman[26] has been assigned by examination of the coupling constant of the proton adjacent to the aromatic ring. Where this is inconclusive, the assignment has been made following nOe analysis or by analogy with other related compounds. A *cis* stereochemistry was always observed. In the case of the tetralone and indanone derivatives synthesised here, the relevant proton signal consistently appeared as an unresolved multiplet between 3.90ppm and 3.94ppm, although the previously synthesised adduct (144) was assigned a *cis* stereochemistry by Gregoire. The novel methylcyclopentadiene adducts have therefore also been assigned *cis* structures by analogy. The available ^{1}H and ^{13}C nmr spectra did however exhibit many similar features. The closely related cyclopentadiene adduct (154) synthesised by Lucchini *et al.*[146] was also found to possess *cis* stereochemistry, which was determined by nOe analysis, and the ring junction proton also appears as a multiplet.


(154)

2.2.5 REACTION WITH AROMATIC AMINO-KETONES AND CYCLOHEXADIENE

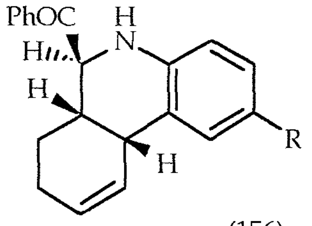
To continue the azasteroid theme, yet contrast with the reactions accomplished thus far, cyclohexadiene was chosen to replace methylcyclopentadiene in this area of aza Diels-Alder reactions, although the same bicyclic amines were retained. Cyclohexadiene, like methylcyclopentadiene had not been previously employed in the aza Diels-Alder studies carried out by Mellor *et al.* The studies with cyclohexadiene commenced with the monocyclisation of 5-amino-α-tetralone, utilising conditions optimised for the reactions with cyclopentadiene. In common with previous experiments, the crude product exhibited signs of decomposition, although to a lesser extent. However, TLC analysis indicated a more complex outcome than anticipated; there appeared to be two minor and two major products. The ^{1}H nmr of the crude product was therefore very intricate, yet it revealed the existence of a cycloadduct. Separation of the two major components was less troublesome than earlier experiences with the methylcyclopentadiene adducts, enabling a small quantity of purified material to become available for analysis. The first of the two major components, corresponding to the third spot by TLC of the crude product, was identified as the expected cycloadduct (155) (Scheme 63).



Scheme 63

(155)

The ^{1}H nmr spectrum was similar to that of the cyclopentadiene adduct of this series; the two signals in the aromatic region suggested the usual reaction of the starting material had taken place, and the protons from the double bond of the six membered ring confirmed the cycloaddition with cyclohexadiene. Additional readily interpreted signals included the broad N-H singlet at 3.81ppm, the multiplet at 3.51ppm arising from the ring junction proton adjacent to the double bond, and the methylene group (3.28ppm) adjacent to the nitrogen. The stereochemistry of the product, could not be confirmed by analysis of the ring junction proton; however, similar fully characterised structures have been reported. The addition of cyclohexadiene to various anils yielded the stereospecific adducts (156).[146]

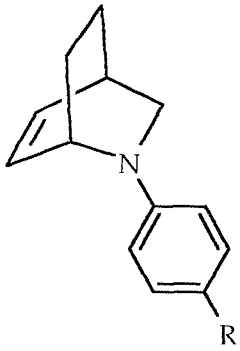


$R = NO_2, Cl, CH_3, OCH_3$

(156)

The identity of the second component, corresponding to the fourth fraction of the crude product was not immediately obvious. The two starting materials were immediately ruled out, yet signals associated with both were present in the spectrum, which also bore a resemblance to that of the steroidal cycloadduct (155). The ^{1}H and ^{13}C nmr spectra indicated identical numbers of protons and carbons in both compounds, while low resolution mass spectroscopy showed their isomeric nature by displaying equal masses for both compounds.

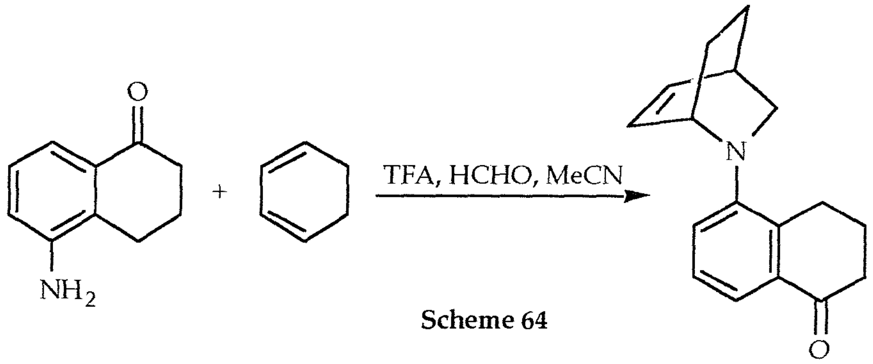
Closer inspection of the nmr data however revealed characteristic features which permitted an unambiguous assignment of structure. The lack of an N-H signal suggested a tertiary amine (also evident in the IR spectrum); three aromatic protons indicated no cyclisation onto the aromatic ring (confirmed by the lack of a fifth quaternary signal in the ^{13}C nmr). The identity of the isomer became unmistakeable upon comparison with Lucchini's[146] research in which cyclohexadiene had reacted not only as a dienophile with various anils to give the hexahydrophenanthridines (156), but also as a diene to give the azabicyclooctenes (157).



$R = NO_2, Cl, CH_3, OCH_3$

(157)

Cyclohexadiene had therefore behaved similarly here, reacting as a diene to give the novel azabicyclo compound (158) (Scheme 64).

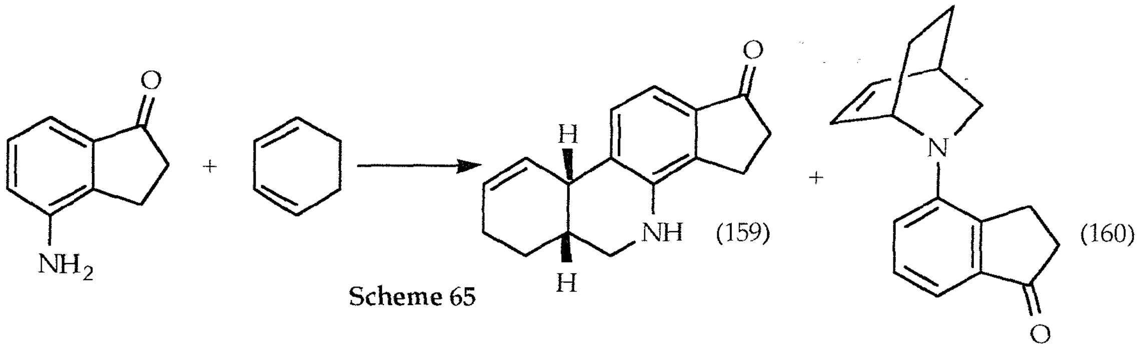


(158)

Scheme 64

Further purification of the products was carried out by small scale preparative HPLC with the aim of improving the quality of the adducts.

The reaction between 4-amino-α-indanone and cyclohexadiene proceeded in a similar fashion. As with the tetralone reaction, the crude product showed some signs of decomposition and TLC analysis indicated two major and two minor products. The nmr spectra of the two isomeric major compounds were very similar to those of the tetralone adducts developed earlier, and the products were therefore assigned the analogous hexahydrophenanthridine (159) and azabicyclooctene (160) structures (Scheme 65).



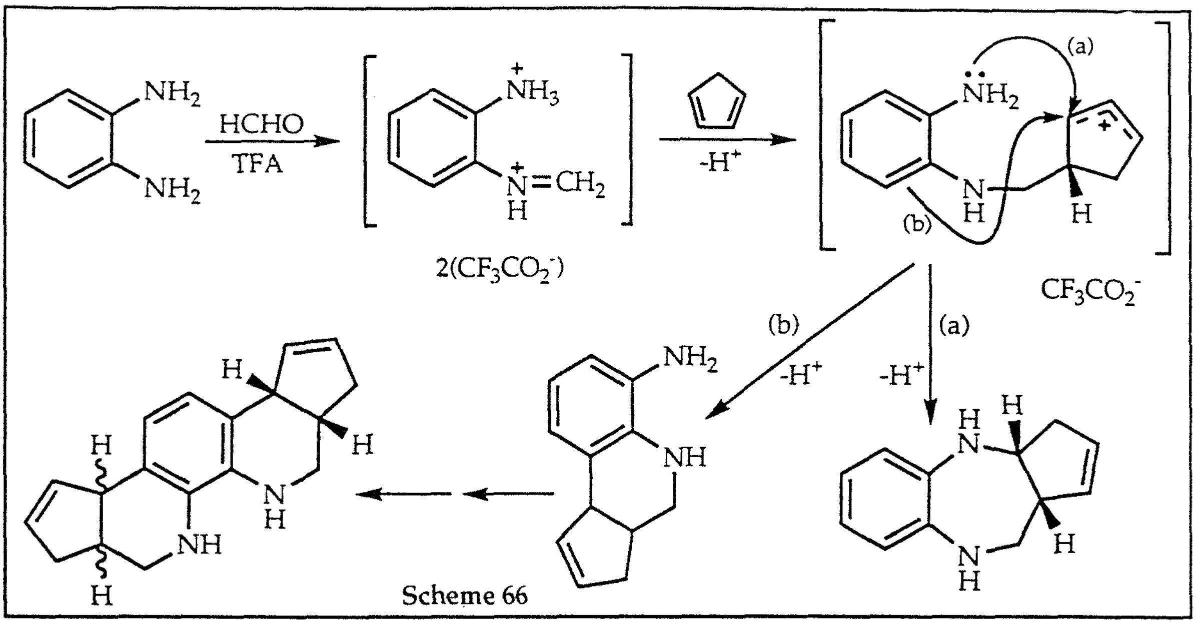
Scheme 65

2.2.6 MECHANISTIC OBSERVATIONS

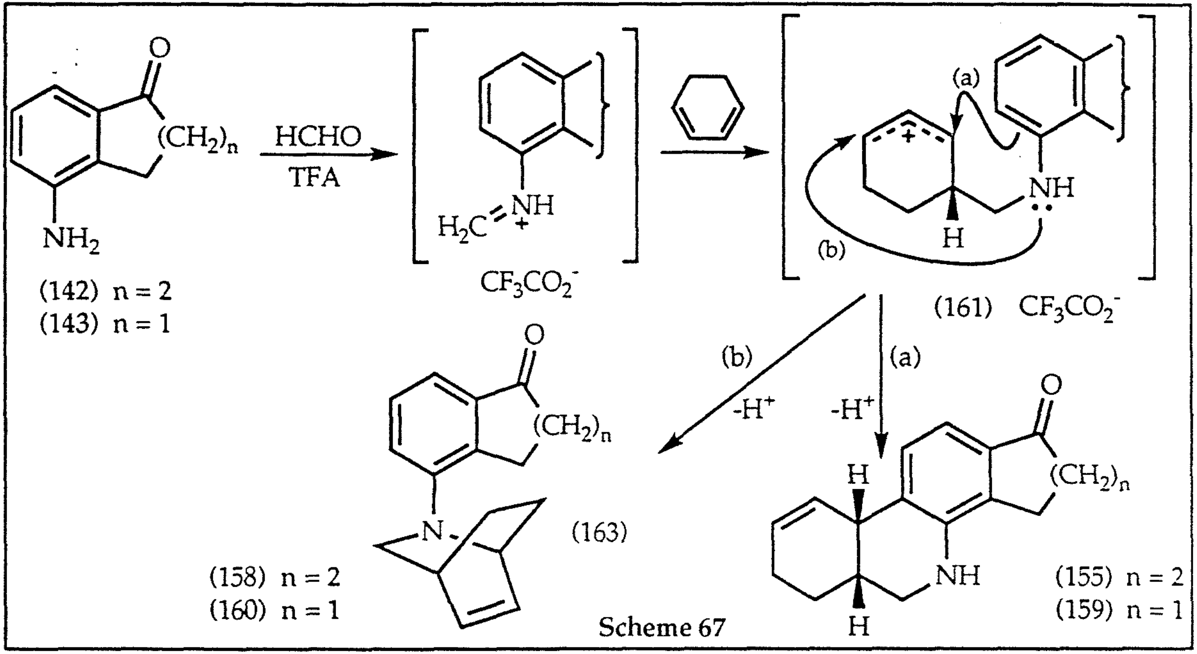
The cycloadditions of the iminium ion and alkene in these Diels-Alder reactions can occur *via* a concerted or stepwise mechanism, as has been discussed in areas of related research. The conclusions reached are often different for each particular area of work, and it is clear that one single mechanism cannot account for all cases.

Merriman's studies revealed the presence of intermediate compounds, which could be isolated and converted into products; therefore a stepwise mechanism was concluded. In the studies presented in this section, no such intermediates were isolated, which could suggest a concerted process, although a stepwise mechanism could not be ruled out. However, the reactions with cyclohexadiene yielded two different products, although neither appeared to be an intermediate. The reaction may be compared to Merriman's experiment with *o*-phenylenediamine and cyclopentadiene[26] in which two different products were isolated, the "expected" cycloadduct and a benzodiazepine derivative (see Scheme 18, page 14). The mechanism proposed involved the formation of an allylic cation following addition of the alkene to the initially formed iminium ion. This could then undergo cyclisation to give the "expected" products (route b) or react with the amino group yielding the benzodiazepine (route a) (Scheme 66). The isolation of the latter clearly implied a non-concerted multi-step mechanism for the formation of the adducts.

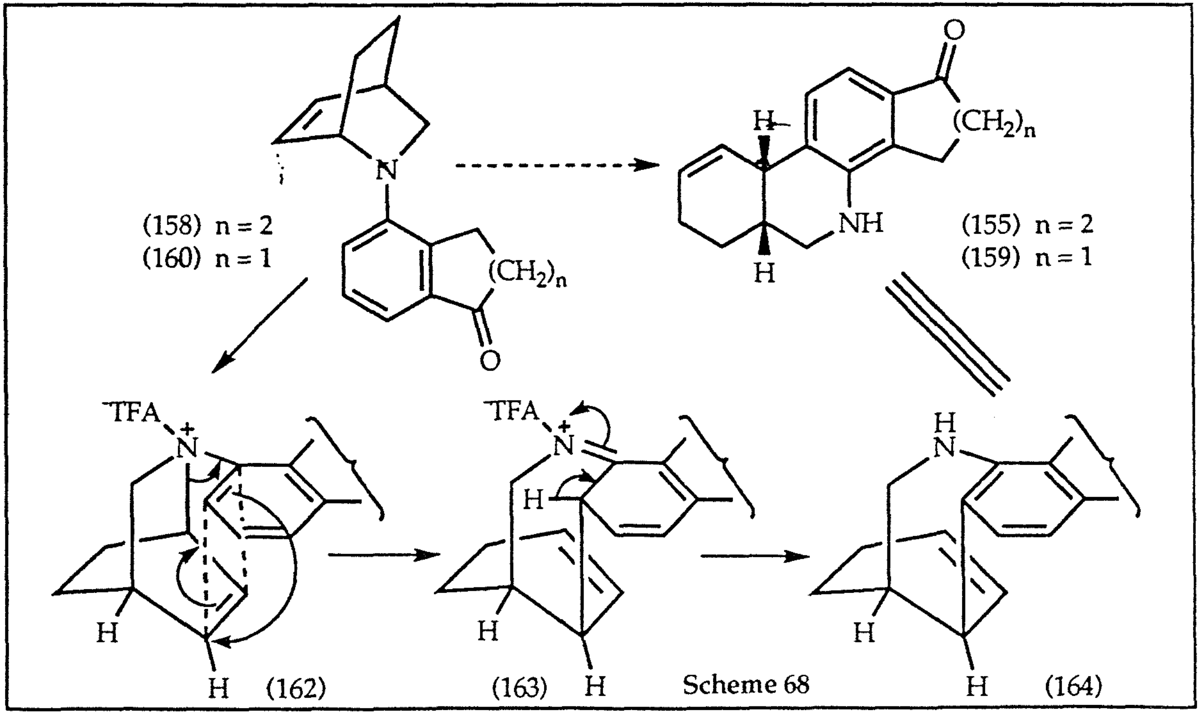
In the cyclohexadiene case presented in the last section, it is possible that an analogous allylic cation (161) is formed which can subsequently cyclise (route a) to yield the steroidal skeletons ((155), (159)), or react with the NH group (route b) to give the bicyclic products ((158), (160)). This would likewise suggest a stepwise mechanism (Scheme 67). Alternatively, another possible mechanism involves the bicyclic product undergoing an amino-Claisen rearrangement to give the steroidal compound (Scheme 68), similar to the mechanism postulated for the formation of phenanthridine derivatives such as (156) from the rearrangements of azabicyclooctenes (157).[146] The boat transition state (162) could undergo a [3,3] sigmatropic rearrangement to give the intermediate (163); rearomatisation then leads to the boat structure (164), which is the azasteroid ((155), (159)).



Scheme 66



Scheme 67



Scheme 68

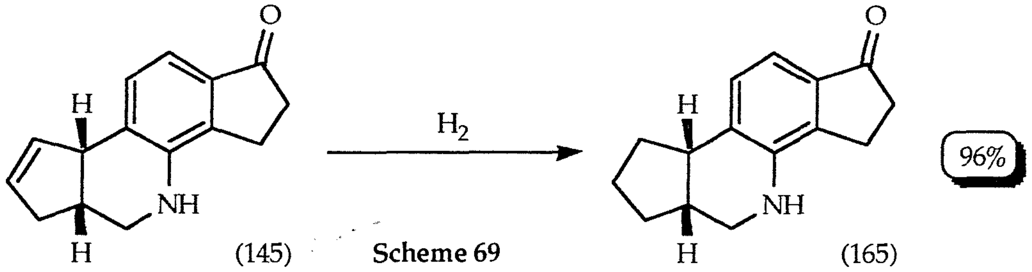
2.2.7 SUMMARY OF TETRALONE AND INDANONE SERIES

The products of the aza Diels-Alder reactions in this series between the two bicyclic amines, amino-tetralone and amino-indanone, are illustrated in Table 1 (overleaf) in order to facilitate comparison. Having established a successful reaction procedure between 2-methyl-4-nitroaniline and cyclopentadiene, its application to the reaction with methylcyclopentadiene yielded isomeric products. Nevertheless, it was demonstrated that the isomers were separable, which encouraged the progression towards the major study in this section, the cyclocondensations of bicyclic amines with electron rich dienes.

Some conclusions can be drawn from the cyclocondensations in this series. The aim to create azasteroidal structures has been achieved with the synthesis of a variety of 7-azasteroids. Reactions with cyclopentadiene were straightforward, with the cycloadducts, produced in good yield, being generally stable and readily characterised. The cyclocondensations occurred equally well with methylcyclopentadiene, although the products were more difficult to handle. Optimisation of the reaction procedure and stringent purification conditions were successful in providing two pure isomers in both the amino-tetralone and amino-indanone cases. The significance of the new adducts is emphasised by their relationship to known natural and synthetic steroids, particularly 7- and 11-azasteroids. Substituting cyclohexadiene in place of methylcyclopentadiene resulted not only in the formation of two new azasteroids, but also of two unexpected Diels-Alder adducts in which cyclohexadiene had acted as a diene. The adducts were nevertheless very interesting by-products which were isolated and purified in good yield.

2.2.8 Further Work with Azasteroids

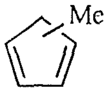
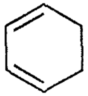
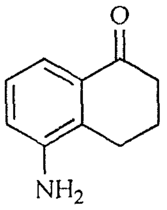
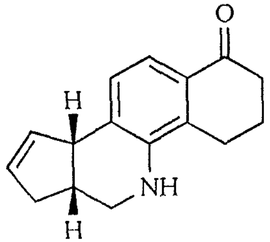
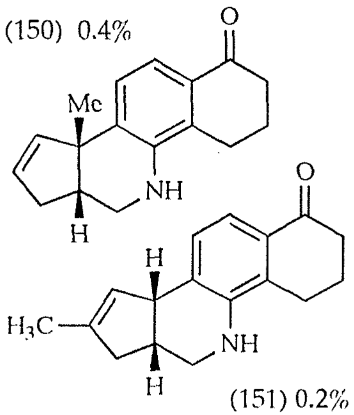
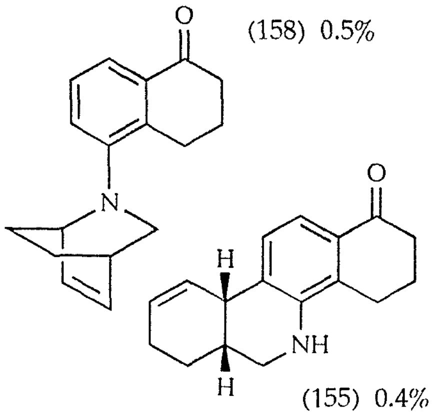
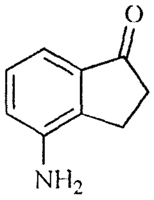
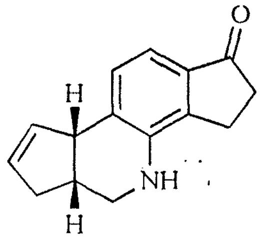
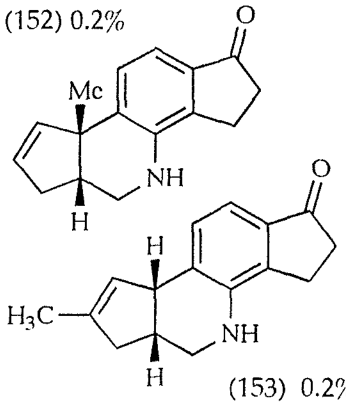
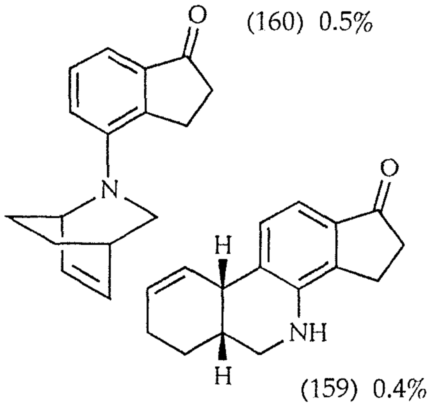
Having achieved the aim of azasteroid synthesis, the potential for further work with these novel compounds was illustrated with the hydrogenation of (145) using palladium on charcoal. The double bond was removed to give the saturated product (165) in excellent yield (Scheme 69).



(145) **Scheme 69** (165)

The ease of this reaction adds to the value of these compounds, since it demostrates their ability to undergo transformations which could ultimately lead to important new structures. Other immediate potential reactions include reduction of the carbonyl group.

Table 1: Reactions of Amino-tetralone and Amino-indanone.

ALKENE **AMINE**			
	 (144) 68%	 (150) 0.4% (151) 0.2%	 (158) 0.5% (155) 0.4%
	 (145) 71%	 (152) 0.2% (153) 0.2%	 (160) 0.5% (159) 0.4%

2.2.9 Biological Testing of Azasteroids

Biological testing of some novel Diels-Alder adducts was one of the initial aims of this project, and this has been undertaken. The compounds selected were tested on their ability to control crop diseases such as powdery mildew of wheat, downy mildew of vine and brown rust of wheat. Initial results were promising; although the control of the diseases varied over a wide range for all of the compounds, some exhibited very high activity against certain diseases. Further testing involving some compounds of a higher purity were however not as encouraging, with little activity observed. The possibility that impurities present in the compounds initially tested may account for high control of disease observed in some cases cannot be discounted, but neither is it certain, since not all the compounds have been tested both times, and therefore the two sets of results are difficult to compare. The results of all the biological tests have been summarised in the table below.

Table 2: Level of Activity Against Pathogens

Control of Disease Compound Tested	PMW	SN	DMV	RB	BRW
(131)	6	1	4	0	4
(132)	3	2	7	0	4
(145)	1	1	0	1	1
(150) - (151)	5	5	5	0	1
(152)	1	1	0	1	1
(153)	1	1	0	3	1
(158)	5	1	0	1	3
(159) + (160)	1	4	4	0	5

Pathogen

PMW = Powdery Mildew of Wheat
SN = Septoria Nodorum
DMV = Downy Mildew of Vine
RB = Rice Blast
BRW = Brown Rust of Wheat

Level of Activity

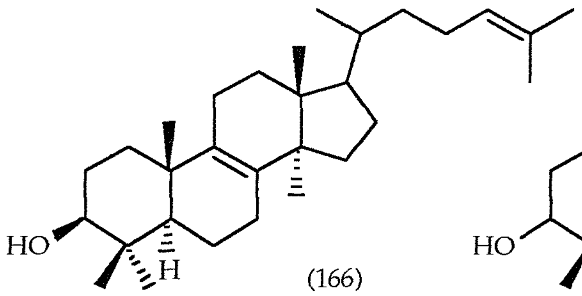
0 = not tested
1 = 0 - 19%
2 = 20 - 29%
3 = 30 - 39%
4 = 40 - 59%
5 = 60 - 74%
6 = 75 - 89%
7 = 90 - 96%
8 = 97 - 99%
9 = 100%

2.3 SYNTHESIS OF MONOAZASTEROIDS : Part 3

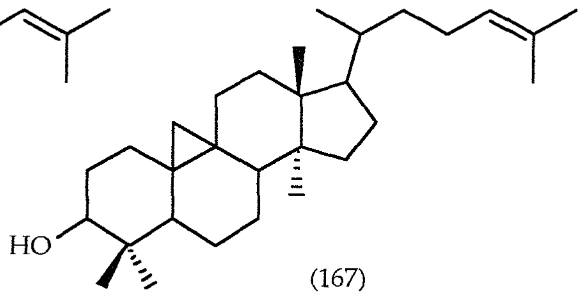
2.3.1 DEGRADATIVE STUDIES USING LANOSTEROL

In general, there are two different approaches to the synthesis of azasteroids. The monoazasteroids presented in the last section (Section 2.2) have been conveniently prepared by total synthesis using aza Diels-Alder reactions as the key steps. An alternative approach is partial synthesis; in this method, azasteroids are synthesised from relatively inexpensive steroid or terpenoid precursors. The syntheses might be accomplished by a sequence of ring opening, introduction of nitrogen, ring closure and appropriate functional group manipulation. Such a route was briefly investigated as an alternative to the total synthesis procedures described earlier.

The route was based on the degradation of lanosterol (166), which offered the possibility of exploiting the nulear double bond in order to generate azasteroids. Lanosterol, which was a readily available starting material, was chosen on the basis that any azasteroids formed might be tested for their anti-fungal activity, since they would have close structural similarities with the intermediates of the biosynthesis of cholesterol. Lanosterol is rarely found in plants but occurs in animal tissue and fungi as part of the biosynthetic pathway of steroids. The biosynthesis in photosynthetic organisms proceeds instead *via* cycloartenol (167). The blocking of the biosynthetic pathway from lanosterol using azasteroids derived from it is therefore a potential solution to the treatment of fungal infections.



(166)

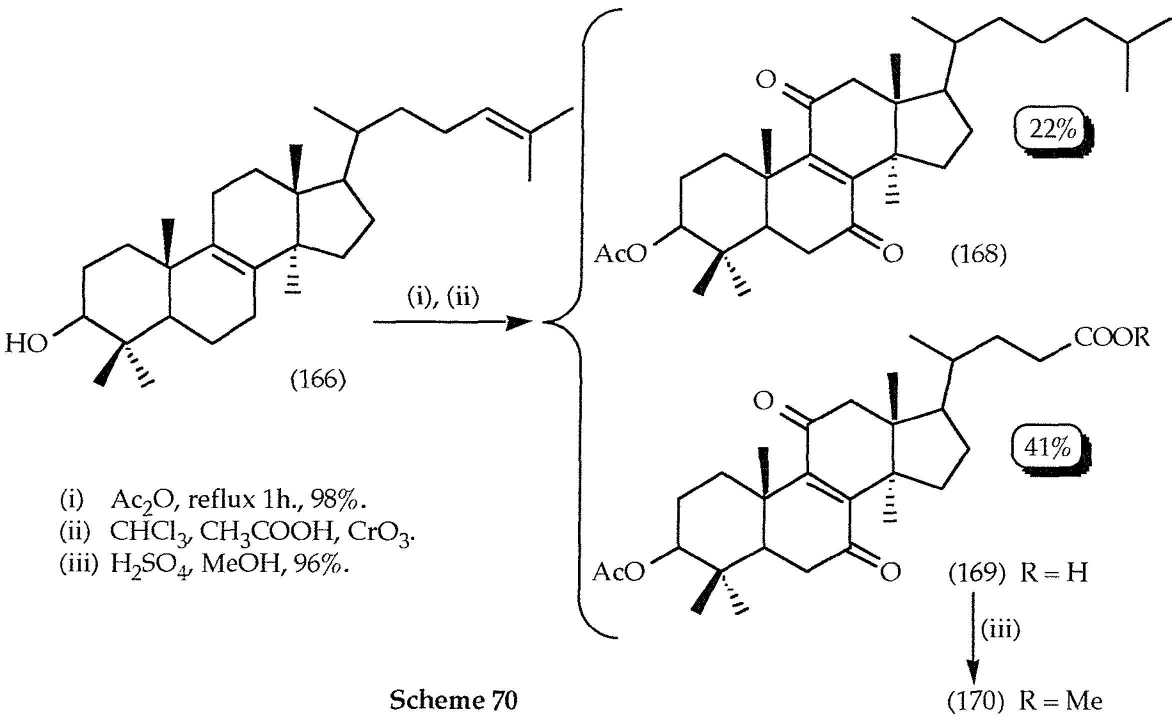


(167)

Commercial lanosterol is available as 'isocholesterol',[147] which consists of four closely related compounds. Lanosterol (5α-lanosta-8,24-dien-3β-ol) (166), one of the two major components, comprises approximately 40% of the material. The second major component, dihydrolanosterol, lacks a double bond in the side chain.

(i) DIKETONE SERIES

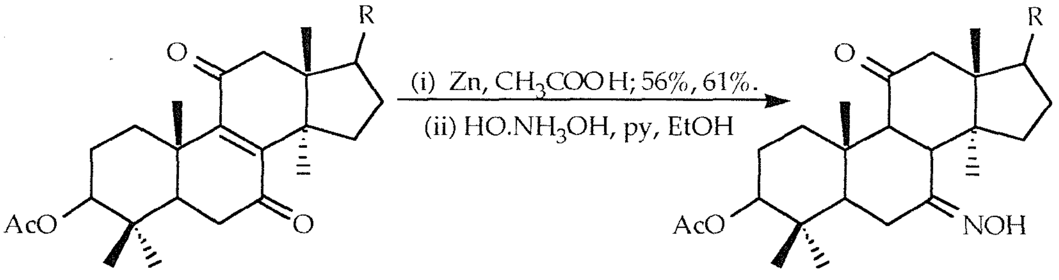
The first of the two major routes followed involved oxidation of the protected steroid to yield two 7,11-diketones (Scheme 70). The hydroxyl group of lanosterol was converted almost quantitatively to the acetate by refluxing in acetic anhydride,[148] and oxidation was carried out using chromium trioxide.[149] The two diketones differed only in the nature of the side chain; the first product isolated (168) using flash column chromatography had a neutral saturated side chain and presumably arose from the oxidation of the dihydrolanosterol component of the starting material. This would account for its lower yield with respect to the second product (169), which possessed an acidic side chain. The acid was subsequently converted into the methyl ester (170) to protect the group in future reactions.



(i) Ac_2O, reflux 1h., 98%.
(ii) $CHCl_3$, CH_3COOH, CrO_3.
(iii) H_2SO_4, MeOH, 96%.

Scheme 70

The nuclear double bond of both diketones, (168) and (170), was reduced using zinc dust before attention was focused on reactions of the carbonyl groups. Treatment of each diketone with hydroxylamine hydrochloride resulted in a reaction at the 7-position to yield the monooximes (171) and (172); the 11-carbonyl remained unchanged (Scheme 71). This provided a means of introducing a nitrogen into the molecule, with the next stage being its incorporation into the skeleton.

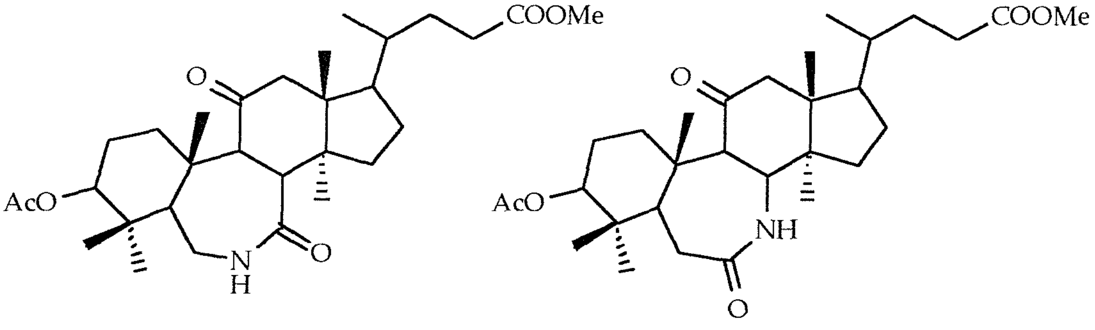


(168) R = C_8H_{17}
(170) R = $C_6H_{11}O_2$

Scheme 71

(171) R = C_8H_{17} (81%)
(172) R = $C_6H_{11}O_2$ (84%)

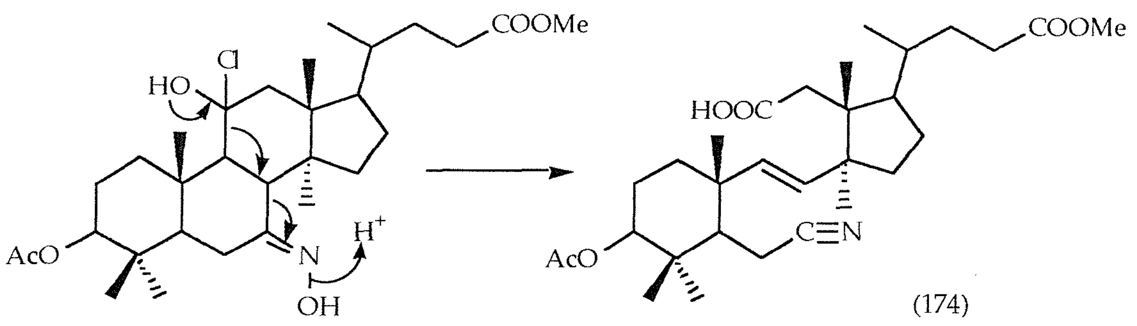
The Beckmann rearrangement of the oxime was expected to yield the 7-membered B-ring azasteroid; this was attempted many times using reagents such as phosphorus pentachloride, thionyl chloride and *p*-toluenesulfonyl chloride under a variety of conditions. The yields of products, when obtained, were very low, and were attributed to steric hindrance preventing the rearrangement, although the Beckmann rearrangement of the related 3β-acetyloxy-7-hydroxyimino-5α-lanost-24-en-11-one, differing only in the nature of the side chain, has been reported[150] in around 50% yield. Successful reactions were obtained using thionyl chloride in dichloromethane; using oxime (172), the amides (173) were usually obtained as a mixture of isomers. The predominant isomer (173b), isolated in 30% yield, was identified from the ^{1}H nmr by the broad N-H singlet at 5.60ppm and a multiplet at 3.62ppm corresponding to the ring junction (C_8) proton.



(173a)

(173b)

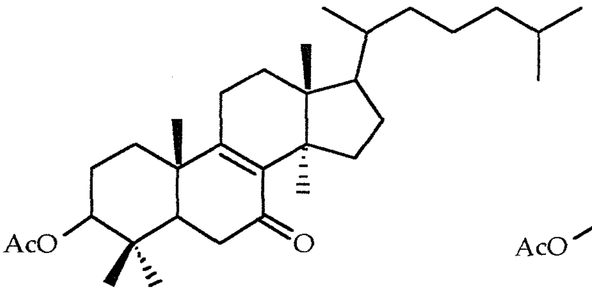
An interesting minor by-product of the Beckmann reactions was regularly isolated and found to be the fragmentation product (174); with the characteristic *trans* coupling (16.0Hz) of the double bond easily recognisable in the ^{1}H nmr. Fragmentations such as this are known in the literature,[151] and the product was thought to result from the action of traces of hydrochloric acid on the oxime (Scheme 72).



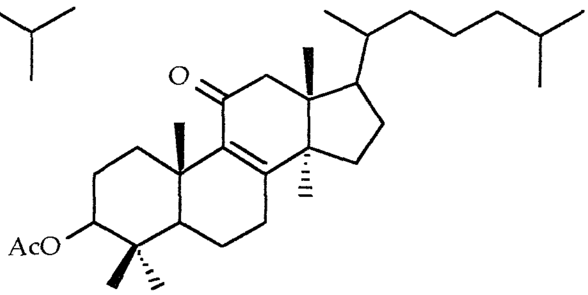
Scheme 72

(ii) MONOKETONE SERIES

In general, the 11-carbonyl group, in addition to undergoing minor reactions to yield unwanted by-products and hence complicating the isolation of major products, was relatively unreactive and was therefore regarded as a hindrance. Attention was therefore focused on the synthesis of the monoketone, 3-acetoxylanost-8-en-7-one (175). The procedure reported by Pinhey *et al.*[152] used 3-acetoxylanost-8-ene as the starting material. Although this was unavailable in a pure form, it was known to be present in acetylated commercial lanosterol; this was therefore employed in the oxidation using hydrogen peroxide to give the monoketone (175) in 10% yield. The figure appears low since the proportion of acetoxylanost-8-ene in the starting material was not known and the calculation was therefore based on the total starting material used. Interestingly, a minor by-product of the reaction was the 11-ketone (176).

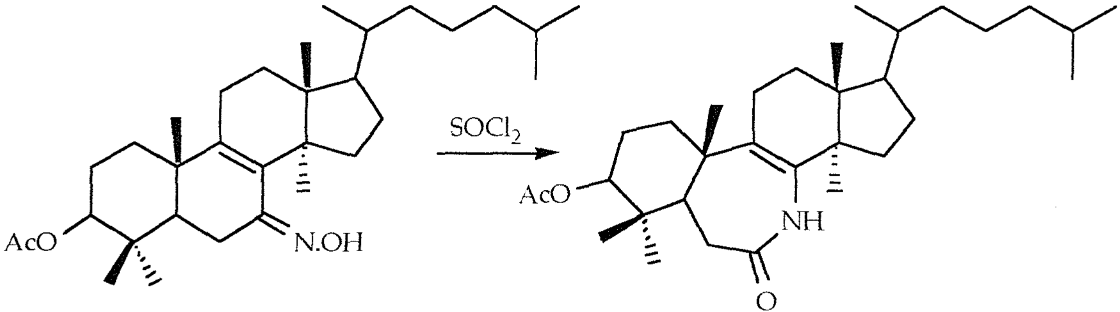


(175)



(176)

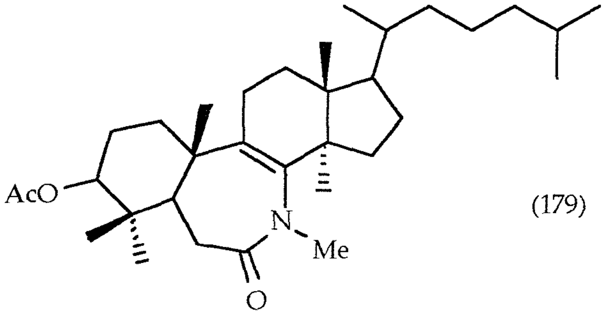
The 7-ketone (175) was transformed into its oxime (177) without removal of the nuclear double bond, as it was thought this might be difficult. The oximation was carried out under conditions followed in the previous route with the diketones, although it was observed by monitoring the reaction by TLC that a much longer duration was required for a maximum 90% yield of the monooxime (80 hours compared with one hour in the diketone series). The Beckmann rearrangement of the oxime was attempted several times, with the most successful results arising from the reaction being carried out in neat freshly distilled thionyl chloride, to give the product in 48% yield (Scheme 73). Interestingly only one isomer of (178) was detected; the N-H signal was observed as a broad singlet at 6.32ppm, and the methylene proton adjacent to the amide carbonyl at 2.48ppm. If adjacent to the N-H group, the signal would be expected to be further downfield. There was no evidence of a fragmentation product similar to those observed in previous Beckmann reactions. The clean reaction in this case was attributed to the lack of impurities in the distilled reagent.



(177) (178)

Scheme 73

A derivative of the B-homoazasteroid was successfully synthesised using methyl iodide to give the tertiary amide (179) in 36% yield. This amide was anticipated to be more stable than its precursor, an advantage in subsequent reactions since the functional group would be better protected. However, initial attempts to convert the ring B amide into an amine were unsuccessful due to the extreme stability of the material. Experiments using sodium borohydride and lithium aluminium hydride were found to affect only the acetyl group in the 3-position, and ring B remained unchanged.



(179)

The degradative studies using lanosterol were therefore successful with the main aim of synthesising azasteroids. The routes developed led to a number of B-homo azasteroids, with the products proving to be stable, especially in the monoketone series. Despite the fact that the stability of the tertiary amide precluded initial attempts to develop the series further, it is likely that progress could be made following additional studies.

2.4 CYCLOCONDENSATIONS OF 2-AMINOPYRIDINES

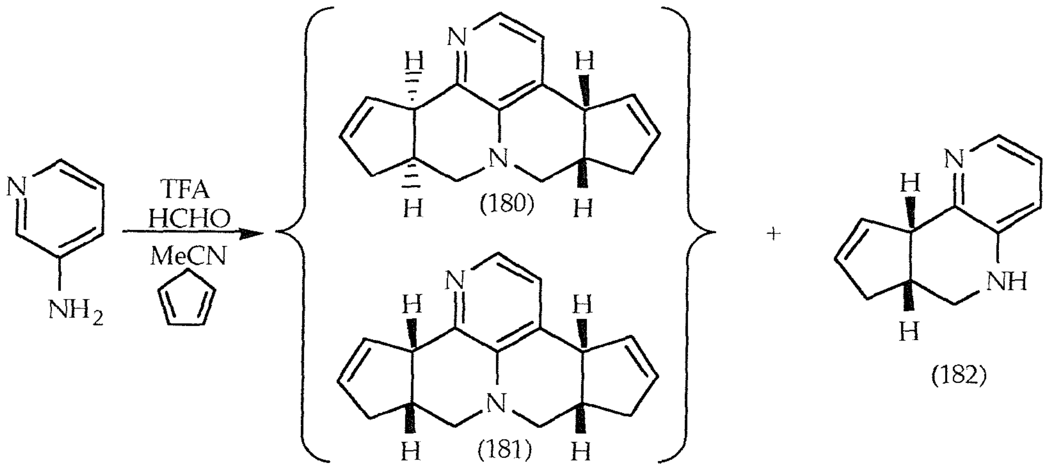
The research initially reported in this thesis focused on the cyclocondensations of carbocyclic aromatic amines and their derivatives with electron rich alkenes. In order to further broaden the aromatic amines studied, the cyclocondensations of aminopyridines were investigated. Fused pyridines can be found in a large number of natural products which invariably possess appreciable biological activity; hence cycloadducts arising from aminopyridines were also expected to be of potential importance.

The initial studies in this section were carried out with a variety of 2-aminopyridine derivatives possessing electron withdrawing or electron donating groups, and subsequently progressed to include investigations into the reactions of a selection of different heterocyclic amines such as aminopyrazines, aminopyrimidines and aminobenzothiazoles.

2.4.1 PREVIOUS WORK CARRIED OUT WITHIN THE GROUP

Merriman's brief study of aminopyridines began with the reactions of 4-aminopyridines. Cyclocondensations of 4-aminopyridine with cyclopentadiene were however unsuccessful, with ^{1}H nmr analysis of the crude products not indicating the presence of cycloadducts; this failure was thought to be due to the tendency for delocalisation of the lone pair of the amino nitrogen onto the pyridine nitrogen, thereby decreasing the nucleophilicity of the group and resulting in the initial iminium ion not forming.

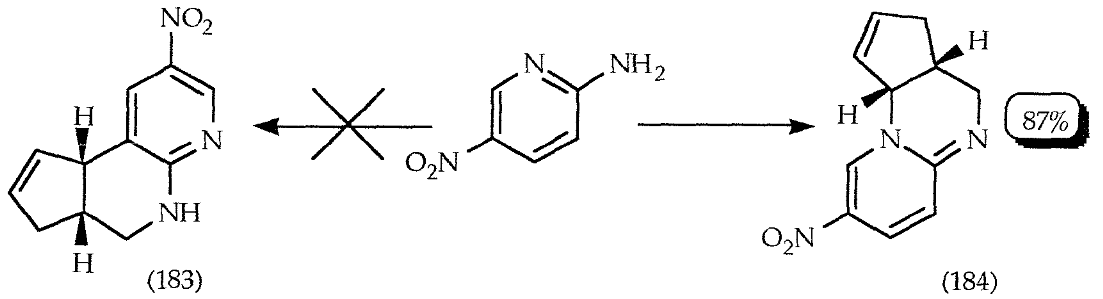
The potential of 3-aminopyridine was next examined, since the delocalisation problem would not occur with this amine. The reaction using five equivalents of formaldehyde and cyclopentadiene led to the isolation of a dicyclocondensation adduct (2%) (it was not possible to distinguish between the isomers (180) and (181)) and a monocyclocondensation adduct (182), also in low yield (5%) (Scheme 74). The low yields precipitated the abandonment of these studies.



Scheme 74

Despite the poor yields from the aminopyridine reactions, attention was next focused on 2-aminopyridine and its 5-nitro derivative, even though, like 4-aminopyridine, the amino group can delocalise its lone pair of electrons onto the nitrogen atom. 2-Amino-5-nitropyridine was selected because the position of the nitro group blocked the position *para* to the amino group on the aromatic ring, thus eliminating the possibility of formation of dimers of any cycloadducts formed (see page 9).

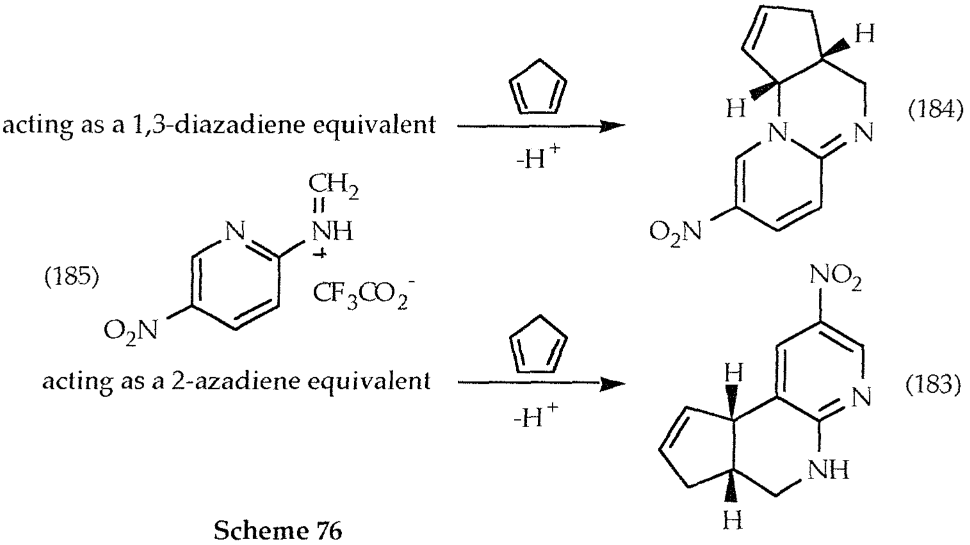
The reaction of 2-amino-5-nitropyridine with two equivalents of formaldehyde and cyclopentadiene was carried out and gave a very polar cycloadduct (184) in good yield (87%) as the only product (Scheme 75). The ^1H nmr spectrum of the adduct showed the presence of the ArC$_3$-H proton at 6.50ppm, indicating that no cycloaddition onto this position of the pyridine ring had occurred, as would be seen for the isomeric cycloadduct (183).



Scheme 75

The infra-red spectrum of the product also distinguished between the two possible isomers, with the lack of N-H stretching bands confirming the structure.

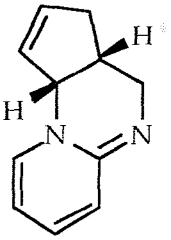
The proposal for the origin of the cycloadduct centred on the iminium ion (185) formed from the amine. This general type of iminium ion had been regarded as a 2-azadiene equivalent in previous cyclocondensations carried out by the group, but in this case, it could be regarded as a 1,3-diazadiene equivalent because of the presence of the pyridine nitrogen atom. Thus, an alternative cycloaddition had occurred, leading to the cycloadduct (184), rather than the type of cycloaddition which had usually been observed, with the iminium ion acting as a 2-azadiene equivalent to give the cycloadduct (183) (Scheme 76).



Scheme 76

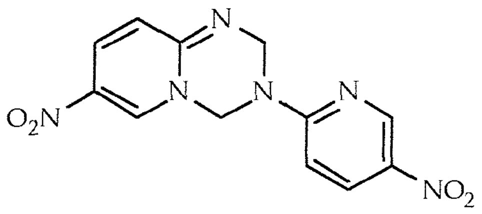
The preferential formation of the cycloadduct (184) over (183) was thought to be a manifestation of the tendency of pyridines to undergo electrophilic substitution at nitrogen rather than onto the carbon of the ring.

When Merriman carried out a similar cyclocondensation using 2-aminopyridine, the analogous cycloadduct (186) was obtained in 46% yield, although it was not as stable as the 5-nitro derivative.


(186)

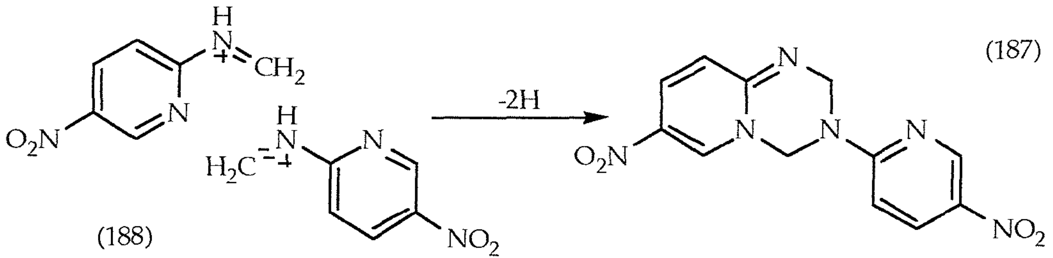
The two successful cyclocondensations of 2-aminopyridines with cyclopentadiene prompted the investigation of whether other electron rich alkenes would undergo similar reactions to lead to analogous derivatives. Given the lower yield and decomposition encountered in the use of 2-aminopyridine, only the 5-nitro derivative was subsequently used to test the viability of styrene and α-methylstyrene as electron rich dienes in the reactions.

The first reaction with styrene using two equivalents of the alkene gave a surprising result, with the triazine (187) being recovered as the only product. The structure of the adduct was confirmed by correct elemental analysis and mass spectroscopy. The infra-red spectrum showed no N-H stretching frequencies, and six aromatic resonances were observed in the ^{1}H nmr corresponding to the fused and substituted pyridine rings. The ^{13}C nmr displayed ten aromatic signals, also verifying the presence of two different pyridine rings.



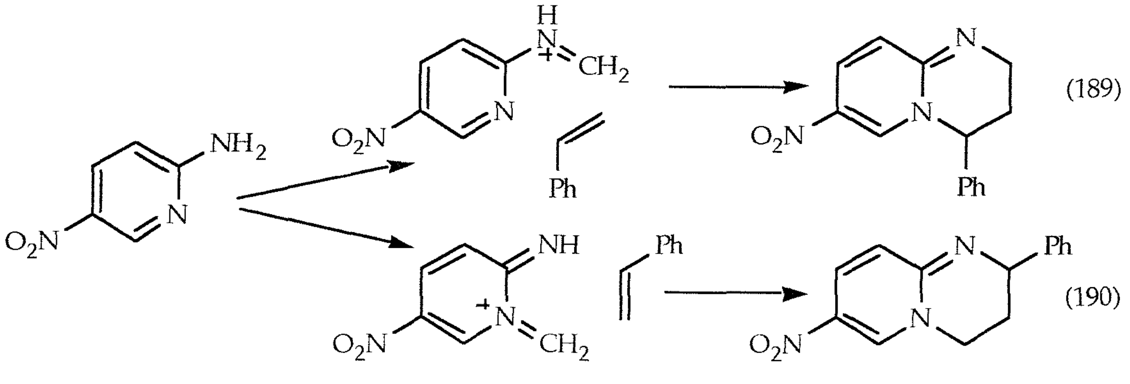
(187)

The formation of the adduct was rationalised by viewing the reaction as a dimerisation of the iminium ion which was thought to occur *via* a (4+2) cycloaddition reaction in which one molecule of (188) acts as a 1,3-diazadiene, and another acts as a 2-azadiene (Scheme 77).



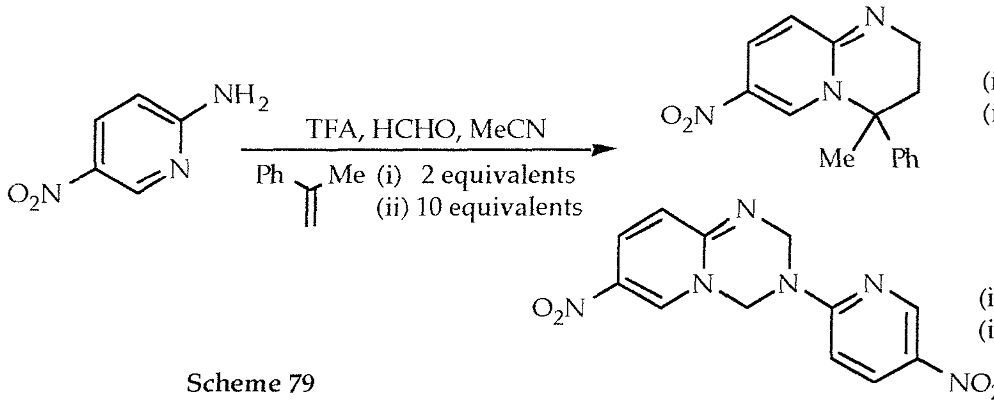
Scheme 77

A second cyclocondensation using ten equivalents of styrene yielded not only the expected cycloadduct (189) (26%), but also a second regioisomer (190) (28%); no trace of the triazine (187) was detected. A repeat experiment matched the initial result by revealing the crude material to be an approximate 1:1 mixture of the two cycloadducts. The formation of the two adducts was thought to be due to the formation of two alternative iminium ions (Scheme 78).



Scheme 78

The reaction of 2-amino-5-nitropyridine with α-methylstyrene however did not produce two isomers, yielding only the expected cycloadduct (191). The yield of the cycloadduct could be improved at the expense of the "dimerised" product when a large excess of the alkene (ten equivalents) was used (Scheme 79).



(191)
(i) 16%
(ii) 94%

(187)
(i) 46%
(ii) 0%

Scheme 79

2.4.2 SUMMARY

The results of the cyclocondensations of 2-amino-5-nitropyridine with formaldehyde and electron rich alkenes demonstrated that these reactions can occur in excellent yields. However the cycloadducts were not those initially expected. Instead of the iminium ion (188) acting as a 2-azadiene equivalent to give 1,8-naphthyridine derivatives such as (183) *via* cycloaddition onto the C_3 position of the pyridine ring, the ion functioned as a 1,3-diazadiene equivalent to give a pyrimidine derivative. The isolation of only one cycloadduct in the cyclocondensations with cyclopentadiene and α-methylstyrene was thought to be unusual in view of the two regioisomeric cycloadducts obtained from the reaction with styrene.

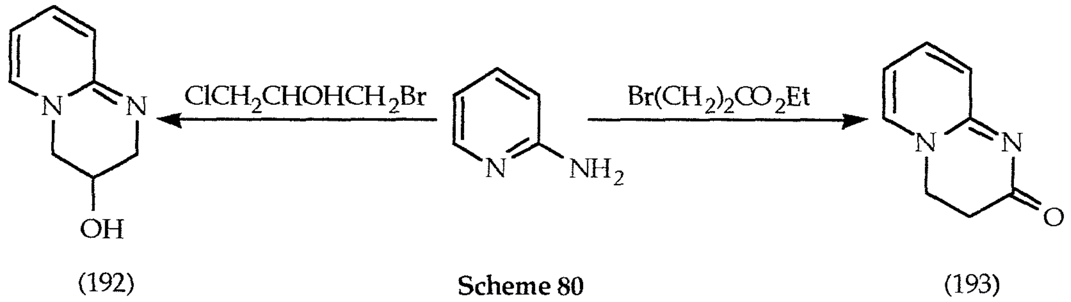
2.4.3 THE IMPORTANCE OF CYCLIC AMIDINES AND RELATED COMPOUNDS

The following sections contain a brief introduction to a variety of cyclic amidines, illustrating some of the synthetic routes employed in their production and describing some of the reasons for the interest focused on them. Beginning with pyridopyrimidines, the similarity with Merriman's products is demonstrated, and the subsequent sections contain details of compounds resembling some of the target structures anticipated from cycloaddition reactions with other aminoheterocycles chosen as starting materials in this section.

The success of the aza Diels-Alder reactions carried out by Merriman were of great interest due to the importance of pyrido[1,2-*a*]pyrimidines, the class of compounds synthesised from 2-aminopyridines. Pyridopyrimidines and cyclic amidines have long been of interest due to their biological activity. Certain types of pyrido[1,2-*a*]pyrimidines have attracted attention as a result of their valuable pharmacological properties, and can be used as synthetic intermediates or as additives to photographic materials and dyes.[153] The chemistry of some pyrido[1,2-*a*]pyrimidines has been reviewed.[153]

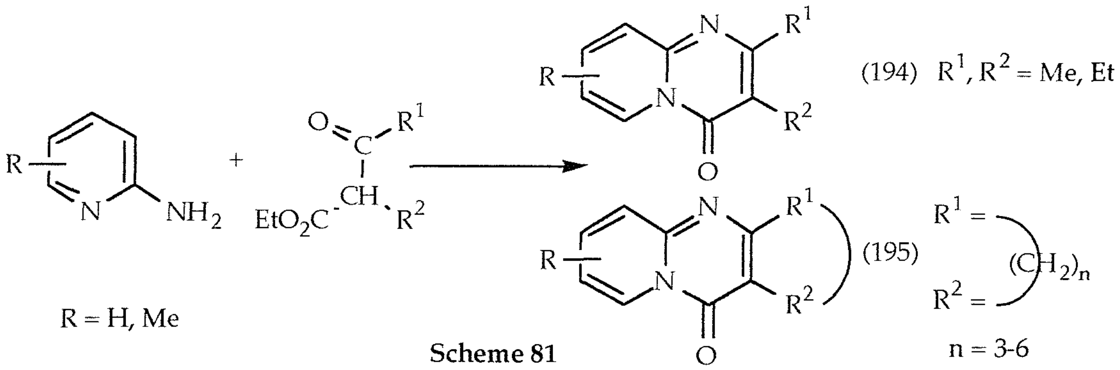
(i) Pyridopyrimidines

A number of synthetic routes to pyrido[1,2-*a*]pyrimidines have been reported in the literature using, as with Merriman's work, 2-aminopyridine derivatives as starting materials. 2-Aminopyridines have been used in the synthesis of pyrido[1,2-*a*]pyrimidine derivatives[154] such as (192) and (193), prepared by reacting the amine in DMF (Scheme 80).



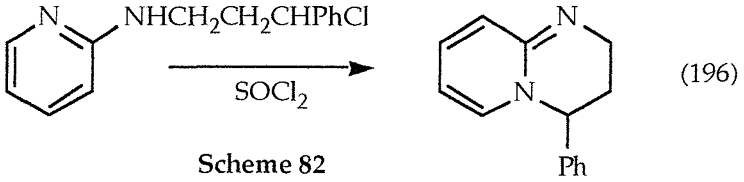
(192) **Scheme 80** (193)

Pyrido[1,2-*a*]pyrimidines and tricyclic nitrogen bridgehead compounds synthesised from 2-aminopyridines have been evaluated for bronchodilator activity. The bicyclic nitrogen bridgehead compounds (194) were prepared by reacting 2-aminopyridines with appropriate β-oxo-esters in a mixture of phosphoryl chloride/polyphosphoric acid;[155] this procedure was also used for the tricyclic compounds (195) (Scheme 81).



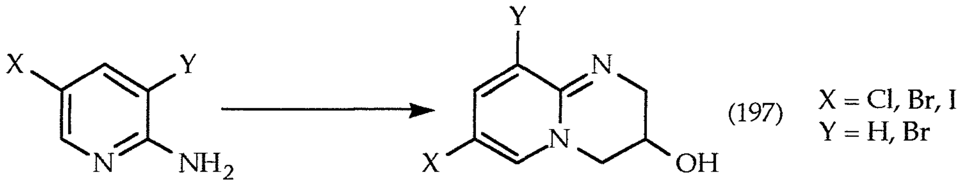
Scheme 81

The pharmacological data obtained on the compounds in biological tests showed that some products exhibited good bronchodilator activity; most of the new compounds also possessed significant analgesic activity. Pyridopyrimidines have also been prepared in excellent yield from chloroalkylaminopyridines.[156] Cyclisation of the starting materials with thionyl chloride gave a range of products (Scheme 82) such as (196), almost identical to (189) page 72, (Scheme 78), synthesised by Merriman (see also page 94).



Scheme 82

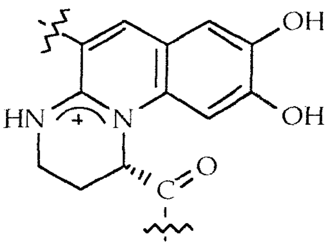
Treatment of halogen substituted aminopyridines with epichlorohydrin or 1,3-dichloro-2-propanol gave pyridopyrimidines as the hydrochloride salts which were hydrolysed to give the free bases (197)[157] (Scheme 75).



Scheme 83

(ii) Pyrimidoquinolines

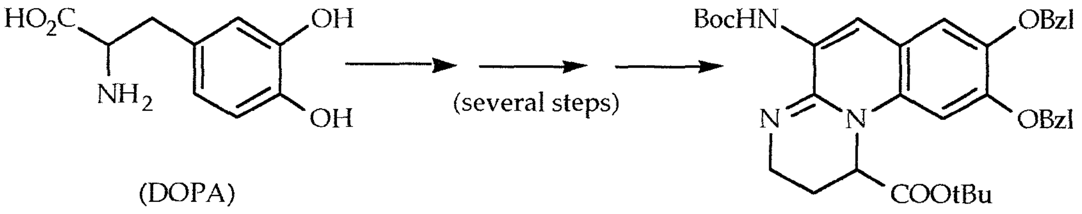
Cyclic amidines such as the chromophore (198) of pseudobactin, a pyrimido[1,2-*a*] quinoline, have been the focus of many studies, some of which concern its synthesis[158a] and biosynthesis.[158b]



(198)

Pseudobactin is a small fluorescent molecule excreted by a common species of bacteria, and was the first metabolite to be completely characterised structurally.[159] This and related pseudomonas metabolites are collectively referred to as the pyoverdins. Since their discovery, the pyoverdins have aroused interest for their possible role in the biological control of a number of plant pathogens.[158-160] Some strains of pseudomonas species rapidly become established in the roots of several types of plants and cause significant increase in crop yields.[159] These bacteria produce pseudobactin which strongly complexes ferric ion and make it unavailable for the growth of other potentially harmful microorganisms.

Numerous pyoverdins have been isolated and characterised, and they all contain a peptide linked to an aromatic chromophore responsible for the fluorescence. The origin of the chromophore is not always clear, hence the interest associated with it. The synthesis of protected forms of the pseudobactin chromophore (199) has been achieved[157] using the amino acid dihydroxy-phenylalanine (DOPA) as the basis of the procedure (Scheme 84).

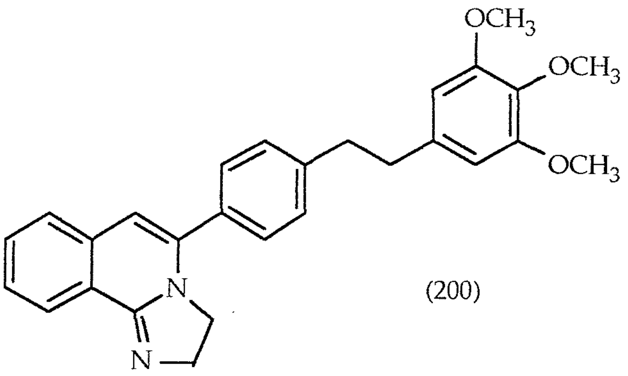


Scheme 84

A biosynthetic study[158] on the other hand revealed that tyrosine rather than DOPA was the primary precursor involved in the biosynthesis of pyoverdin chromophores. The chromophore moiety of various pyoverdins is therefore often a focus of interest for many different reasons.

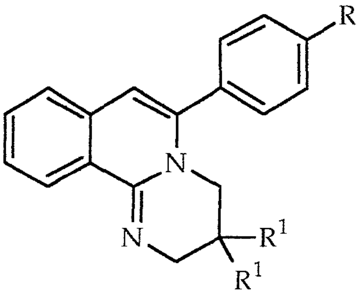
(iii) Imidazoisoquinolines

Other cyclic amidines have exhibited many types of biological activity. The ability of 5-aryl-2,3-dihydro-imidazo[2,1-*a*]isoquinolines such as (200) to antagonise platelet activating factor (PAF) has been demonstrated.[161]

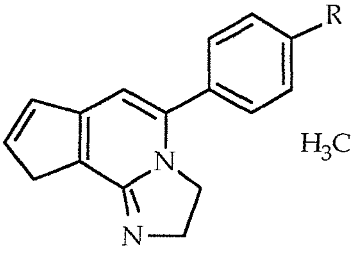


(200)

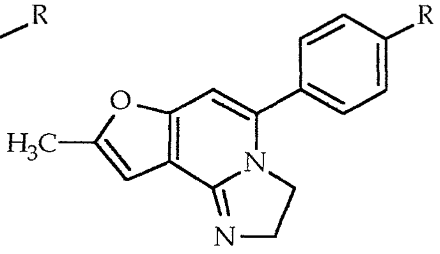
Furthermore, modification of the imidazo-isoquinoline portion of (200) resulted in compounds of similar or greater PAF antagonist activity. These include (201), altered by expansion of the imidazo ring, and (202) and (203), where a hetero ring system has replaced the benzene ring.



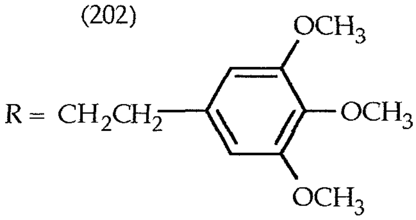
(201a) R^1 = H
(201b) R^1 = CH$_3$



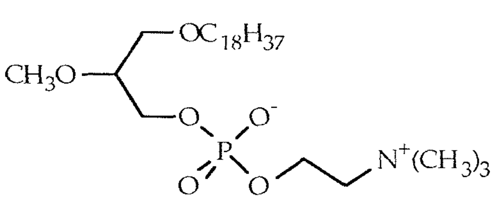
(202)



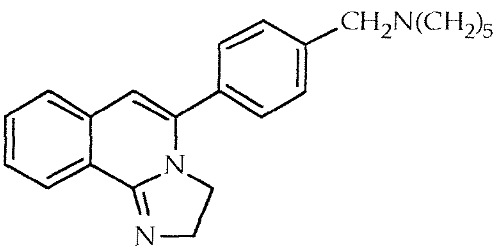
(203)



Further studies on a series of 5-aryl-2,3-dihydroimidazo[2,1-*a*]isoquinolines originally designed to be PAF receptor antagonists showed that the compounds also represented a novel class of potential antitumour agents.[162] Several analogues gave an in vitro cytotoxicity against two tumour cell lines that were considerably more effective than the clinical cytostatic agent edelfosine (204). One compound in particular (205) was entered into phase 1 clinical trials in cancer patients.



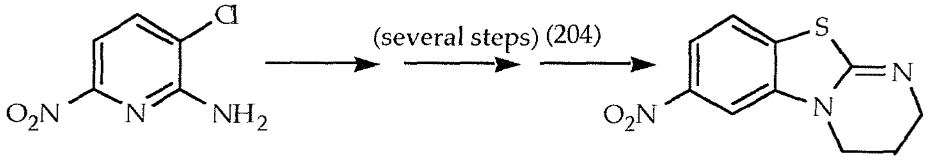
(204)



(205)

(iv) Pyrimidobenzothiazoles

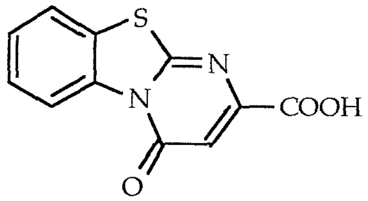
The biological role of isothioureas such as pyrimido[2,1-*b*]benzothiazoles has also provoked interest in these compounds. Pyrimidobenzothiazoles such as (206) and their benzo derivatives and salts have been prepared for use as antidepressants and anti-Parkinsonism agents[163] (Scheme 85).



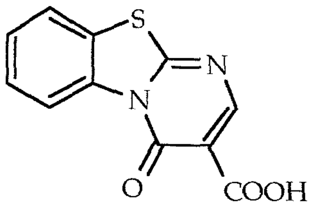
Scheme 85

(206)

Aminobenzothiazole derivatives have exhibited antiallergic activity[164] and benzodiazepine receptor binding ability.[165] Acidic derivatives of 4*H*-pyrimido[2,1-*b*]benzothiazol-4-ones were synthesised by the reaction of 2-aminobenzothiazoles with dimethyl aminofumarate or diethyl ethoxymethylenemalonate to ultimately yield 2- and 3- carboxylic acids (207) and (208).[164] These were tested as potential antiallergic agents and some were found to display activity comparable to commercial drugs such as disodium cromoglycate.

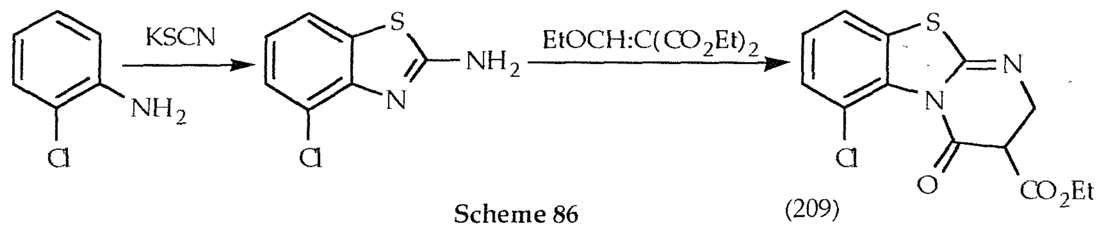


(207)



(208)

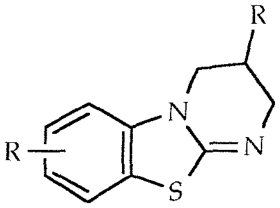
Similar compounds have also been synthesised more recently[165] and showed an ability for benzodiazepine receptor binding with potency greater than chlorodiazepoxide. Substituted anilines were cyclised with potassium thiocyanide to give benzothiazoles which were used to synthesise the pyrimido[2,1-*b*]benzothiazol-4-ones (Scheme 86). The most active compound (209) was thought to be a potential agonist for the benzodiazepine receptor.



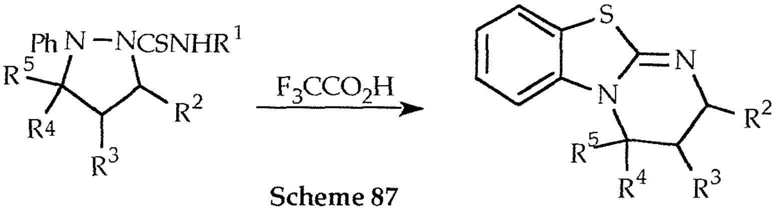
Scheme 86

(209)

2-Aminobenzothiazoles have been employed in condensations with 1,3-dibromopropane and 1,3-dibromo-2-propanol[166] to give pyrimidobenzothiazoles (210); similar compounds have been formed from cyclisations of 1-thiocarbamoyl-2-phenylpyrazolidines[167] (Scheme 87).



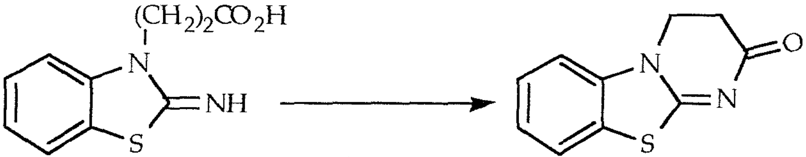
(210)



R^1 - R^5 = H, Me, Ph

Scheme 87

Iminobenzothiazoles can undergo thermolysis to afford tetrahydropyrimidobenzothiazoles[168] (Scheme 88).

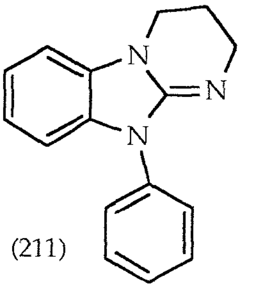


(41%)

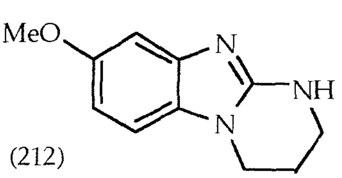
Scheme 88

In addition to benzothiazoles, benzimidazole derivatives have also been shown to possess biological activity. Pyridobenzimidazoles such as (211) have been synthesised and were found to be useful as antidiabetics and antihypertensives.[169]

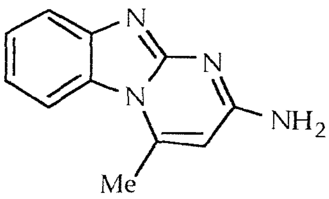
Pyrimido[1,2-*a*]benzimidazoles (212) prepared from 4-methoxy-3-nitroaniline and $CH_2{:}CHCN$ in six steps have variable antidepressant activity.[170]



(211)



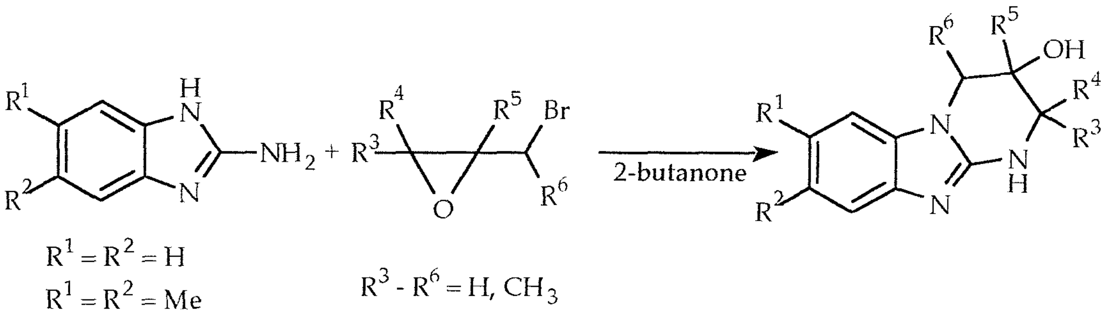
(212)



(213)

Functionalised pyrimido[1,2-*a*]benzimidazoles such as (213) have been synthesised from (benzimidazol-2-yl)-cyanamide and β-dicarbonyl compounds using nickel complexes and salts.[171]

2-Aminobenzimidazoles can react with various epoxy bromides in refluxing 2-butanone to provide a convenient supply of tetrahydropyrimido[1,2-*a*]benzimidazoles[172] (Scheme 89).



Scheme 89

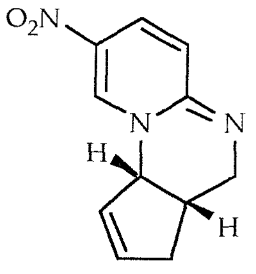
Summary

The importance of cyclic amidines and related compounds is well illustrated in the diverse selection examined in these sections. The pharmacological properties range from analgesic and antidepressant activity to potential antitumour agents. Because of their high biological activity, molecules such as these represent valuable and challenging targets. With initial investigations by Merriman showing a route to pyridopyrimidines as being successful, it is possible that this Diels-Alder methodology could play a prominent role in meeting this challenge.

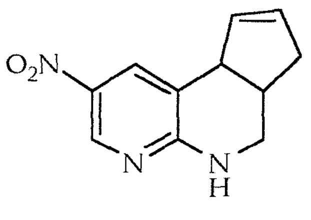
2.4.4 REACTIONS OF 2-AMINOPYRIDINES

(i) 2-Amino-5-nitropyridine

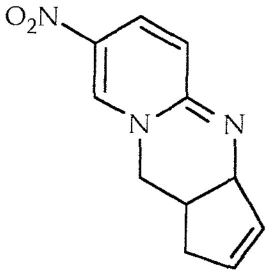
As a starting point, the reaction between 2-amino-5-nitropyridine and cyclopentadiene carried out by Merriman[26] was repeated in order to establish an optimum procedure for maximum yield; this gave the cycloadduct (184) in good yield (85%). Purification of the brown oil by flash column chromatography required elution with 95:5 ethyl acetate / methanol since the product was very polar. There was no trace of unreacted starting material or any other product such as (183) which could arise from cyclisation at the carbon rather than the nitrogen of the aromatic ring, or (214) which could arise from the initial formation of an alternative iminium ion. The structure of the cycloadduct was confirmed by examination of nmr, ir and ms data.



(184)



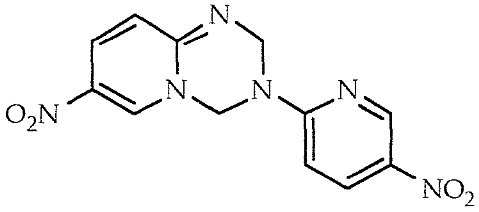
(183)



(214)

The successful reproduction of Merriman's result in this case prompted the investigation of whether other electron rich alkenes would undergo similar cyclocondensations to lead to analogous pyrido[1,2-*a*]pyrimidine derivatives. Indene was chosen since this bicyclic alkene would be an interesting alternative to the alkenes already studied with 2-aminopyridines, such as cyclopentadiene, styrene and α-methylstyrene. It would also, if successful, extend the range of alkenes suitable for aza Diels-Alder reactions. The potential for interesting and unusual skeletons arising from any reactions with indene added to its suitability. Due to the lower yields and decomposition reported with the reactions of 2-aminopyridine, the 5-nitro derivative was initially used in the reaction with indene.
The initial experiment was carried out under conditions similar to those employed in the cyclocondensation with cyclopentadiene. Hence the reaction with two equivalents of indene at room temperature gave a dark brown oil, which was confirmed as a cycloadduct by ^1H nmr. Flash column chromatography yielded unreacted starting material (approximately 30%) and three minor fractions. The three fractions remained unidentified, although they did not appear to contain a cycloaddition product.

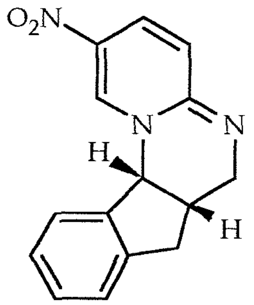
The reaction was subsequently repeated, varying only the temperature, since the presence of unreacted starting material and the initial indication by nmr of a successful cyclisation suggested that the reaction may not have gone to completion, and any product formed had decomposed during purification attempts. The experiment was therefore refluxed for 30 minutes and yielded a yellow solid which was shown to be one product by TLC and was readily recrystallised from acetonitrile to give a yellow powder. The product was identified by ^{1}H nmr as 3,4-dihydro-7-nitro-3-(5-nitro-2-pyridyl)-2*H*-pyrido[1,2-*a*][1,3,5]triazine (187), identical to the adduct observed by Merriman[26]. Further analysis confirmed the structure. The triazine was presumably formed as reported previously (page 72), with the dimerisation of the iminium ion initially formed from the starting material (Scheme 77).

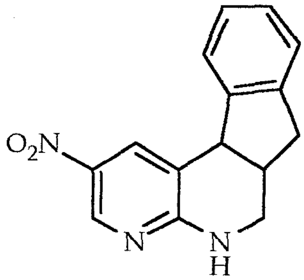


(187)

The formation of this adduct was avoided in the subsequent reaction by using a large excess of indene (10 equivalents) which appeared to solve the problem since no trace of the triazine was detected by TLC analysis of the crude product. Flash column chromatography yielded the cycloadduct (215) as a dark yellow oil (57%), although decomposition occurred upon standing. Further purified material acquired from repeat experiments was therefore crystallised in a freezer and recrystallised from ethyl acetate yielding the pure and stable cycloadduct.

(215)



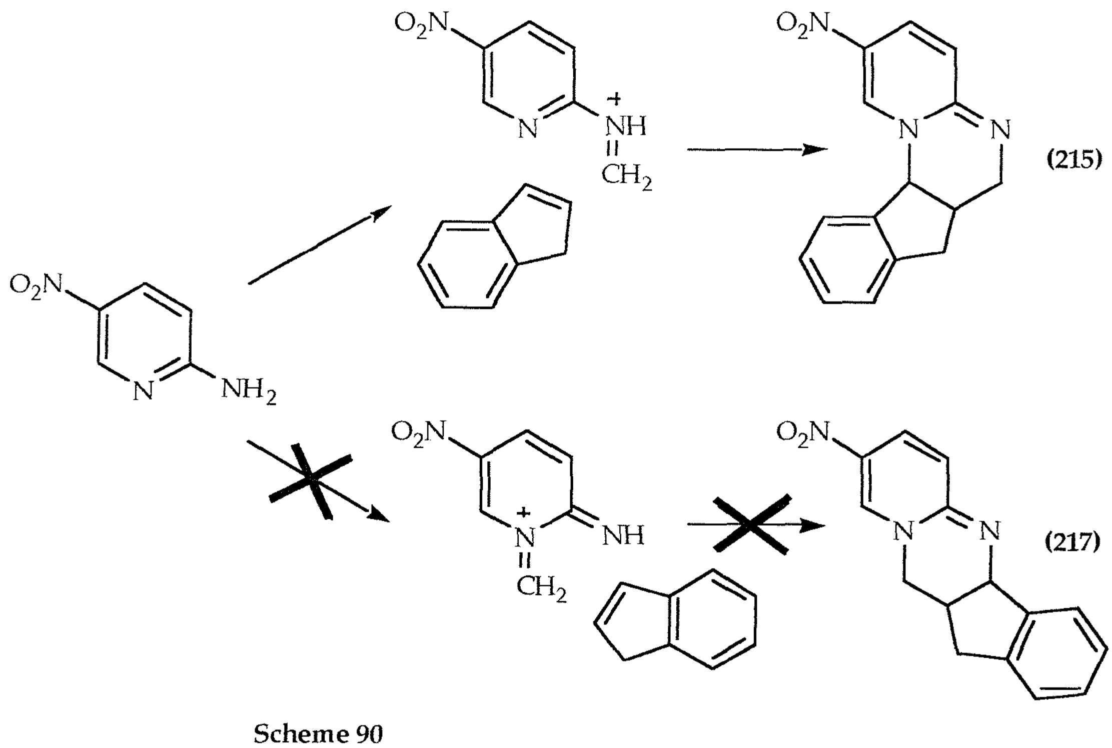


(216)

There was no trace in any of the experiments of other products or unreacted starting material. This result was consistent with the others reported in this series. Comparison of the nmr data with that for the cyclopentadiene adduct confirmed that no cycloaddition onto the carbon of the pyridine ring had taken place, which would have resulted in the isomeric adduct (216).

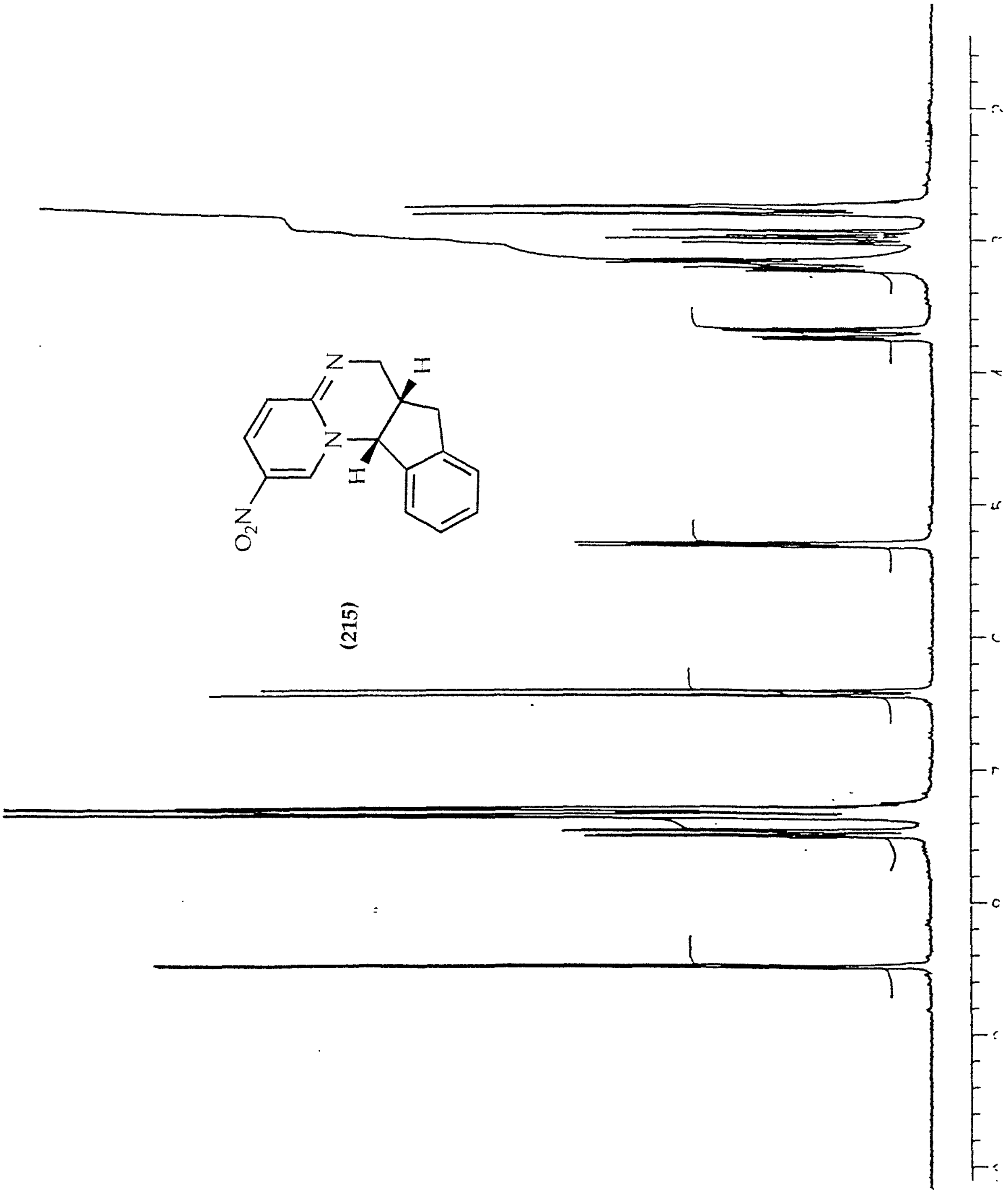
The ^1H nmr of (215) (Figure 4) showed the ArC3-H proton at 6.41ppm and the ^{13}C nmr confirmed that the corresponding carbon was not a quaternary. Both features would clearly be different in the alternative cycloadduct (216). The *cis* stereochemistry was assigned by analogy with the cyclopentadiene adduct (184), and on the basis of the 6.0Hz coupling constant of the methine proton.

In light of the regioisomeric cycloadducts (189) and (190) isolated by Merriman, there was also a third product (217) possible from the reaction which could be formed from an alternative iminium ion (Scheme 90). The cycloadduct synthesised was not assigned this structure based on examination of analytical data. The ^1H nmr of the cycloadduct (215) shows the CH-N proton at 5.30ppm; this proton occurs at 5.15ppm in the analogous styrene adduct (189), and at 4.76ppm in its isomer (190).

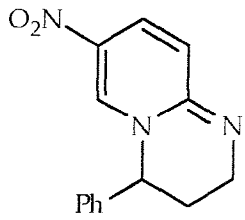


Scheme 90

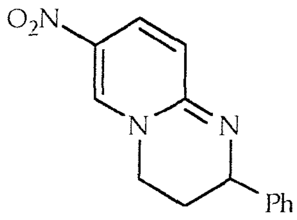
Figure 4: ^{1}H NMR of Indene Adduct (215).



The alternative structure (217) would therefore expect to show this signal further upfield. The same pattern was also observed in the ^{13}C nmr, with the carbon adjacent to nitrogen at 65.92ppm for the indene adduct (215), at 63.45ppm for the analogous styrene adduct (189) and at 56.94ppm for the isomeric adduct (190).



(189)



(190)

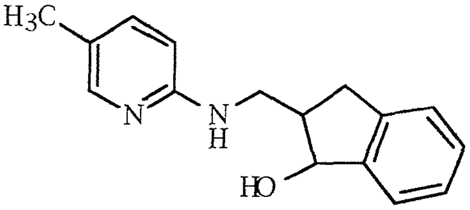
Another noticeable difference between the anomalous styrene adduct (190) and the other derivatives in this series was the generally higher upfield positions of the $C\underline{H}_2$-N protons. The mass spectrum of the indene adduct showed the molecular ion at m/z=267 (30%), and the base peak at m/z=116 corresponding to loss of $C_6H_5N_3O_2$, which is consistent with the base peaks of the other adducts in this series, with the exception of the second styrene adduct (190).

The lack of products analogous to the second styrene adduct (190) detected or isolated in any reactions with cyclopentadiene or indene prompted the investigation of the original experiment. The reaction with styrene was repeated using the exact conditions employed by Merriman. Despite this, the only adduct detected in the crude product was the regioisomer most commonly observed in these reactions (189),which was isolated in good yield (52%) following purification. Further attempts to synthesise the two isomers by varying the reaction conditions including temperature, duration and reagent equivalents consistently produced fair yields of the single isomer, and only one product was ever observed by TLC analyses of the reaction mixtures. Since the only variables unaccounted for, the starting materials and reagents used in the original reaction, could not be examined, the inference from these studies is that some aspect of these variables was responsible for the formation of the two isomers.

(ii) 2-Amino-5-methylpyridine

Having demonstrated the successful cyclocondensations of 2-amino-5-nitropyridine with a range of electron rich alkenes, attention now shifted to broadening the scope of this type of cyclocondensation by varying the aminopyridine. The utility of 2-amino-5-methylpyridine was therefore examined. This compound was particularly interesting due to the presence and position of the methyl group. With the methyl group occupying the same position as the nitro group in the earlier studied aminopyridine, the new material would complement the earlier one, yet it would also contrast, due to the positive inductive effect of the methyl group which could alter the outcome of the reaction.

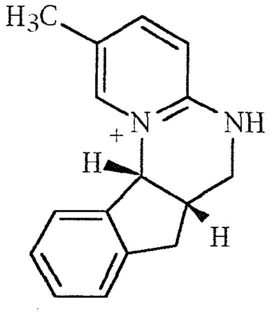
The initial reaction was carried out with indene and gave the product as a white powder following recrystallisation from ethanol/toluene. The ^1H nmr appeared initially to be very similar to those of other products in this series; however, closer examination revealed some important differences. A singlet at 11.16ppm, which gradually disappeared upon shaking with D_2O, suggested the presence of an NH group in the product. The signal commonly associated with the ring junction proton (CH-N) was further downfield than usual at 5.58ppm and the methylene proton signals were slightly modified in their position and splitting pattern. Also, in contrast to the other aminopyridine derivatives which had sharp melting points, the product was instead observed to decompose slowly over a large temperature range. The reaction between the two starting materials had therefore yielded an unexpected product, initially thought to be the alcohol (218), a possible intermediate in the formation of the expected cycloadduct.



(218)

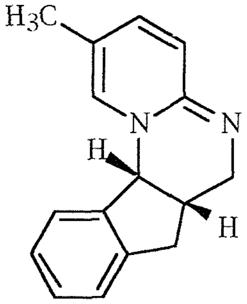
Alcohols of this type had occasionally been observed by Merriman.[26] If the product was an intermediate then it could be possible to form the actual cycloadduct from the alcohol under similar experimental conditions to those of the cyclisation reaction. This strategy was employed by Merriman, with the intermediate alcohols being successfully cyclised to give the cycloadducts in excellent yields. Hence, trifluoroacetic acid (two equivalents) was added to a suspension of the product (218) in acetonitrile and the mixture stirred at reflux. Monitoring by TLC showed that no reaction had occurred after 1h. and after addition of more trifluoroacteic acid. The reaction was worked up after two hours and the product was shown by nmr to be unchanged. Further cyclisation attempts were also unsuccessful, as the material proved to be very stable. It was therefore likely that the material was not an intermediate alcohol but a stable cyclised product isolated as a trifluoroacetate salt (219a). This structure would account for the slight differences observed in the nmr spectra compared with those of the neutral cyclic amidines.

(219a)



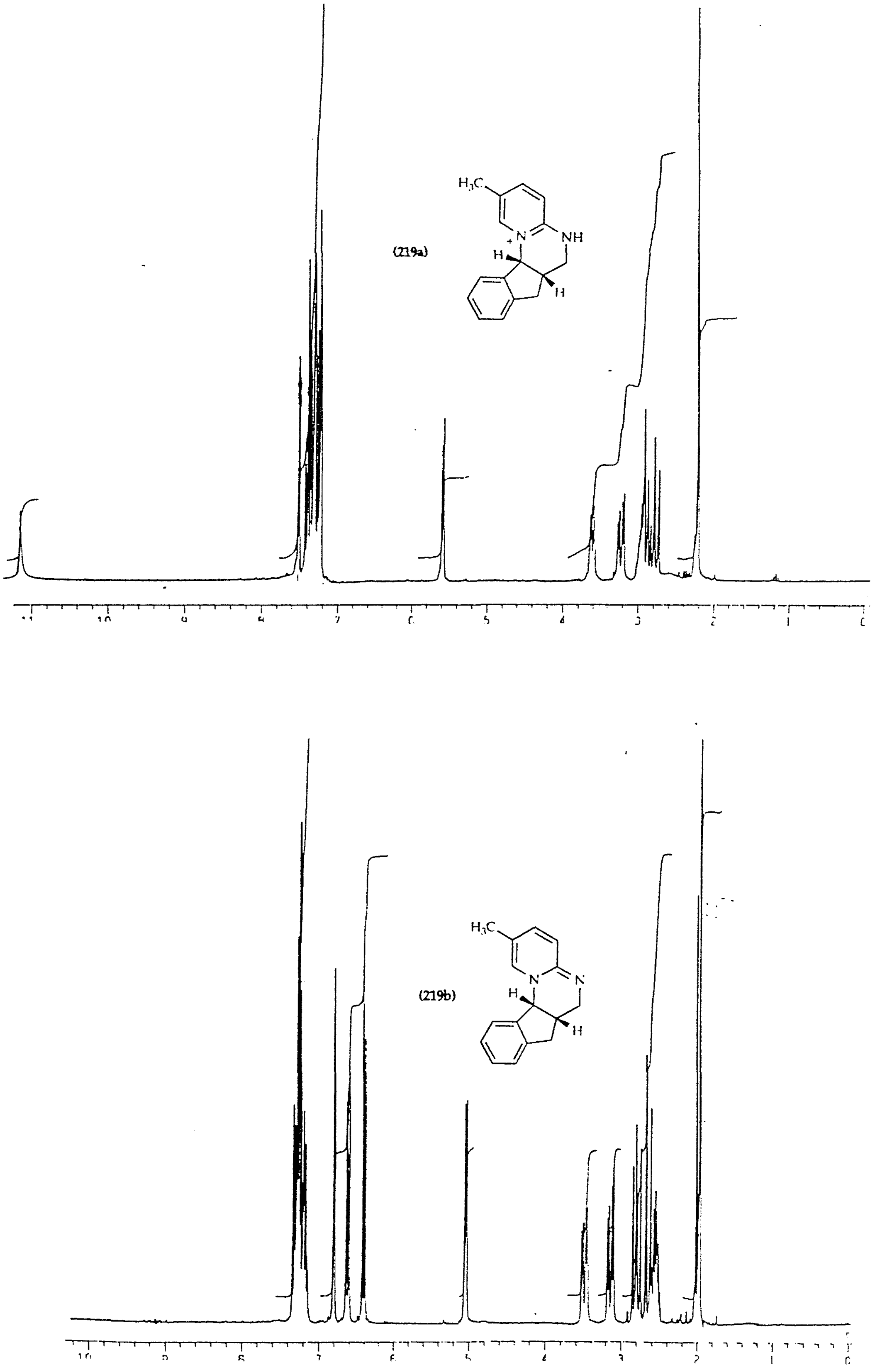
Further evidence for this type of structure came from a simple experiment to convert it to the neutral amidine. Basification of the salt was expected to achieve this; hence a solution of the salt in dichloromethane was washed with sodium hydroxide solution and the product was isolated as a yellow oil. Nmr analysis confirmed the presence of the neutral amidine (219b).

(219b)

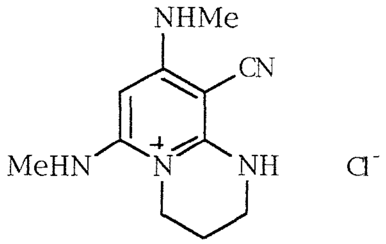


Spectroscopic analysis of both the trifluoroacetate salt and the neutral amidine yielded results consistent with the deduced structures. (^{1}H nmr spectra of (219a) and (219b) shown in Figure 5). The *cis* stereochemistry was assigned on the basis of the coupling constsnts of the methine proton, 5.4Hz and 6.0Hz for the salt and neutral products respectively. It was observed that of the two possible compounds the salt was the only product of the cyclisation reaction with 2-amino-5-methylpyridine, in contrast with similar reactions involving nitropyridines which yielded only the neutral amidines. The nature of the product isolated was therefore a reflection of the basicity of the appropriate amidine. Salts of this type, such as (220) have been reported in the literature[173]; they were formed in several steps from 2,4,6-tris(alkylamino)-3-pyridinecarbonitriles.

Figure 5: ^{1}H NMR of Salt (219a) and Neutral (219b) Indene Adducts.

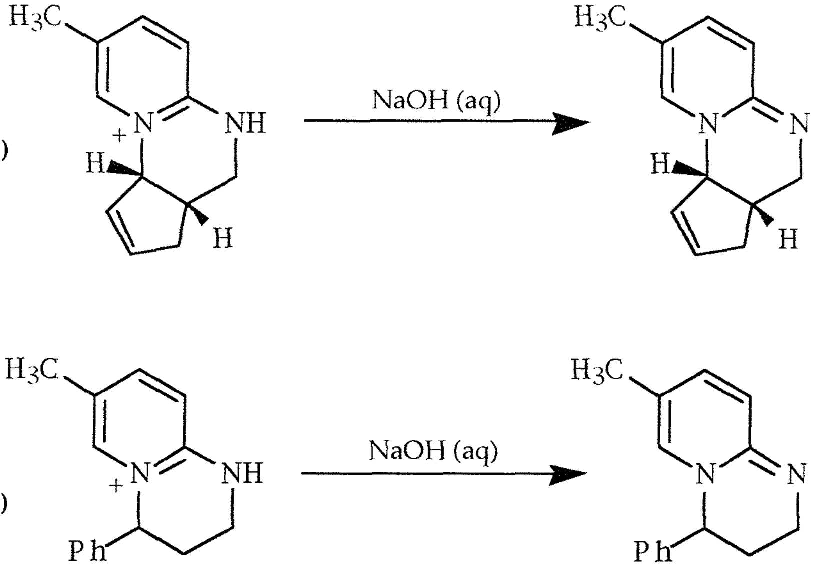


(220)



In the subsequent reactions carried out between 2-amino-5-methylpyridine and other electron rich alkenes the same reaction was observed: only the trifluoroacetate salts were isolated as very stable products in good yields. Hence the reactions with cyclopentadiene and styrene gave the cycloadducts (221) and (222) respectively. Both of these products were transformed into the neutral amidines (223) and (224) in excellent yield by washing with sodium hydroxide solution.

(221) **(223)** **(222)** **(224)**



Scheme 91

In all cases the neutral amidines were very unstable oils and much more prone to decomposition than their trifluoroacetate salts.

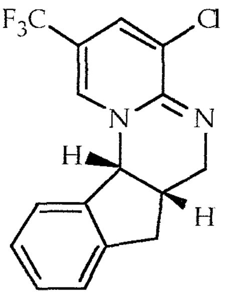
Although the structures of the products shown could be deduced from spectroscopic observations, indisputable confirmation of the structures was desirable. It was not possible to grow suitable crystals for X-ray analysis from the aminopicoline derivatives, therefore further experiments were undertaken with 2-amino-3-chloro-5-trifluoromethyl pyridine.

(iii) 2-Amino-3-chloro-5-trifluoromethylpyridine

The investigations into the syntheses of pyrido[1,2-*a*]pyrimidines were extended to include a new, interesting and readily available starting material, 2-amino-3-chloro-5-trifluoromethylpyridine. With its electron withdrawing trifluoromethyl group at the 5-position, any cyclisation reactions with formaldehyde and electron rich alkenes were expected to yield novel neutral cyclic amidines. Furthermore, it was anticipated that a crystalline product could be obtained and developed for X-ray analysis of the structure.

The cyclocondensation between 2-amino-3-chloro-5-trifluoromethylpyridine and indene was initially addressed. The reaction was carried out at reflux for 30 minutes using 10 equivalents of the alkene. The excess indene in the crude product was removed by washing with petrol and the resulting solid was readily recrystallised from ethyl acetate to give the cyclic amidine (225) as yellow needles in very good yield (88%).

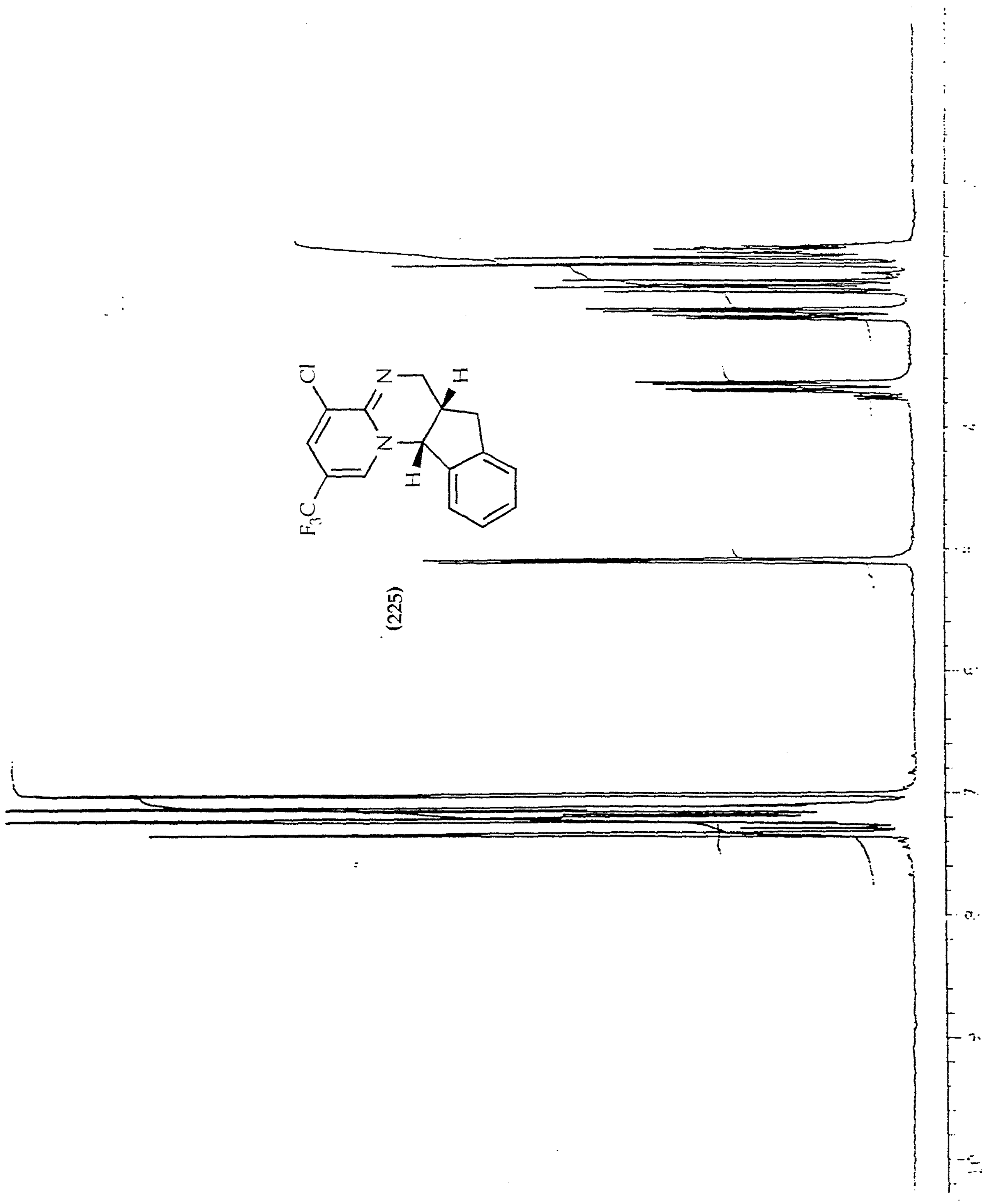
(225)



The nmr data (^{1}H nmr shown in Figure 6) was similar to the indene adduct of 2-amino-5-nitropyridine (215). The C$\underline{H}$-N proton was observed at 5.30ppm in (215) and at 5.08ppm in (225), with the corresponding carbon ($\underline{C}$H-N) signals at 65.93ppm and 65.45ppm. The C$\underline{H}_2$-N signals at 3.70ppm and 3.19ppm of (215) matched the corresponding protons at 3.66ppm and 3.05ppm of (225), with the carbon signals appearing at 45.50ppm and 45.73ppm respectively. All other analytical data were consistent with the assigned structure.

Although the ^{1}H nmr methylene signals could be readily assigned to either C$\underline{H}_2$-N or C$\underline{H}_2$-CH on the basis of their coupling constants, it was interesting to examine the structure in greater detail in order to differentiate between the four protons. The first methylene proton observed at 3.66ppm (Figure7), assigned to the CH$_2$ group adjacent to nitrogen since it was the furthest downfield, has a large geminal coupling of 16.0Hz. The second value of 5.3Hz due to the vicinal coupling with the CH proton suggests that the first signal represents the proton H$_a$ since the angle between these two protons is approximately 40°. Furthermore, the very small, although unresolved, splitting of each of the four peaks in this signal is an

Figure 6: ^{1}H NMR of Indene Adduct (225).



(225)

indication of a third long range coupling of H_a, which is likely to be a W coupling with H_d. The second signal at 3.05ppm has a different large geminal coupling of 15.6Hz and is therefore due to a proton from the other methylene group. The 6.0Hz vicinal coupling indicates the proton H_d is responsible, again due to the size of the angle between the coupling protons. The third signal at 2.83ppm with a geminal coupling of 16.0Hz is therefore assigned to H_b, confirmed by the large vicinal coupling of 10.1Hz due to the large angle between the protons. Finally, the H_c signal at 2.63ppm shows only a geminal coupling of 15.6Hz; no vicinal coupling is observed since the angle is near 90°.

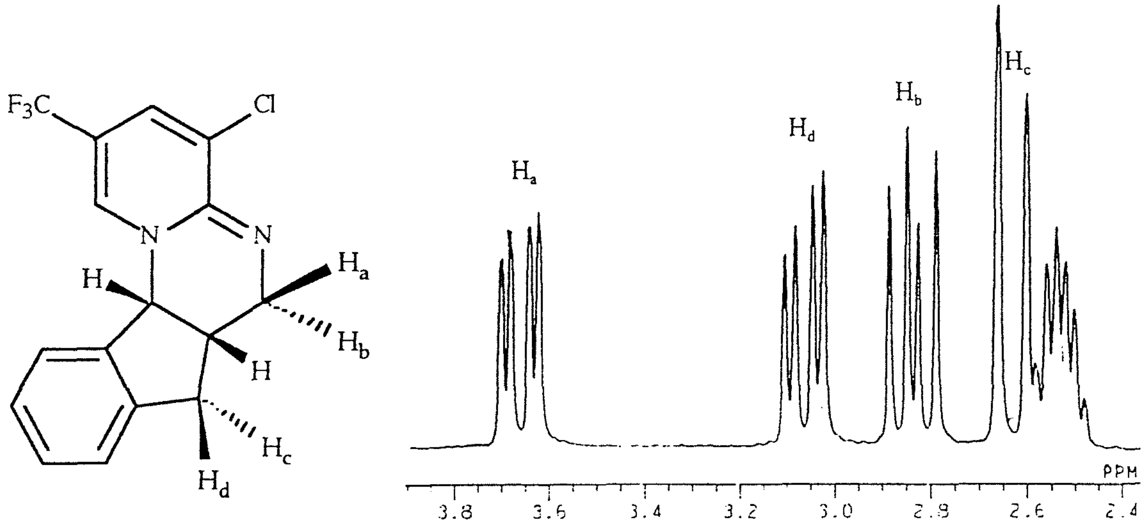
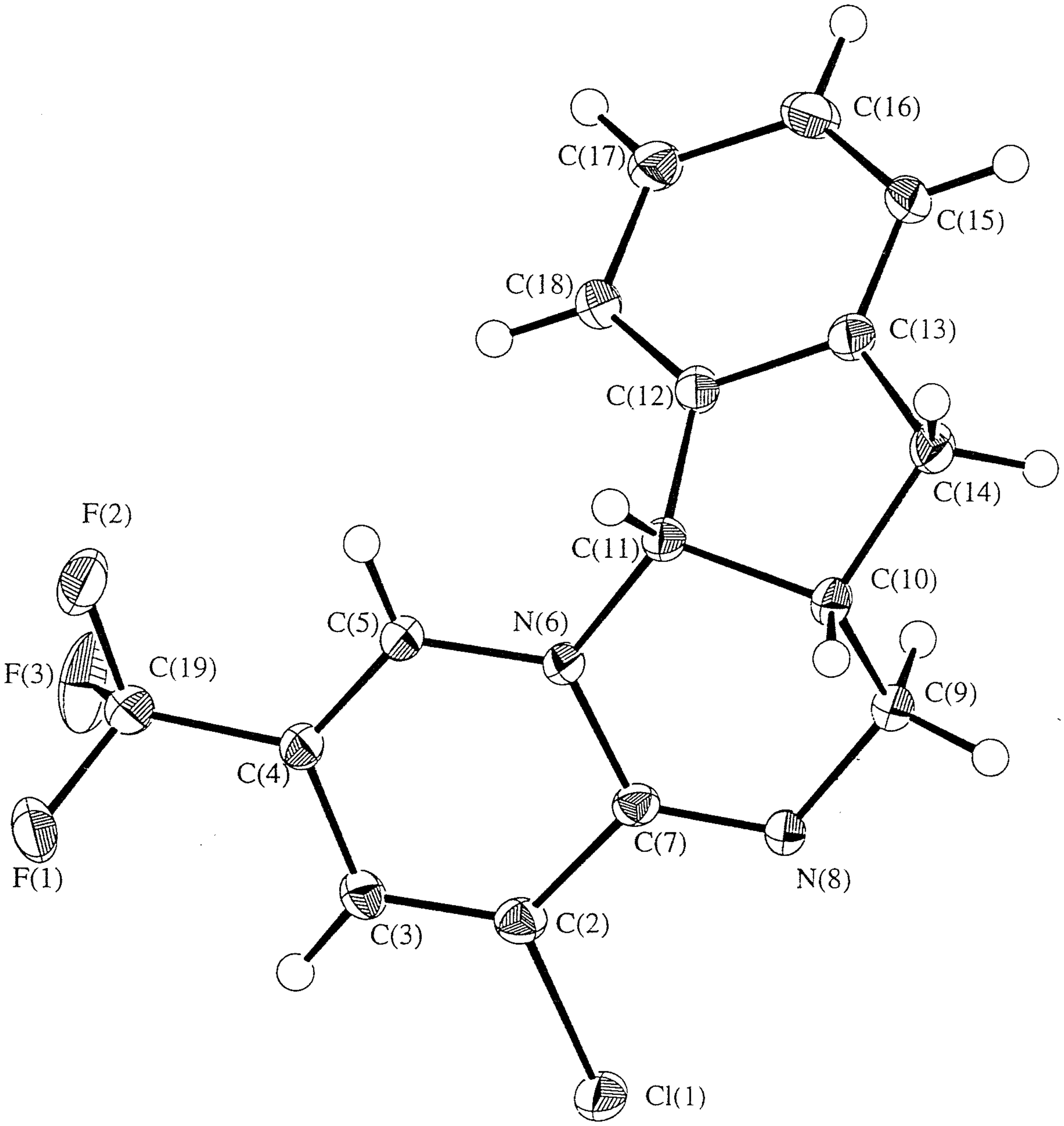


Figure 7: Expanded ^1H NMR of Methylene Signals in (225).

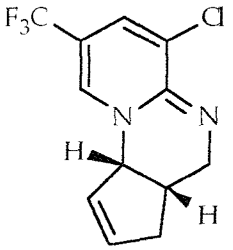
Further recrystallisations of the pure product yielded crystals suitable for single crystal X-ray analysis (Figure 8) which confirmed the structure of (225). The added advantage of the positive X-ray analysis was the possibility of confirming earlier and future structures by comparison of their spectroscopic data with data for this particular adduct. A number of interesting points regarding these reactions were also established from this result. The confirmation of the regiochemistry shows that the reaction with formaldehyde takes place at the amino group rather than the pyridine nitrogen, in contrast to previous studies which show that 2-aminopyridines can react with electrophiles at both nitrogen centres.[153] The subsequent cyclisation onto nitrogen rather than onto carbon (although this is clearly not possible in this particular case) shows the selectivity towards these amidines, yet cyclisation at carbon affording naphthyridines are standard in the literature.[153] The *cis* stereochemistry is also confirmed by the X-ray.

Figure 8: X-ray Analysis of (225).



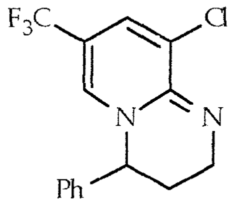
The cyclisation with cyclopentadiene was next examined. The yellow solid isolated after removal of excess cyclopentadiene was easily recrystallised from ethyl acetate. The product (226), obtained in 90% yield, was identified by nmr analysis. The characteristic signals were observed at 4.49ppm (C<u>H</u>-N), 3.55ppm, 2.96ppm ($C\underline{H}_2$-N), 2.34ppm and 2.05ppm ($C\underline{H}_2$-CH); the corresponding carbon signals were at 66.18ppm, 46.29ppm and 36.84ppm.

(226)



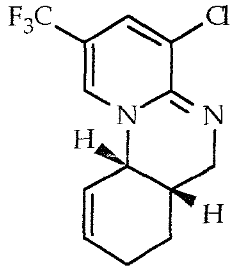
In line with the other reactions examined in this series, it was decided to expand the studies on 2-amino-3-chloro-5-trifluoromethylpyridine by carrying out additional experiments with other alkenes. Consequently, the reaction with styrene gave the product (227) in excellent yield (70%) after recrystallisation from ethyl acetate. The nmr spectra of this styrene adduct were comparable to those of the analogous 2-amino-5-nitropyridine derivative (189). No trace of a regioisomer was detected.

(227)



Cyclohexadiene, not previously employed in the reactions with aminopyridines, had met with some success in the cyclocondensations with amino-tetralone and amino-indanone as reported earlier. The alkene had reacted both as a diene and a dienophile, giving two interesting products from each reaction. It was therefore interesting to continue the aminopyridine studies with cyclohexadiene. The reaction with 2-amino-3-chloro-5-trifluoromethylpyridine produced the amidine (228) in good yield (85%); no other product was detected.

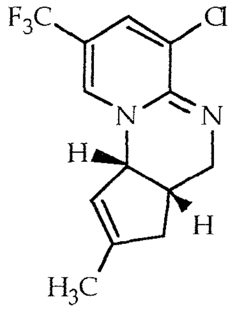
(228)



Since this starting material was clearly producing very good results with all the alkenes tested, it was an excellent opportunity to attempt the reaction with methylcyclopentadiene. This had proved problematic in the reactions with amino-tetralone and amino-indanone due to the difficulties encountered in handling the products. Nevertheless, the interesting products ultimately recovered from those reactions prompted the investigation of the cycloaddition of methylcyclopentadiene in this series. The reaction with 2-amino-3-chloro-5-trifluoromethylpyridine consistently yielded a mixture of two isomers detected by nmr analysis of the crude material. The isomers were thought to differ only in the position of the methyl group, as expected, and as observed in earlier reactions of this alkene. The difficulty encountered in the attempts at separation of the isomers and the instability of the products resulted in generally poor yields of both compounds.

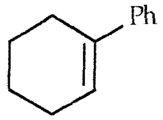
The first isomer could not be isolated without contamination from the second, although a small quantity of the pure second isomer (229) was eventually isolated as a yellow oil. The nmr spectra were compared with the spectra from the analogous cyclopentadiene adduct, (226) and with the methylcyclopentadiene derivatives from the indanone and tetralone series in order to establish the position of the methyl group. Replacement of a =CH proton by the methyl group was demonstrated in the ^{1}H nmr with only one =CH signal being observed; the methyl group also shifted the position of the adjacent CH_2 group slightly downfield. Both features were also evident in the ^{13}C nmr.

(229)

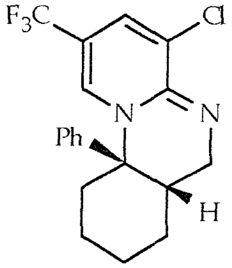


The generally very favourable results obtained with the use of this starting material prompted the investigation of the utility of new electron rich alkenes, not previuosly employed in these Diels-Alder reactions. This excellent opportunity to include different alkenes would provide valuable information regarding the scope of the reaction. Hence the next experiment carried out with 2-amino-3-chloro-5-trifluoromethylpyridine was a cycloaddition with phenylcyclohexadiene (230); this electron rich alkene was synthesised by Merriman.[26] The reaction proceeded smoothly to give the cycloadduct (231) in good yield (70%) despite the fact that the alkene was slightly impure and there was insufficient material to allow a large excess of the alkene to be used. Nevertheless, the novel product was stable and hence readily isolated and purified, suggesting that in more favourable conditions the reaction would prosper. All analytical data was consistent with the assigned structure.

(230)



(231)



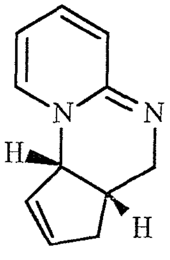
Further experiments were carried out with pyrrole or indole as the electron rich alkenes, although no significant products were observed. The tendency for both alkenes to polymerise could not be overcome by altering a variety of reaction conditions such as the temperature. Only when the temperature was reduced from reflux to 0°C were products other than isoluble polymer isolated, however, these appeared to be merely a pyrrole dimer and a starting material "dimer" linked by a methylene group. Nevertheless these disappointing results should not detract from the successes encountered earlier; also, they were useful in eliminating the possibility of using pyrrole and indole in future reactions.

(iv) 2-Aminopyridine

Having examined the reactions of two very different aminopyridines in terms of basicity, one containing a nitro group and one containing a methyl group, it was therefore interesting to pursue the investigation of the simple 2-aminopyridine which has no substituents, despite the fact that this starting material had been rejected for further study by Merriman following its unsuccessful reaction with cyclopentadiene.

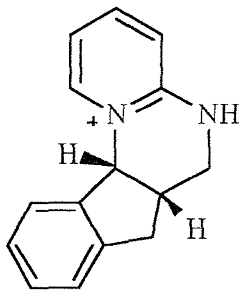
The product (186) had been isolated in relatively low yield and was found to be very unstable. Nevertheless it was thought that a cyclisation with indene might produce a more stable cycloadduct, and it would also be very interesting to investigate the nature of the adduct, salt or neutral, that would arise from the basic starting material containing no substituents.

(186)



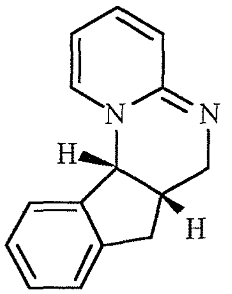
The reaction proceeded smoothly yielding the product in the form of large clear crystals following recrystallisation from ethyl acetate / ethanol. The ^{1}H nmr indicated that the product was actually a salt (232), in contrast to the neutral amidine obtained from the reaction with cyclopentadiene by Merriman.

(232)



The characteristic features in the nmr distinguishing the salt from the neutral product, such as the NH signal, the CH-N signal shifted downfield and the different positions and splitting pattern of the methylene protons observed in the ^{1}H nmr of the 2-amino-5-methylpyridine derivative (219a) were also recognised in this case. Recrystallisation of the white solid from ethanol yielded large clear crystals. The high quality and stability of the crystals made them suitable for X-ray analysis, which would complement the X-ray of the neutral amidine (225). The X-ray (Figure 9) rigorously confirmed the structure of the trifluoroacetate salt. As observed with the neutral product, the X-ray showed that the regiochemistry is controlled by the reaction of formaldehyde at the primary amino site; it also verified the cyclisation at nitrogen rather than carbon and the *cis* stereochemistry. No unusual bond lengths or angles were noted. The salt was readily transformed in excellent yield (98%) into the neutral amidine (233) using sodium hydroxide under the conditions reported earlier, although as before the product was very unstable. The ^{1}H nmr spectra of (232) and (233) are illustrated in Figure 10.

(233)



In order to establish a complete set of results with 2-aminopyridine, and also because of the inconsistent nature of the products (ie.a salt from the reaction with indene and a neutral product with cyclopentadiene obtained by Merriman), the reaction with cyclopentadiene was carried out. Under the conditions employed for the indene reaction, the product

Figure 9: X-ray Analysis of (232).

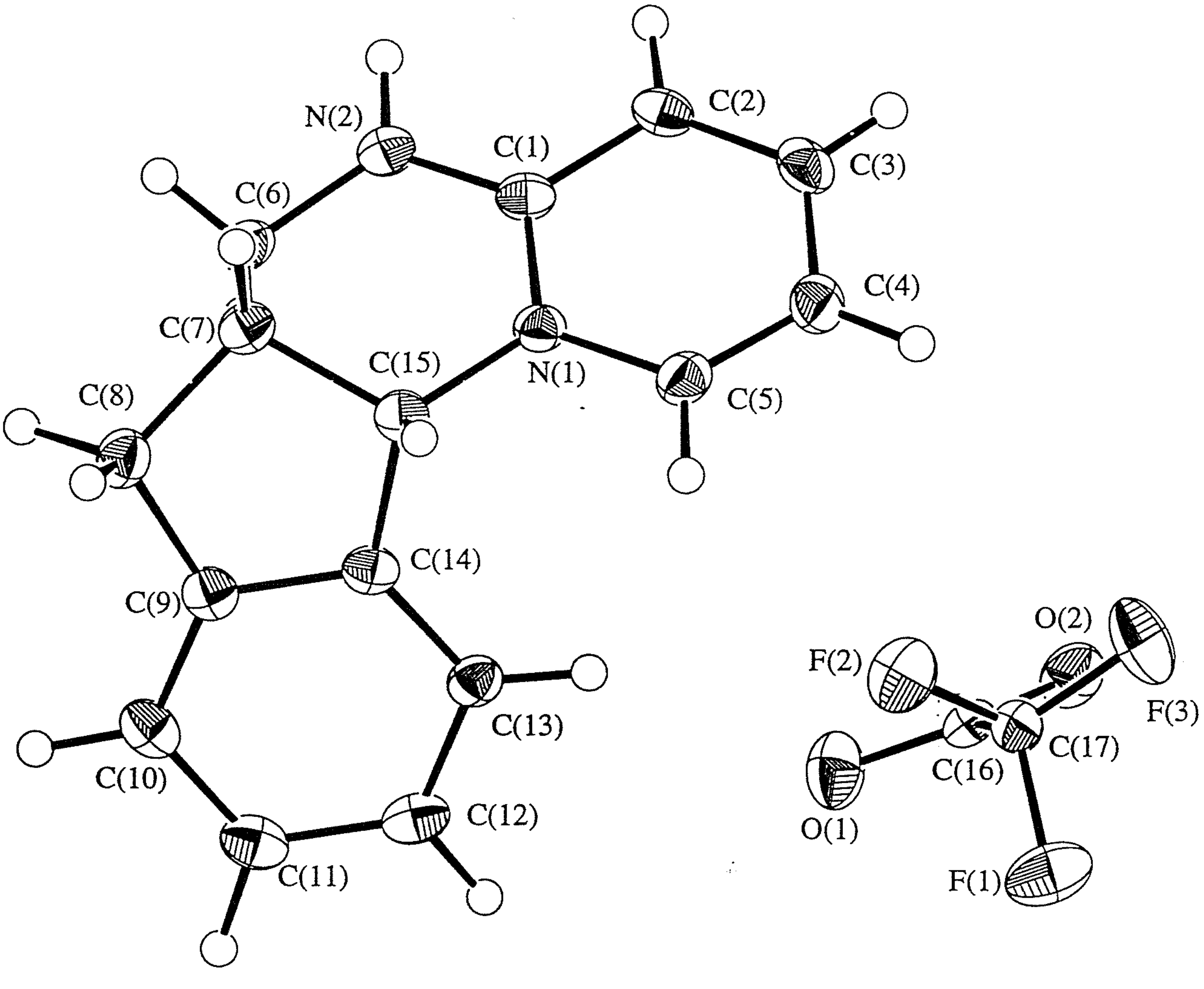
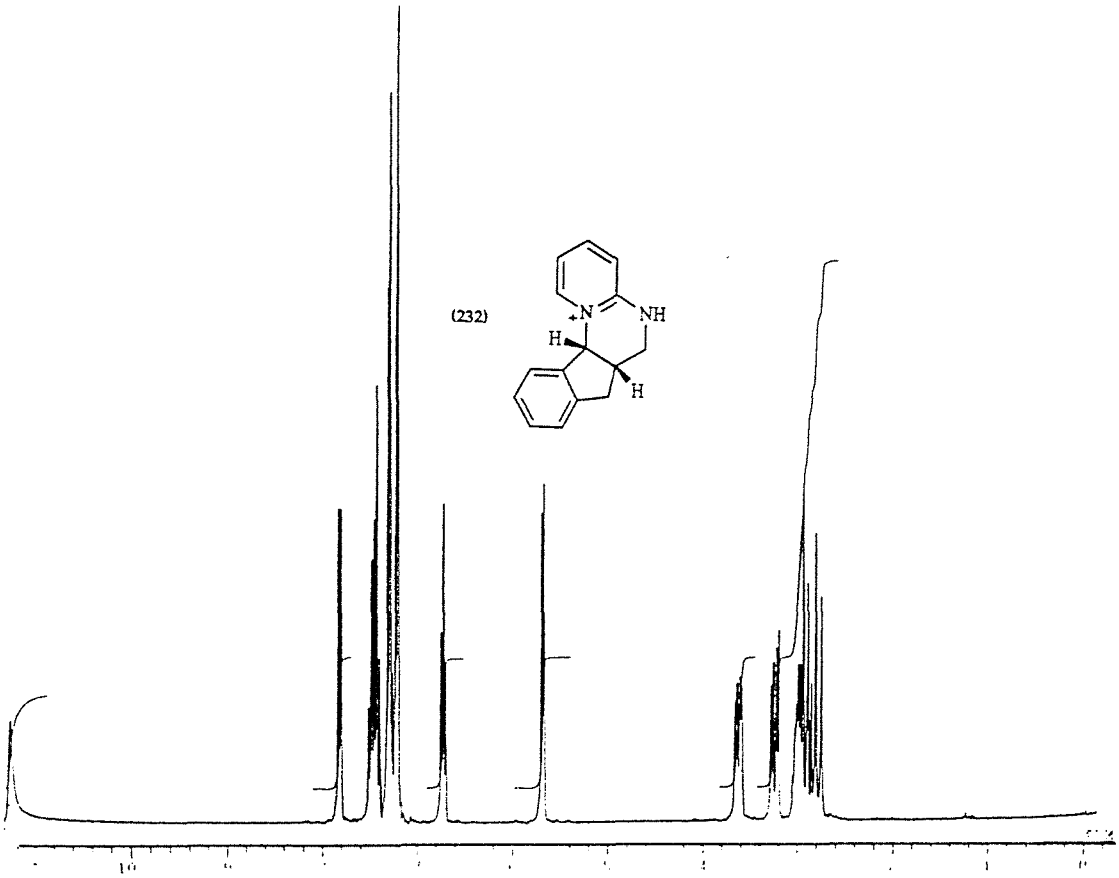
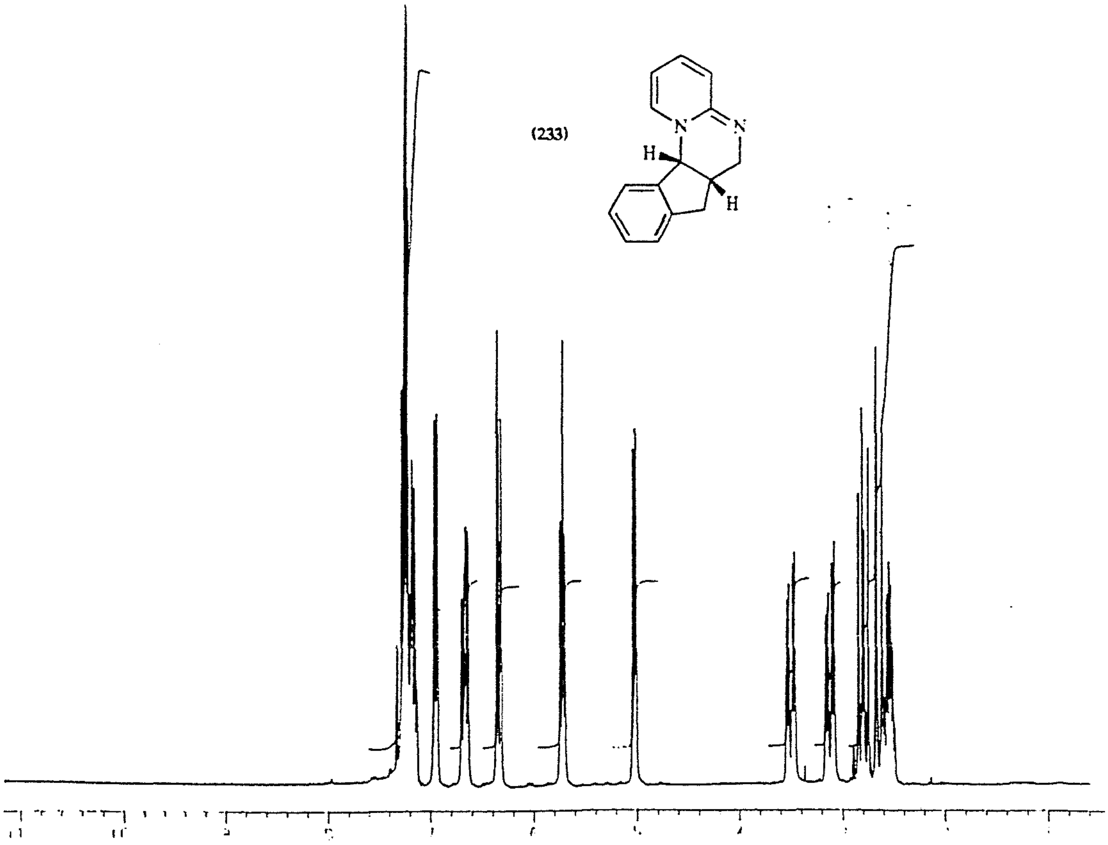
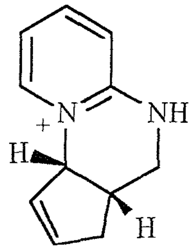


Figure 10: ^1H NMR of Salt (232) and Neutral (233) Indene Adducts.





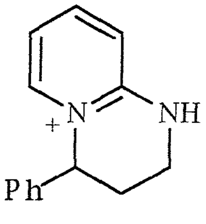
obtained again contrasted with Merriman's result, the salt (234) being obtained in fair yield (42%). The spectra of the cycloadduct (234) were very similar to those of the picoline derivative (221), allowing for the absence of the methyl substituent. When the reaction was repeated using the conditions employed by Merriman, the salt was once more obtained.



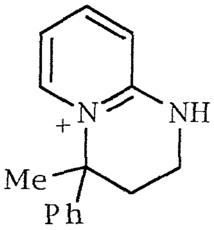
(234)

Basification of the salt gave the unstable neutral amidine (186). Since there was therefore no inconsistency with the nature of the 2-aminopyridine derivatives, the discrepancy with Merriman's result is presumably due to some aspect of the reagents used.

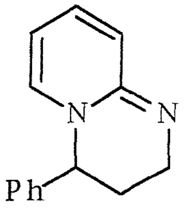
Additional studies with styrene and α-methylstyrene as the electron rich alkenes were next investigated; the analogous cycloadducts, (235) and (236), were produced, followed by the neutral species (196) and (237) upon treatment with sodium hydroxide. Interestingly, pyridopyrimidine (196) has been reported in the literature as having been synthesised from a chloroalkylaminopyridine[155] (see also page 75 (Scheme 82)).



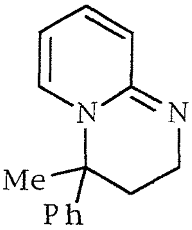
(235)



(236)



(196)



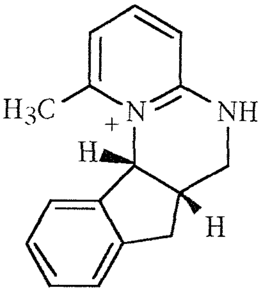
(237)

(v) 2-Amino-6-methylpyridine

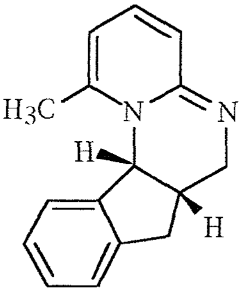
It was interesting to examine next the reaction of 2-amino-6-methylpyridine with indene. The effect of a methyl substituent had already been investigated; however, the methyl group was now in a different position that could cause steric hindrance problems in the cyclisation reaction and perhaps force an alternative reaction. In this case however, nothing unusual was observed in the product of the reaction. In accordance with the results from 2-amino-5-

methylpyridine, the trifluoroacetate salt (238) was isolated in good yield (62%). The neutral amidine (239) was readily obtained in excellent yield (98%) by basification of the salt with sodium hydroxide.

(238)

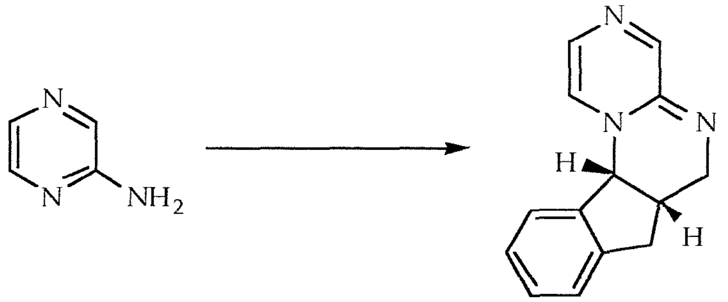


(239)



(vi) 2-Aminopyrazine

As an alternative to the 2-aminopyridines, the cyclisation between 2-aminopyrazine and indene was undertaken. since it was interesting to examine the effect that the presence of a second nitrogen in the ring would have on the outcome of the reaction. The neutral pyrazinopyrimidine (240) was isolated in fair yield (44%) as a yellow oil. Neat methanol was required to isolate the extremely polar product by flash column chromatography; hence the time and temperature needed to remove the solvent may have contributed to the decomposition of the product observed. No other products were isolated. The use of the isomeric 2-aminopyrimidine however did not give rise to a product.



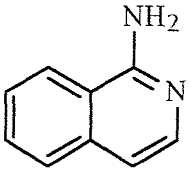
(240)

Scheme 92

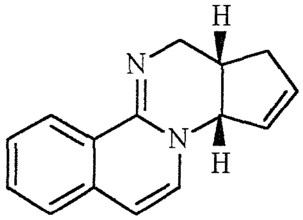
(vii) 2-Aminoisoquinoline

The syntheses of pyridopyrimidines had been successfully achieved with the use of various 2-aminopyridines, and the reaction had also been applied to the synthesis of a pyrazinopyrimidine (240) from the appropriate starting material. These favourable outcomes suggested that similar reactions of electron rich alkenes with other nitrogen heterocycles would create a general route to novel cyclic amidines. The reactions could subsequently be extended to the reactions of sulfur heterocycles, giving cyclic isothioureas.

The synthetic strategy was initially expanded with 1-aminoisoquinoline (241) as the starting amine. Although a bicyclic starting material had not previously been investigated in these reactions, the particular attraction of this amine lay in the position of the amino group. In contrast to the 2-aminopyridines, cyclisation of 1-aminoisoquinoline with an alkene was expected to yield an altogether different skeleton. In view of the interest of this thesis in azasteroids, it was appropriate that the products were likely to be steroidal amidines.
The experiment with cyclopentadiene was carried out several times since the product was found to be quite unstable during purification attempts. Nevertheless the reaction produced an excellent result, an 8,11-diazasteroid (242), which was isolated and purified in 24% yield. The nmr data was very similar to that of other cyclic amidines formed from cyclopentadiene.

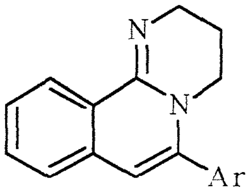


(241)



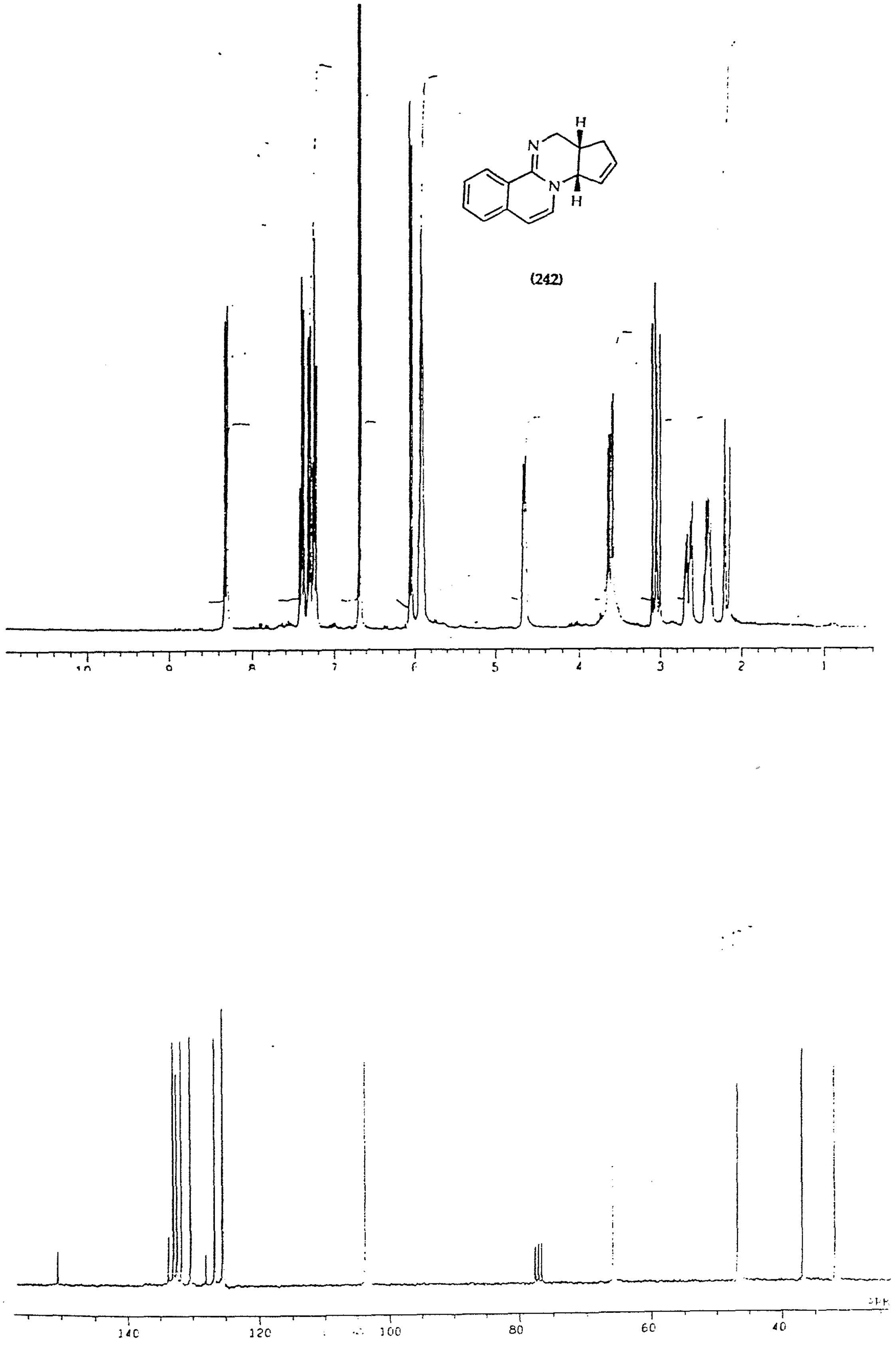
(242)

As expected, the reaction with indene proceeded smoothly and the product was easily purified to give the steroidal amidine (243) in 84% yield. In both reactions of 1-aminoisoquinoline, only the diazasteroid was isolated; no other products were detected. ^{1}H and ^{13}C nmr spectra of (242) are illustrated in Figure 11. The formation of the steroidal skeletons in a single step suggests the possibility of developing an effective route to these diazasteroids. The significance of these experiments is emphasised by considering the importance of related pyrimidoisoquinolines such as (244) which have been shown to act as antagonists to platelet activating factor.[174]

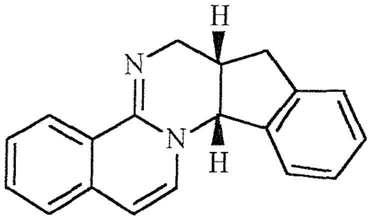


(244)

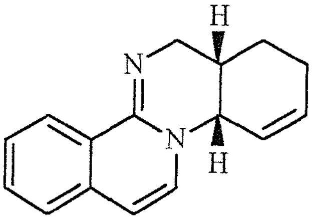
Figure 11: ^1H and ^{13}C NMR of Cyclopentadiene Adduct (242).



Having synthesised an azasteroid containing a five-membered D ring with the use of cyclopentadiene, cyclohexadiene was introduced in order to obtain a new azasteroid with a six-membered ring. The diazasteroid (245) was successfully formed and identified by ^{1}H nmr, although the purified pruduct was isolated in very low yield (5%) due to the instability of the material. ^{1}H and ^{13}C nmr spectra of (243) are illustrated in Figure 12.



(243)

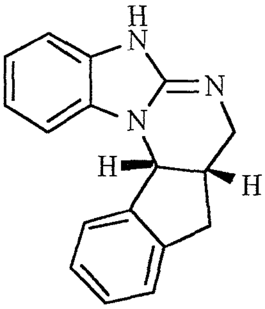


(245)

(viii) 2-Aminobenzimidazole

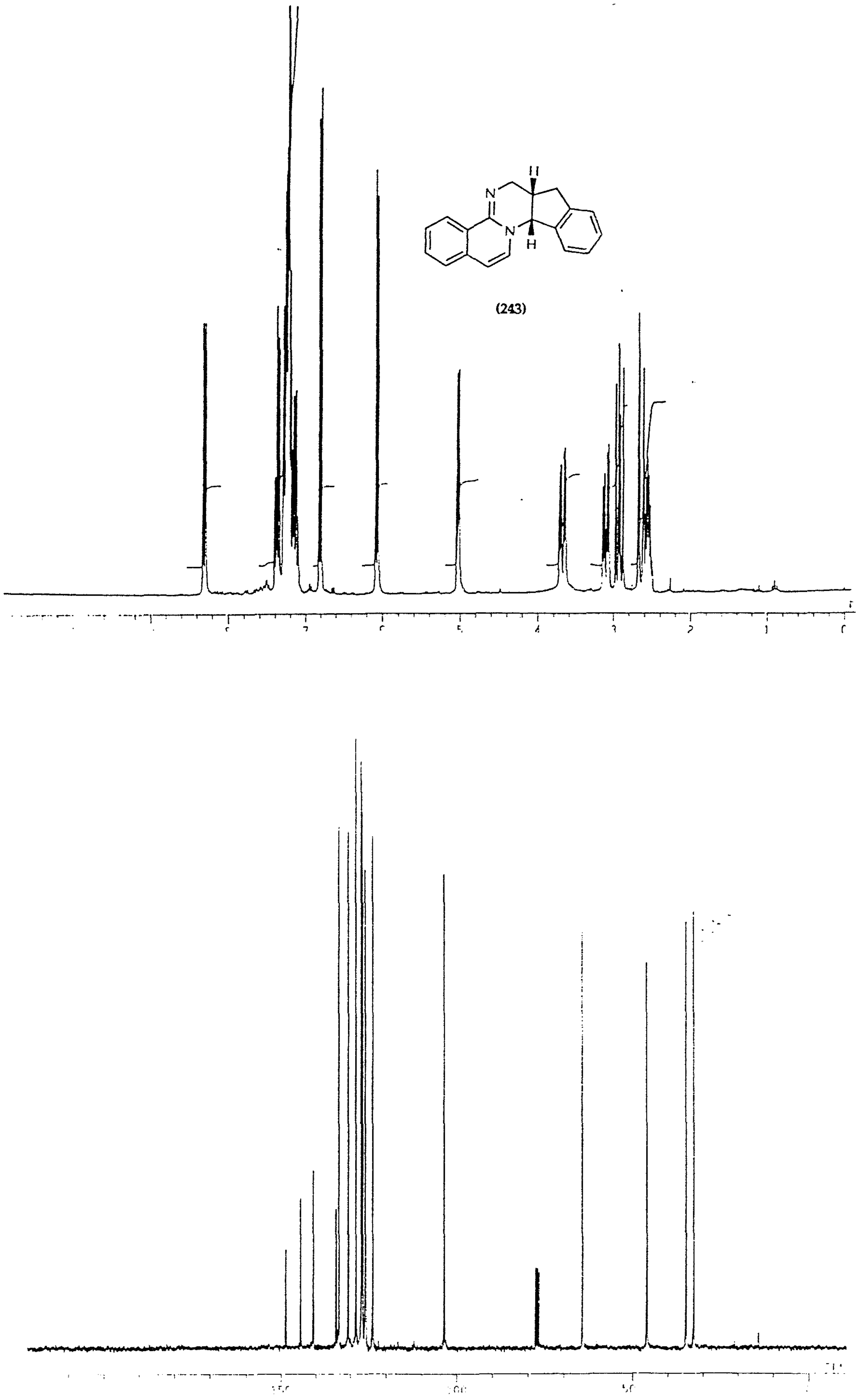
In extending the syntheses of cyclic amidines by the use of other bicyclic amines, the reaction between 2-aminobenzimidazole and indene was considered. However the reaction could not be optimised beyond a 12% yield of the product (246). The difficulties encountered during the purification attempts resulted only in impure samples being isolated, although the presence of the product was confirmed by ^{1}H nmr.

(246)



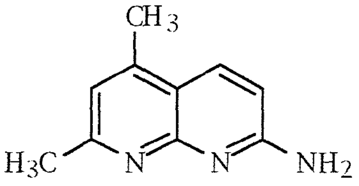
Pyrimidobenzimidazoles are well documented in the literature[169-172] and have been shown to have a wide range of biological activity.

Figure 12: ^{1}H and ^{13}C NMR of Indene Adduct (243).

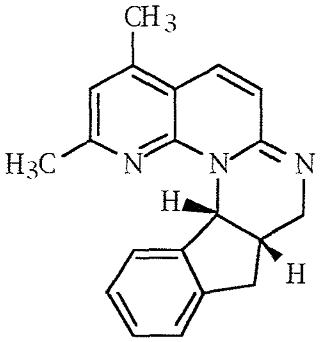


(ix) 2-Amino-5,7-dimethylnaphthyridine

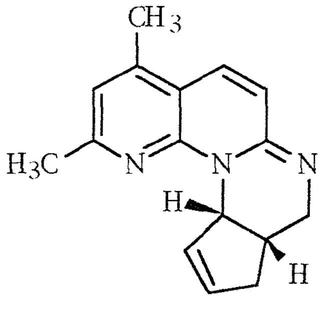
Attention was next focused on the reactions of 2-amino-5,7-dimethylnaphthyridine (247) which was successfully cyclised with indene to give the adduct (248) in 48% yield. The characteristic methylene proton signals were observed to have the usual splitting and chemical shift associated with the indene adducts previously synthesised in this series. Due to the structure of the pyrimidonaphthyridine however, the CH-N proton was in a different environment compared with the other structures in this series and was therefore observed shifted downfield at 6.42ppm. The *cis* stereochemistry was confirmed by the coupling of 5.8Hz. The reaction with cyclopentadiene gave a slightly lower yield (34%) of the product (249) which was identified from the spectroscopic data.



(247)



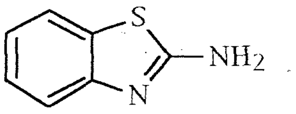
(248)



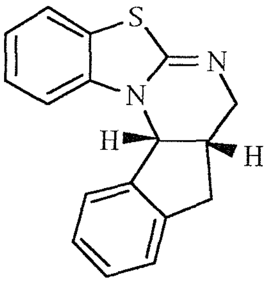
(249)

(x) 2-Aminobenzothiazole

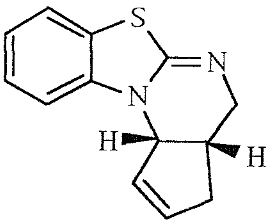
The expansion to include sulfur heterocycles in the investigations of these aza Diels-Alder reactions was initiated with the use of 2-aminobenzothiazole (250) as the starting amine. The initial reaction between the amine and indene gave the pyrimidobenzothiazole (251) in excellent yield (90%). The structure was assigned following comparison of the spectroscopic data with that of similar adducts synthesised. Reaction with cyclopentadiene also gave the adduct (252) in excellent yield (88%).



(250)



(251)

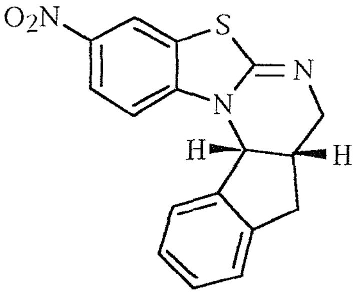


(252)

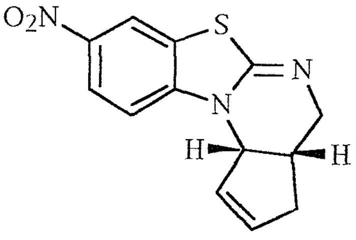
A large number of pyrimidobenzothiazoles have been reported in the literature,[163-167] and a number have been reviewed earlier in Section 2.4.3(iv). They have been shown to exhibit a wide range of biological activity and a variety of routes has been employed in their synthesis. The cyclisations shown here could prove to be a competitive route to these valuable compounds.

(xi) 2-Amino-6-nitrobenzothiazole

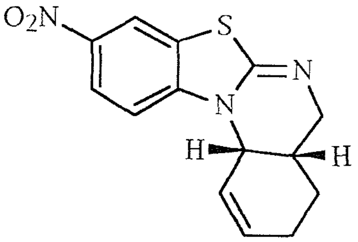
With the success of the reactions of 2-aminobenzothiazole established, it was interesting to examine the effect of a substituent in the starting material on the outcome of the reaction. The reactions of 2-amino-6-nitrobenzothiazole were therefore investigated. The nitro group was expected to increase the stability of the cycloadducts, as had been observed in the case of 2-aminopyridine investigated earlier. Basification of the trifluoroacetate salt obtained as the product in each cyclisation with 2-aminopyridine gave the very unstable neutral amidine. However, reactions of 2-amino-5-nitropyridine yielded a fairly stable product in each case. Although the pyrimidobenzothiazoles (251) and (252) had been isolated in very good yield, the products were relatively unstable once purified.
The initial reaction with indene gave the product (253) in 72%; although the yield was lower than for the corresponding adduct lacking the nitro substituent, the material was indeed more stable. The yellow solid was readily isolated and recrystallised, permitting easy identification by comparison of the spectroscopic data with the former analogue (251). The data was very similar, allowing for the presence of the nitro substituent.
Similar reactions carried out with cyclopentadiene and cyclohexadiene also gave good yields of pyrimidobenzothiazoles (254) and (255).



(253)

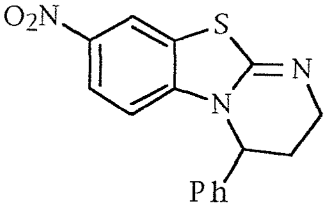


(254)

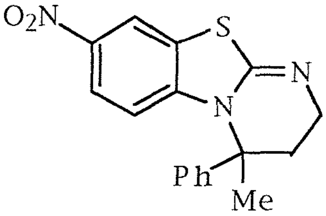


(255)

Since the reactions with 2-amino-6-nitrobenzothiazole had thus far produced stable products in good yields, the study was continued to include investigation of styrene and α-methylstyrene as the electron rich partners. The reactions were also successful and gave the adducts (256) and (257).



(256)



(257)

2.4.5 SUMMARY

The results of the cyclocondensations of 2-aminopyridines and other diverse aminoheterocycles with electron rich alkenes demonstrate that these reactions can occur in excellent yields. In contrast to work reported earlier in this thesis (Section 2.2), the iminium ion behaves as a 1,3-diazadiene equivalent to yield a variety of cyclic amidines and cyclic isothioureas. The regiochemistry is dictated by the reaction of formaldehyde at the primary amino site and selectivity is also observed in the cyclisation onto nitrogen; naphthyridine derivatives were not detected. The *cis* stereochemistry is consistent with earlier related work and was confirmed by the X-ray analyses. Aminopyridines having electron withdrawing substituents afforded neutral amidine adducts; in cases where trifluoroacetate salts were isolated it was found that the neutral amidines were very unstable. No intermediate or by-products were observed, suggesting a concerted reaction mechanism, although a stepwise process cannot be ruled out.

2.5 CONCLUSION

The main focus of the work presented in this thesis is the synthesis of two target structures, azasteroids and cyclic amidines, with the aza Diels-Alder reaction employed as the principal synthetic tool in the routes illustrated.

The importance of azasteroids can be attributed to two main factors: their bioactivity and the challenge of their synthesis. Here, the synthesis of novel azasteroids with potential anti-fungal activity was approached using two complementary routes: total synthesis (via aza Diels-Alder reactions) and partial synthesis (via the degradation of lanosterol). The acid catalysed Diels-Alder reactions reported by Grieco[22] were extended by Gregoire[25] and Merriman[26] who produced a variety of interesting skeletons using diverse amines and dienophiles. Subsequently, we have applied this method to the total synthesis of azasteroids involving the cycloaddition reactions of aromatic iminium ions, generated from bicyclic amines, with electron rich alkenes. With the iminium ions acting as 2-azadiene equivalents, the reactions with methylcyclopentadiene and cyclohexadiene yielded a selection of 7-azasteroids. The behaviour of cyclohexadiene as both dienophile and diene to give interesting azabicyclo compounds, in addition to azasteroids, was significant in the consideration of the reaction mechanism and a non-concerted process was proposed, consistent with the conclusions of Gregoire and Merriman. Although the biological testing of the novel azasteroids as anti-fungal agents proved inconclusive, the significant aspect of this work was the development of a simple route to these desireable molecules. In contrast, the complementary partial synthesis route involving the degradation of lanosterol was based on a series of reactions designed to manipulate the molecule. The oxime derivatives formed were rearranged to incorporate nitrogen into the steroid skeleton and yielded some B-homo azasteroids which were very stable, hindering further progress. Hence we conclude that the Diels-Alder route is the more successful in this work due to the rapid and facile access to azasteroids.

As with azasteroids, the biological activity of cyclic amidines has long attracted interest and the application of the aza Diels-Alder reaction to establish a new route to such compounds was an interesting prospect. In contrast to the behaviour of iminium ions as 2-azadienes in the formation of azasteroids, the iminium ion formed from 2-aminopyridines acted as a 1,3-diazadiene equivalent in the reactions with diverse electron rich alkenes such as indene and styrene to give rise to a variety of pyrido[1,2-*a*]pyrimidines. The nature of the isolated products, either neutral amidines or trifluoroacetate salts, was a reflection of the basicity of the appropriate amidine and the structure of these products was confirmed by single crystal X-ray analysis of both types of product. As a consequence these structural studies established the regiochemistry and *cis* stereochemistry, which was consistent with spectroscopic observations, and therefore by analogy could be assigned in related processes. Finally, the high yielding simplicity of these reactions encouraged the expansion of these studies to include other aminoheterocyclic starting materials such as 2-aminobenzothiazoles and 1-aminoisoquinoline, resulting in a series of cyclic isothioureas and diazasteroids. Considering the close relationship of the diverse series of skeletons synthesised and reported in this thesis to compounds of known biological activity, it is evident that the aza Diels-Alder reaction may be regarded as a powerful synthetic tool.

EXPERIMENTAL

3.1 GENERAL PROCEDURES AND ANALYTICAL INSTRUMENTATION

(1) In the following script, "ether" refers to diethyl ether and "petrol" refers to petroleum ether (b.p. 40-60°C).

(2) Cyclopentadiene, methylcyclopentadiene and indene were freshly distilled before use.

(3) Analytical thin layer chromatography (t.l.c) was carried out using precoated silica gel plates (SIL G-25UV$_{254}$,0.25mm. Macherey-Nagel) or precoated basic aluminium oxide plates (SIL G-25UV$_{254}$, 0.25mm. Macherey-Nagel). Compounds were visualised by UV fluorescence.

(4) Flash column chromatography was carried out according to the method of Still *et al*[179] using silica gel (C60 Sorbisil, May and Baker) or deactiviated (3% by weight of water) basic aluminium oxide (pH 9.3-9.7, type 5016A, Fluka).

(5) Melting points were determined using Electrothermal melting point apparatus and are uncorrected.

(6) Elemental analyses were performed at DowElanco Laboratories, Wantage.

(7) Analytical and preparative high performance liquid chromatography was carried out at DowElanco Laboratories, Wantage.

(8) Mass spectra were run using the electron impact ionisation technique (source temperature 200°C, ionisation energy 70eV, source voltage 6kV) on a normal geometry, double-focusing VG analytical 70-250-SE spectrometer or Finnigan-MAT TSQ 70 triple sector quadrupole mass spectrometer at DowElanco Laboratories, Wantage.

(9) Infrared spectra were recorded on a Perkin-Elmer 298 spectrometer as a Nujol mull or as chloroform solutions in sodium chloride cells (0.1mm thickness). Absorption maxima are quoted in wave numbers (cm^{-1}) relative to the polystyrene standard. The following abbreviations are used to describe the absorpton: s-strong, m-medium, w-weak, br-broad. Spectra measured at DowElanco Laboratories, Wantage were recorded using a Perkin Elmer 1760X FTIR.

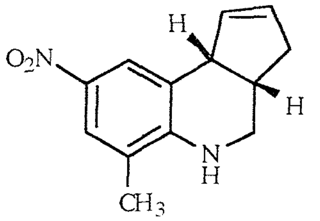
(10) ^1H Nuclear magnetic resonance spectra were recorded at 270MHz on a Jeol JNM-GX270 spectrometer or at 300MHz on a Bruker WH-300 spectrometer. The operating frequency of the spectrometer is given in brackets. Chemical shifts are quoted as δ-values

and coupling constants (J) are given in Hz. Tetramethysilane was used as the internal standard and deuteriochloroform was used as the solvent unless otherwise stated. The following abbreviations are used to describe the resonances: s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet and br-broad. Spectra measured at DowElanco Laboratories, Wantage were recorded on a Bruker AC 250 spectrometer.

(10) ^{13}C Nuclear magnetic resonance spectra were recorded at 68MHz on a Jeol JNM-GX270 spectrometer or at 75MHz on a Bruker WH-300 spectrometer (^{1}H decoupled).

3.2 TETRALONE AND INDANONE SERIES

(3aα, 9bα)- 3a,4,5,9b-Tetrahydro-6-methyl-8-nitro-3*H*-cyclopenta[c]quinoline (131)

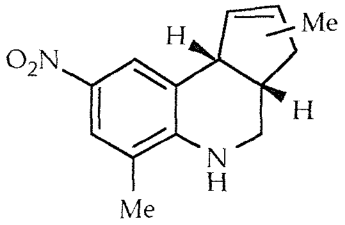


2-Methyl-4-nitroaniline (1.52g, 10mmol) was added to acetonitrile (7.1ml) containing one equivalent of trifluoroacetic acid (1.14g, 10mmol) to give a 1.4M amine concentration. To this yellow suspension was added with stirring, a heterogeneous mixture at 0°C of cyclopentadiene (3.3g, 50mmol) and 37% formalin solution (4.05g, 50mmol) which gave a yellow solution after 5min. The mixture was stirred at room temeperature under nitrogen for 1h. and then worked up to give a brown oil (4.12g) which was purified using flash chromatography on deactivated basic alumina to give the adduct (131) as a yellow solid (1.22g, 53%, eluant 3/1 dichloromethane / petrol). Recrystallisation of (131) from methanol gave a dark yellow crystalline solid (mp. 150-152°C).

δH(270MHz) 7.90 (1H, d, *J* 2.7, ArC$_9$-$\underline{H}$); 7.87 (1H, d, *J* 2.7, ArC$_7$-$\underline{H}$); 5.92 (1H, m, =C$\underline{H}$); 5.85 (1H, m, =C$\underline{H}$); 4.52 (1H, br.s, N-$\underline{H}$); 3.72 (1H, m, C$\underline{H}$); 3.21 (1H, ddd, *J* 11.6, 4.7, 3.6, C$\underline{H}_2$-N); 2.84 (1H, m, C$\underline{H}_2$-N); 2.72-2.68 (2H, m, C$\underline{H}_2$-C=C$\underline{H}$); 2.12-2.10 (4H, m, C$\underline{H}_2$-C=ArC$_2$-C$\underline{H}_3$).

δC(68MHz) 150.24 (Ar$\underline{C}_{5a}$-N); 137.53 (Ar$\underline{C}_8$-NO$_2$); 135.28 (=$\underline{C}$H); 128.91 (=$\underline{C}$H'); 124.35 (Ar$\underline{C}_9$-H); 123.67 (Ar$\underline{C}_7$-H); 122.19 (Ar$\underline{C}_{9a}$-C); 121.18 (Ar$\underline{C}_6$-CH$_3$); 46.27 ($\underline{C}$H); 43.39 ($\underline{C}$H$_2$-N); 37.25 ($\underline{C}$H$_2$-C=); 34.76 ($\underline{C}$H); 17.11 (ArC$_6$-$\underline{C}$H$_3$).

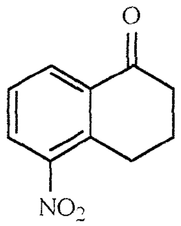
Cyclocondensation of 2-methyl-4-nitroaniline with methylcyclopentadiene leading to isomeric mixture (132)



2-Methyl-4-nitroaniline (1.00g, 6.58mmol) was added to acetonitrile (4.7ml) containing one equivalent of trifluoroacetic acid (0.75g, 10mmol) to give a 1.4M amine concentration. To this yellow suspension was added with stirring, a heterogeneous mixture at 0°C of methylcyclopentadiene (2.63g, 32.9mmol) and 37% formalin solution (2.66g, 50mmol) which gave a dark yellow solution after 5min. The mixture was stirred at room temeperature under nitrogen for 1h. and then worked up to give a dark brown oil (4.68g) which was purified using flash chromatography on deactivated basic alumina to give the isomeric mixture (132) as a dark yellow oil (1.55g, eluant 3/1 dichloromethane / petrol). ^{1}H nmr analysis indicated three major isomers which could not be separated by HPLC. GC-MS analysis detected four fractions.

Fraction 1 (3a- or 9b-methyl): m/z=Found: 244 (M^+ 52%); 229 (100); 212 (10); 183 (51); 168 (26). $C_{14}H_{16}N_2O_2$ requires 244.
Fraction 2 (cyclopentadiene adduct (131)): m/z=Found: 230 (M^+ 100%); 215 (22); 202 (31); 189 (33); 183 (26); 168 (22); 143 (20). $C_{13}H_{14}N_2O_2$ requires 230.
Fraction 3 (1- or 2-methyl): m/z=Found: 244 (M^+ 100%); 229 (29); 216 (22); 202 (26); 189 (40); 143 (24). $C_{14}H_{16}N_2O_2$ requires 244.
Fraction 4 (1- or 2-methyl): m/z=Found: 244 (M^+ 100%); 229 (54); 197 (23); 189 (51); 183 (30); 168 (20); 143 (22). $C_{14}H_{16}N_2O_2$ requires 244.

5-Nitro-α-tetralone (134)

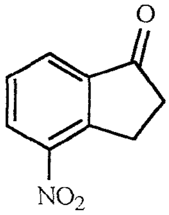


α-Tetralone (1.00g, 6.84mmol) was added dropwise over 30 min. with stirring to fuming nitric acid (10.0ml) so that the yellow mixture was maintained below -5°C. The solution was stirred for a further 1h. at this temperature. The yellow mixture was poured into ice and stirred for 40 min. The heterogeneous mixture obtained was filtered and the residue was washed with cold water and dried to give a dark yellow solid. Flash column chromatography on silica gel (eluant petrol / ethyl acetate 80/20 - 50/50) gave two main fractions.

(134) 5-Nitro-α-tetralone (0.29g, 22%).
Recrystallisation from ethanol gave pale yellow needles, mp. 102°C, lit[139] 102.5°C.
δH (270MHz, $CDCl_3$) 8.35 (1H, dd, *J* 8.0, 1.6, ArC$_6$-$\underline{H}$); 8.08 (1H, dd, *J* 8.1, 1.6, ArC$_8$-$\underline{H}$); 7.50 (1H, t, *J* 7.9, ArC$_7$-$\underline{H}$); 3.10 (2H, t, *J* 6.0, C$_2$-$\underline{H}_2$); 2.70 (2H, t, *J* 6.0, C$_4$-$\underline{H}_2$); 2.10 (2H, m, C$_3$-$\underline{H}_2$).
δC (68MHz, $CDCl_3$) 196.12 ($\underline{C}$=O); 149.45 (Ar$\underline{C}$-NO_2); 138.59 (Ar$\underline{C}_{quat}$); 134.55 (Ar$\underline{C}_{quat}$); 132.22 (Ar$\underline{C}$-H); 128.96 (Ar$\underline{C}$-H); 127.13 (Ar$\underline{C}$-H); 38.27 ($\underline{C}H_2$); 26.49 ($\underline{C}H_2$); 22.30 ($\underline{C}H_2$).

(135) 7-Nitro-α-tetralone (0.72g, 55%).
Recrystallisation from ethanol gave yellow needles, mp. 105°C, lit[139] 105°C.
δH (270MHz, $CDCl_3$) 8.80 (1H, d, *J* 2.5, ArC$_8$-$\underline{H}$); 8.27 (1H, dd, *J* 9.0, 2.5, ArC$_6$-$\underline{H}$); 7.50 (1H, d, *J* 9.0, ArC$_5$-$\underline{H}$); 3.12 (2H, t, *J* 6.0, C$_2$-$\underline{H}_2$); 2.75 (2H, t, *J* 6.0, C$_4$-$\underline{H}_2$); 2.23 (2H, m, C$_3$-$\underline{H}_2$).

4-Nitro-α-indanone (137)

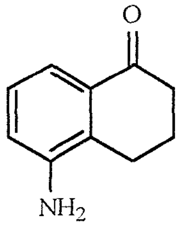


Potassium nitrate (1.67g, 16.5mmol); dissolved in concentrated sulfuric acid (6.0ml) was added dropwise with stirring over 30min. to a solution of α-indanone (2.0g, 15.1mmol) in concentrated sulfuric acid (17.0ml), previously cooled to 0°C, which caused the temperature of the mixture to rise to 5°C. The orange mixture was stirred for 4h. and the temperature maintained between 0°C and 10°C. The red reaction mixture was poured onto ice, stirred for 30 min. and extracted with dichloromethane (5x100ml). The organic fractions were combined, dried over anhydrous magnesium sulfate, and the solvent evaporated to yield a brown solid. Flash column chromatography on silica gel (eluant petrol / ethyl acetate 80/20 - 50/50) gave two main fractions.

(137) 4-Nitro-α-indanone (0.51g, 20%).
Recrystallisation from ethanol gave pale yellow needles, mp. 104-105°C, lit[140] 105°C.
δH (270MHz, $CDCl_3$) 8.48 (1H, d, *J* 8.1, $ArC_5\text{-}\underline{H}$); 8.09 (1H, d, *J* 7.5, $ArC_7\text{-}\underline{H}$); 7.64 (1H, dd, *J* 8.1, 7.5, $ArC_6\text{-}\underline{H}$); 3.66 (2H, m, $C_3\text{-}\underline{H}_2$); 2.82 (2H, m, $C_2\text{-}\underline{H}_2$).
δC (68MHz, $CDCl_3$) 204.64 ($\underline{C}$=O); 149.81 ($Ar\underline{C}\text{-}NO_2$); 146.40 ($Ar\underline{C}_{quat}$); 140.19 ($Ar\underline{C}_{quat}$); 130.03 (Ar$\underline{C}$-H); 129.73 (Ar$\underline{C}$-H); 128.86 (Ar$\underline{C}$-H); 35.85 ($\underline{C}H_2$); 26.94 ($\underline{C}H_2$).

(138) 6-Nitro-α-indanone (1.12g, 44%).
Recrystallisation from ethanol gave yellow/brown crystals, mp. 74-75°C, lit[140] 75°C.
δH (270MHz, $CDCl_3$) 8.45 (2H, m, $ArC_5\text{-}\underline{H}$, $ArC_7\text{-}\underline{H}$); 7.75 (1H, d, *J* 8.0, $ArC_4\text{-}\underline{H}$); 3.36 (2H, m, $C_3\text{-}\underline{H}_2$); 2.88 (2H, m, $C_2\text{-}\underline{H}_2$).

5-Amino-α-tetralone (142)

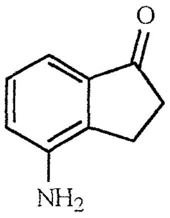


5-Nitro-α-tetralone (0.28g, 1.46mmol) was dissolved in glacial acetic acid (5.0ml) to give a yellow liquid. While warming, water (3.0ml) was slowly added with stirring to give a homogeneous yellow solution at approximately 60°C. Iron powder (0.33g, 5.91mmol) was added slowly with further stirring so that the temperature was maintained between 70°C and 90°C. The dark grey heterogeneous mixture was stirred under these conditions for 40 min. and was allowed to cool to room temperature, diluted with water (150ml) and neutralized to pH=8 by the slow addition of solid sodium bicarbonate. The mixture was extracted with dichloromethane (5x100ml); the organic layers were combined, dried over anhydrous magnesium sulfate, filtered, and the solvent removed to yield a brown solid. Flash column chromatography on silica gel (eluant petrol / ethyl acetate 50/50) gave the title compound as a yellow powder (0.23g, 96%), mp. 116-118°C, lit[143] 119-120°C.

δH (270MHz, $CDCl_3$) 7.50 (1H, dd, *J* 7.7, 1.4, ArC_8-H); 7.10 (1H, t, *J* 7.8, ArC_7-H); 6.90 (1H, dd, *J* 7.8, 1.4, ArC_6-H); 3.70 (2H, s, NH_2); 2.60 (4H, m, C_2-H_2, C_4-H_2); 2.10 (2H, m, C_3-H_2).

δC (68MHz, $CDCl_3$) 199.02 (C=O); 144.25 (ArC-NH_2); 133.24 (ArC_{quat}); 128.72 (ArC_{quat}); 126.76 (ArC-H); 119.72 (ArC-H); 117.31 (ArC-H); 38.51 (CH_2); 23.80 (CH_2); 22.21 (CH_2).

4-Amino-α-indanone (143)

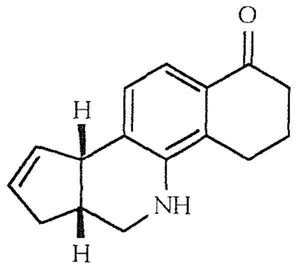


4-Nitro-α-indanone (2.0g, 11.4mmol) was dissolved in glacial acetic acid (20.0ml). While warming the solution, water (16.0ml) was slowly added with stirring to give a homogeneous yellow solution at approximately 60°C. Iron powder (2.55g, 45.5mmol) was added slowly with stirring with the temperature being maintained between 70°C and 90°C. The dark grey heterogeneous mixture was stirred under these conditions for 2h. The solution was allowed to cool to room temperature, diluted with water (300ml) and neutralized to pH=8 by the slow addition of solid sodium bicarbonate. The mixture was extracted with dichloromethane (5x100ml); the organic fractions were combined, dried over anhydrous magnesium sulfate, filtered, and the solvent evaporated to yield a brown solid. Flash column chromatography on silica gel (eluant petrol / ethyl acetate 50/50) gave the title compound as a pale yellow powder (1.43g, 86%), mp. 164-166°C, lit[143] 167°C.

δH (270MHz, $CDCl_3$) 7.17 (2H, m, ArC_5-H, ArC_7-H); 6.87 (1H, dd, *J* 6.2, 2.5, ArC_6-H); 4.00 (2H, s, NH_2); 2.86 (2H, m, C_2-H_2); 2.66 (2H, m, C_3-H_2).

δC (68MHz, $CDCl_3$) 203.02 (C=O); 146.25 (ArC-NH_2); 138.33 (ArC_{quat}); 133.28 (ArC_{quat}); 124.67 (ArC-H); 120.63 (ArC-H); 109.52 (ArC-H); 38.99 (CH_2); 29.05 (CH_2).

(6aα, 9aα)-1-Oxo-1,2,3,4,5,6,6a,9a-octahydro-benzo[*h*]-7*H*-cyclopenta[1,2-*c*]quinoline (144)



Trifluoroacetic acid (0.14g, 1.23mmol) in acetonitrile (1.0ml) was added to 5-amino-α-tetralone (0.20g, 1.24mmol) dissolved in acetonitrile (5.0ml) to give a 0.21M solution of the amine. After 10min. of stirring under nitrogen, a mixture at 0°C of cyclopentadiene (0.08g, 1.21mmol) and formalin solution 37% (0.10g, 1.23mmol) in acetonitrile (2.0ml) was added to the yellow solution which turned dark red. The reaction mixture was stirred under nitrogen at room temperature for a further 35min. The reaction mixture was added to a saturated sodium bicarbonate solution (100ml) and was extracted with dichloromethane (3x100ml). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure to yield a brown oil. Flash column chromatography on silica gel (eluant petrol / ethyl acetate 90/10) gave the title compound as a yellow solid (0.21g, 68%), mp. 121-128°C. Recrystallisation of the cycloadduct was attempted with no significant improvement in purity.

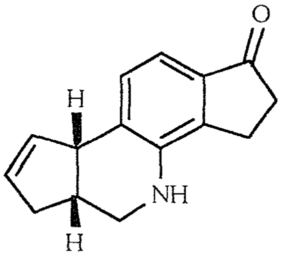
δH (270MHz, $CDCl_3$) 7.56 (1H, d, *J* 7.9, ArC_{11}-$\underline{H}$); 7.11 (1H, d, *J* 7.9, ArC_{10}-$\underline{H}$); 5.88 (1H, m, =C_9-$\underline{H}$-CH); 5.67 (1H, m, =C_8-$\underline{H}$-CH_2); 3.90 (1H, m, C_{9a}-$\underline{H}$-CH=); 3.83 (1H, m, N$\underline{H}$); 3.23 (1H, dd, *J* 11.0, 4.1, C_6-$\underline{H}_2$-NH); 2.80 (1H, m, C_6-$\underline{H}_2$-NH); 2.70 (2H, m, C_7-$\underline{H}_2$-CH=, C_{6a}-$\underline{H}$-CH_2); 2.60 (4H, m, C_2-$\underline{H}_2$, C_4-$\underline{H}_2$); 2.24 (3H, m, C_3-$\underline{H}_2$, C_7-$\underline{H}_2$-CH=).

δC (68MHz, $CDCl_3$) 198.71 ($\underline{C}$=O); 143.29 (Ar$\underline{C}_{quat}$-NH); 135.33 ($\underline{C}_9$-H=CH); 130.88 (Ar$\underline{C}_{quat}$); 129.72 (Ar$\underline{C}_{quat}$); 128.19 ($\underline{C}_8$-H=CH); 127.17 (Ar$\underline{C}_{quat}$); 126.68 (Ar$\underline{C}$-H); 116.27 (Ar$\underline{C}$-H); 46.92 ($\underline{C}_{9a}$-H-CH=); 44.56 ($\underline{C}_6$-H_2-NH); 38.34 ($\underline{C}H_2$); 37.48 ($\underline{C}H_2$); 35.69 ($\underline{C}_{6a}$-H-CH_2); 23.71 ($\underline{C}H_2$); 22.24 ($\underline{C}H_2$).

υ_{max}/cm^{-1} ($CHCl_3$) 3440 (w, N-H); 3010 (w); 2950 (m); 2860 (w, C-H); 1690 (s, C=O); 1600 (m); 1575 (s); 1480 (m); 1345 (s); 1325 (s); 1285 (s).

m/z= Found: 239.13 (M^+ 100%); 224 (22); 211 (30); 198 (41); 183 (37); 168 (15). $C_{16}H_{17}NO$ requires 239.13.

(5aα, 8aα)-1-Oxo-1,2,4,5,5a,8a-hexahydro-3*H*, 6*H*-dicyclopenta[1,2-*c*:1,2-*h*]quinoline (145)



Trifluoroacetic acid (0.16g, 1.40mmol) in acetonitrile (1.0ml) was added to 4-amino-α-indanone (0.20g, 1.36mmol) dissolved in acetonitrile (5.0ml) to give yellow solution. After 10min. of stirring under nitrogen, a mixture at 0°C of cyclopentadiene (0.09g, 1.36mmol) and formalin solution 37% (0.12g, 1.40mmol) in acetonitrile (5.0ml) was added to the former solution which turned dark red. The reaction mixture was stirred under nitrogen at room temperature for a further 1h. The reaction mixture was added to saturated sodium bicarbonate solution (100ml) and was extracted with dichloromethane (3x100ml). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure to yield a brown oil. Flash column chromatography on silica gel (eluant petrol / ethyl acetate 90/10) isolated one major fraction as a yellow solid, (0.21g, 68%), mp 138-142°C. Recrystallisation of the cycloadduct was attempted with no significant improvement in purity.

δH (270MHz, $CDCl_3$) 7.18 (1H, d, *J* 7.8, ArC_{10}-$\underline{H}$); 7.12 (1H, d, *J* 7.8, ArC_9-$\underline{H}$); 5.81 (1H, m, $=C_8$-$\underline{H}$-CH); 5.71 (1H, m, $=C_7$-$\underline{H}$-CH_2); 3.94 (1H, m, C_{8a}-$\underline{H}$-CH=); 3.85 (1H, s, N-$\underline{H}$); 3.21 (1H, dd, *J* 10.8, 4.4, C_5-$\underline{H_2}$-NH); 2.91 (1H, dd, *J* 10.8, 8.5, C_5-$\underline{H_2}$-NH); 2.75 (4H, m, C_6-$\underline{H_2}$-CH=, C_{5a}-$\underline{H}$-CH_2, C_2-$\underline{H_2}$); 2.65 (2H, m, C_3-$\underline{H_2}$); 2.19 (1H, m, C_6-$\underline{H_2}$-CH=).

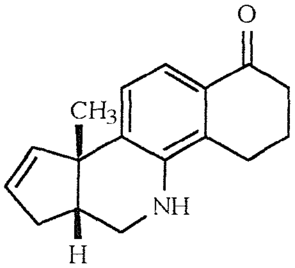
δC (68MHz, $CDCl_3$) 207.10 ($\underline{C}$=O); 143.07 (Ar$\underline{C}_{quat}$-NH); 140.86 (Ar$\underline{C}_{quat}$); 135.30 ($\underline{C}_8$-H=CH); 129.81 (Ar$\underline{C}_{quat}$); 129.32 (Ar$\underline{C}$-H); 129.15 (Ar$\underline{C}$-H); 112.42 (Ar$\underline{C}$-H); 46.47 ($\underline{C}_{8a}$-H-CH=); 44.04 ($\underline{C}_5$-H_2-NH); 37.17 ($\underline{C}H_2$); 36.32 ($\underline{C}H_2$); 35.73 ($\underline{C}_{5a}$-H-CH_2); 22.37 ($\underline{C}H_2$).

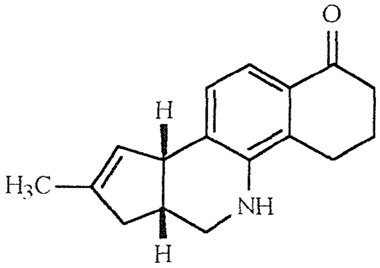
υ_{max}/cm^{-1} ($CHCl_3$) 3445 (w, N-H); 3013 (w); 2948 (m); 2871 (w, C-H); 1686 (s, C=O); 1610 (m); 1585 (s); 1345 (s); 1328 (s); 1287 (s).

m/z= Found: 225.13 (M+ 100%); 213 (20); 189 (32); 172 (31); 143 (33); 112 (15). $C_{16}H_{17}NO$ requires 225.12.

(6aα, 9aα)-1-Oxo-1,2,3,4,5,6,6a,9a-octahydro-benzo[*h*]-7*H*-9a-methyl-cyclopenta[1,2-*c*]quinoline (150)

(6aα, 9aα)-1-Oxo-1,2,3,4,5,6,6a,9a-octahydro-benzo[*h*]-7*H*-8-methyl-cyclopenta[1,2-*c*]quinoline (151)





Trifluoroacetic acid (0.70g, 6.21mmol) in acetonitrile (20.0ml) was added to 5-amino-α-tetralone (1.00g, 6.21mmol) dissolved in acetonitrile (20.0ml) to give a yellow solution of the amine. After 15min. of stirring under nitrogen, a mixture at 0°C of methylcyclopentadiene freshly distilled from its dimer (0.50g, 6.21mmol) and formalin solution 37% (0.50g, 6.21mmol) in acetonitrile (20.0ml) was added to the former solution which turned dark brown. The reaction mixture was stirred under nitrogen at room temperature for a further 35min. and then added to saturated sodium bicarbonate solution (100ml) and was extracted with dichloromethane (3x100ml). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure to yield a brown oil. Flash column chromatography on silica gel (eluant petrol / ethyl acetate 90/10) afforded the two title compounds in one major fraction as a brown oil, 1.10g, 70%). Small scale preparative reverse phase HPLC using methanol and water afforded the pure title compounds in approximately 1:1 ratio.

(150) 3.4mg, 0.2% (based on total starting material initially used).
δH (250MHz, $CDCl_3$) 7.47 (1H, d, *J* 7.7, ArC_{11}-$\underline{H}$); 7.13 (1H, d, *J* 7.8, ArC_{10}-$\underline{H}$); 5.41 (1H, m, =C_9-$\underline{H}$-CH); 3.94 (1H, m, C_{9a}-$\underline{H}$-CH=); 3.70 (1H, s, N-$\underline{H}$); 3.20 (1H, dd, *J* 10.6, 2.4, C_6-$\underline{H}_2$-NH); 2.95 (1H, dd, *J* 10.6, 5.6, C_6-$\underline{H}_2$-NH); 2.75 (6H, m, C_{6a}-$\underline{H}$-CH_2, C_7-$\underline{H}_2$-CH=, C_2-$\underline{H}_2$, C_4-$\underline{H}_2$); 2.21 (1H, m, C_7-$\underline{H}_2$-CH=, C_3-$\underline{H}_2$); 1.72 (3H, s, $C\underline{H}_3$).

δC (68MHz, $CDCl_3$) 198.58 ($\underline{C}$=O); 142.98 (Ar$\underline{C}_{quat}$-NH); 139.43 (Ar$\underline{C}_{quat}$); 138.64 ($\underline{C}_9$-H=CH); 133.88 (Ar$\underline{C}_{quat}$); 131.63 (Ar$\underline{C}_{quat}$); 128.27 (Ar$\underline{C}$-H); 122.75 (Ar$\underline{C}_{quat}$); 115.96 (Ar$\underline{C}$-H); 47.79 ($\underline{C}_{9a}$-H-CH=); 43.38 ($\underline{C}_6$-H_2-NH); 41.69 ($\underline{C}H_2$); 34.43 ($\underline{C}H_2$); 34.20 ($\underline{C}_{6a}$-H-CH_2); 22.48 ($\underline{C}H_2$); 18.39 ($\underline{C}H_3$).

υ_{max}/cm^{-1} ($CHCl_3$) 3410 (w, N-H); 3005 (w); 2920 (m, C-H); 2830 (m); 1680 (s, C=O); 1585 (m); 1500 (w, N-H); 1353 (m); 1325 (m); 1282 (s); 1222 (m); 754 (s, ArC-H); 665 (w).

m/z= Found: 253.15 (M^+ 100%); 214 (8); 202 (14); 173 ($(M-C_6H_8)^+$ 21); 125 (9); 91 (13); 61 (34). $C_{17}H_{19}NO$ requires 253.15.

Elemental Analysis= Found: $\underline{C}$ 79.9; $\underline{H}$ 8.0; $\underline{N}$ 5.4%.
$C_{17}H_{19}NO$ requires $\underline{C}$ 80.6; $\underline{H}$ 7.6; $\underline{N}$ 5.5%.

(151) 2.1mg, 0.4% (based on total starting material initially used).
δH (250MHz, $CDCl_3$) 7.49 (1H, d, *J* 7.8, ArC$_{11}$-$\underline{H}$); 7.19 (1H, d, *J* 7.8, ArC$_{10}$-$\underline{H}$); 5.84 (1H, m, =C$_9$-$\underline{H}$-CH); 5.60 (1H, m, =C$_8$-$\underline{H}$-CH$_2$); 3.98 (1H, s, N-$\underline{H}$); 3.35 (1H, dd, *J* 9.9, 2.2, C$_6$-$\underline{H_2}$-NH); 3.05 (1H, dd, *J* 10.0, 8.6, C$_6$-$\underline{H_2}$-NH); 2.60 (4H, m, C$_7$-$\underline{H_2}$-CH=, C$_{6a}$-$\underline{H}$-CH$_2$, C$_2$-$\underline{H_2}$); 2.40 (3H, m, C$_7$-$\underline{H_2}$-CH=, C$_4$-$\underline{H_2}$); 2.20 (2H, m, C$_3$-$\underline{H_2}$); 1.45 (3H, s, CH$_3$).

δC (68MHz, $CDCl_3$) 198.68 ($\underline{C}$=O); 142.84 (Ar$\underline{C}_{quat}$-NH); 140.26 (Ar$\underline{C}_{quat}$); 139.99 ($\underline{C}_9$-H=CH); 134.53 (Ar$\underline{C}_{quat}$); 132.48 (Ar$\underline{C}_{quat}$); 127.47 (Ar$\underline{C}$-H); 126.16 (Ar$\underline{C}$-H); 116.66 (Ar$\underline{C}$-H); 49.32 (C$_{9a\,quat}$); 44.96 ($\underline{C}_6$-H$_2$-NH); 43.70 ($\underline{C}H_2$); 38.22 ($\underline{C}H_2$); 35.62 ($\underline{C}_{6a}$-H-CH$_2$); 29.69 (CH$_3$); 23.73 ($\underline{C}H_2$); 22.23 ($\underline{C}H_2$).

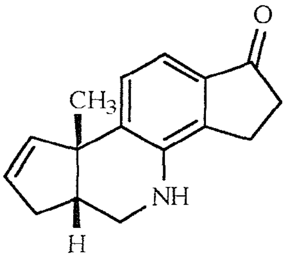
υ_{max}/cm^{-1} ($CHCl_3$) 3420 (m, N-H); 3390 (w); 2910 (m, Ar-H); 2842 (w); 1685 (s, C=O); 1590 (m); 1500 (w); 1325 (m); 1286 (s); 1231 (m); 765 (s, Ar-H); 686 (m).

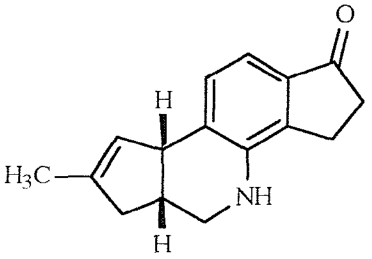
m/z= Found: 253.13 (M^+ 100%); 238 (11); 212 (9); 202 (14); 174 ($(M-C_6H_8)^+$ 26); 91 (8); 61 (10). $C_{17}H_{19}NO$ requires 253.15.

Elemental Analysis= Found: $\underline{C}$ 80.3; $\underline{H}$ 7.8; $\underline{N}$ 5.5%.
$C_{17}H_{19}NO$ requires $\underline{C}$ 80.6; $\underline{H}$ 7.6; $\underline{N}$ 5.5%.

(5aα, 8aα)-1-Oxo-1,2,4,5,5a,8a-hexahydro-3*H*, 6*H*-8a-methyldicyclopenta[1,2-*c*:1,2-*h*]quinoline (152)

(5aα, 8aα)-1-Oxo-1,2,4,5,5a,8a-hexahydro-3*H*, 6*H*-7-methyldicyclopenta[1,2-*c*:1,2-*h*]quinoline (153)





Trifluoroacetic acid (1.17g, 10.3mmol) in acetonitrile (10.0ml) was added to 4-amino-α-indanone (1.40g, 10.20mmol) dissolved in acetonitrile (45.0ml) to give a yellow solution of the amine. After 10min. of stirring under nitrogen, a mixture at 0°C of methylcyclopentadiene freshly distilled from its dimer (0.82g, 10.30mmol) and formalin solution 37% (0.83g, 10.21mmol) in acetonitrile (18.0ml) was added to the former solution which turned dark brown. The reaction mixture was stirred under nitrogen at room temperature for a further 1h. The reaction mixture was added to saturated sodium bicarbonate solution (200ml) and was extracted with dichloromethane (3x100ml). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure to yield a brown oil. Flash column chromatography on silica gel (eluant petrol / ethyl acetate 90/10) afforded the two title compounds in the one major fraction as a brown solid, 2.10g, 92%). Small scale preparative reverse phase HPLC using methanol and water afforded the pure title compounds in approximately 1:1 ratio.

(152) 3.2mg, 0.2% (based on total starting material initially used); mp 150-154°C.
δH (270MHz, CDCl$_3$) 7.18 (2H, m, ArC$_9$-$\underline{H}$, ArC$_{10}$-$\underline{H}$); 5.40 (1H, m, =C$_8$-$\underline{H}$-CH); 3.92 (1H, m, C$_{8a}$-$\underline{H}$-CH=); 3.72 (1H, s, N-$\underline{H}$); 3.24 (1H, dd, *J* 10.9, 4.7, C$_5$-$\underline{H}_2$-NH); 2.98 (1H, dd, *J* 10.8, 9.1, C$_5$-$\underline{H}_2$-NH); 2.70 (6H, m, C$_{5a}$-$\underline{H}$-CH$_2$, C$_6$-$\underline{H}_2$-CH=, C$_2$-$\underline{H}_2$, C$_3$-$\underline{H}_2$); 2.04 (1H, m, C$_6$-$\underline{H}_2$-CH=); 2.04 (3H, s, C$\underline{H}_3$).

δC (68MHz, CDCl$_3$) 209.26 ($\underline{C}$=O); 142.76 (Ar$\underline{C}_{quat}$-NH); 140.64 (Ar$\underline{C}_{quat}$); 138.98 ($\underline{C}_8$-H=CH); 135.21 (Ar$\underline{C}_{quat}$); 130.60 (Ar$\underline{C}_{quat}$); 128.58 (Ar$\underline{C}$-H); 123.49 (Ar$\underline{C}_{quat}$); 112.69 (Ar$\underline{C}$-H); 46.37 ($\underline{C}_{8a}$-H-CH=); 44.31 ($\underline{C}_5$-H$_2$-NH); 41.21 ($\underline{C}$H$_2$); 36.63 ($\underline{C}$H$_2$); 36.20 ($\underline{C}_{5a}$-H-CH$_2$); 22.26 ($\underline{C}$H$_2$); 16.55 ($\underline{C}$H$_3$).

υ_{max}/cm^{-1} (CHCl$_3$) 3381 (m, N-H); 2951 (m); 2830 (m); 1689 (s, C=O); 1594 (m); 1511 (m); 1448 (w); 1343 (w); 1297 (s); 795 (m, Ar-H).

m/z= Found: 239.20 (M+ 100%); 221 (18); 201 (16); 160 ((M-C$_6$H$_8$)$^+$ 25); 123 (20); 91 (30); 61 (44). C$_{16}$H$_{17}$NO requires 239.13.

Elemental Analysis= Found: $\underline{C}$ 79.2; $\underline{H}$ 7.7; $\underline{N}$ 5.8%.
C$_{16}$H$_{17}$NO requires $\underline{C}$ 80.3; $\underline{H}$ 7.2; $\underline{N}$ 5.9%.

(153) 4.5mg, 0.2% (based on total starting material initially used); mp 141-145°C.
δH (270MHz, CDCl$_3$) 7.24 (1H, d, J 8.1, ArC$_{10}$-$\underline{H}$); 7.16 (1H, d, J 8.0, ArC$_9$-$\underline{H}$); 5.85 (1H, ddd, J 5.6, 2.0, 2.0, =C$_8$-$\underline{H}$-CH); 5.61 (1H, m, =C$_7$-$\underline{H}$-CH$_2$); 3.78 (1H, s, N-$\underline{H}$); 3.39 (1H, dd, J 11.3, 4.2, C$_5$-$\underline{H_2}$-NH); 3.11 (1H, dd, J 11.4, 6.6, C$_5$-$\underline{H_2}$-NH); 2.80 (2H, m, C$_6$-$\underline{H_2}$-CH=, C$_{5a}$-$\underline{H}$-CH$_2$); 2.67 (2H, m, C$_2$-$\underline{H_2}$); 2.40 (3H, m, C$_6$-$\underline{H_2}$-CH=, C$_3$-$\underline{H_2}$); 1.46 (3H, s, C$\underline{H_3}$).

δC (68MHz, CDCl$_3$) 210.31 ($\underline{C}$=O); 141.93 (Ar$\underline{C}_{quat}$-NH); 140.72 (Ar$\underline{C}_{quat}$); 139.85 ($\underline{C}_8$-H=CH); 135.13 (Ar$\underline{C}_{quat}$); 135.03 (Ar$\underline{C}_{quat}$); 127.91 (Ar$\underline{C}$-H); 127.65 (Ar$\underline{C}$-H); 112.69 (Ar$\underline{C}$-H); 48.86 ($\underline{C}_{8a\,quat}$); 45.22 ($\underline{C}_5$-H$_2$-NH); 42.89 ($\underline{C}$H$_2$); 36.23 ($\underline{C}$H$_2$); 35.51 ($\underline{C}_{5a}$-H-CH$_2$); 29.69 (CH$_3$); 22.37 ($\underline{C}$H$_2$).

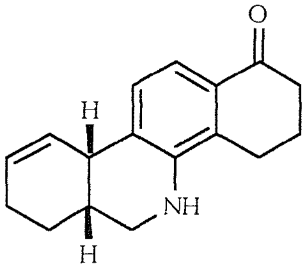
υ_{max}/cm^{-1} (CHCl$_3$) 3439 (m, N-H); 3408 (w, Ar-H); 2902 (m, C-H); 2851 (w); 1698 (s, C=O); 1593 (m); 1505 (m, N-H); 1446 (w); 1314 (m); 1290 (s); 1272 (m); 1051 (m); 815 (m, ArC-H); 742 (m); 723 (m).

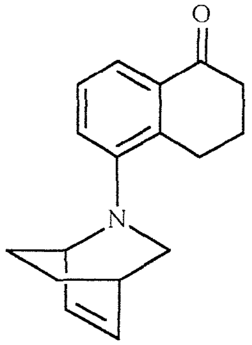
m/z= Found: 239.20 (M+ 100%); 224 (10); 118 (12); 160 ((M-C$_6$H$_8$)$^+$ 19); 139 (10); 111 (16); 61 (31). C$_{16}$H$_{17}$NO requires 239.13.

Elemental Analysis= Found: $\underline{C}$ 80.0; $\underline{H}$ 7.6; $\underline{N}$ 5.8%.
C$_{16}$H$_{17}$NO requires $\underline{C}$ 80.3; $\underline{H}$ 7.2; $\underline{N}$ 5.9%.

(6aα, 10aα)-1-Oxo-1,2,3,4,5,6,6a,7,8,10a-decahydro-benzo[*h*]-phenanthridine (155)

5-(2'-Aza-bicyclo-oct-5'-(2,2,2)en-yl)-1-tetralone (158)





Trifluoroacetic acid (0.36g, 3.12mmol) in acetonitrile (10.0ml) was added to 5-amino-α-tetralone (0.50g, 3.12mmol) dissolved in acetonitrile (15.0ml) to give a yellow solution of the amine. After 10min. of stirring under nitrogen, a mixture at 0°C of cyclohexadiene (0.26g, 3.26mmol) and formalin solution 37% (0.26g, 3.20mmol) in acetonitrile (6.0ml) was added to the former solution which turned dark brown. The reaction mixture was stirred under nitrogen at room temperature for a further 1h. The reaction mixture was added to saturated sodium bicarbonate solution (100ml) and was extracted with dichloromethane (3x70ml). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure to yield a brown oil. Flash column chromatography on silica gel (eluant petrol / ethyl acetate 90/10) afforded two compounds in the one major fraction as a brown oil, 0.52g, 66%). Small scale preparative reverse phase HPLC using methanol and water afforded the pure title compounds in approximately 1:2 ratio.

(155) 2.8mg, 0.4% (based on total starting material initially used).
δH (250MHz, CDCl$_3$) 7.45 (1H, d, *J* 8.1, ArC$_{12}$-$\underline{H}$); 7.13 (1H, d, *J* 8.0, ArC$_{11}$-$\underline{H}$); 5.82 (1H, m, =C$_{10}$-$\underline{H}$-CH); 5.67 (1H, m, =C$_9$-$\underline{H}$-CH$_2$); 3.81 (1H, m, N-$\underline{H}$); 3.51 (1H, m, C$_{10a}$-$\underline{H}$-CH=); 3.28 (2H, m, C$_6$-$\underline{H}_2$-NH); 2.61 (4H, m, C$_8$-$\underline{H}_2$, C$_2$-$\underline{H}_2$); 2.23-1.78 (7H, m, C$_7$-$\underline{H}_2$-CH=, C$_{6a}$-$\underline{H}$-CH$_2$, C$_4$-$\underline{H}_2$, C$_3$-$\underline{H}_2$).

δC (68MHz, CDCl$_3$) 198.64 ($\underline{C}$=O); 141.29 (Ar$\underline{C}_{quat}$-NH); 130.98 (Ar$\underline{C}_{quat}$); 130.16 (Ar$\underline{C}$-H); 129.70 (Ar$\underline{C}_{quat}$); 128.02 (Ar$\underline{C}_{quat}$); 127.36 (Ar$\underline{C}$-H); 125.63 (Ar$\underline{C}$-H); 115.71 (Ar$\underline{C}$-H); 43.26 ($\underline{C}_{10a}$-H-CH=); 38.26 ($\underline{C}_6$-H$_2$-NH); 37.18 ($\underline{C}$H$_2$); 30.20 ($\underline{C}_{6a}$-H-CH$_2$); 24.15 ($\underline{C}$H$_2$); 23.61 ($\underline{C}$H$_2$); 22.19 ($\underline{C}$H$_2$); 21.97 ($\underline{C}$H$_2$).

υ_{max}/cm^{-1} (CHCl$_3$) 3410 (m, N-H); 3010 (w); 2928 (s, C-H); 2882 (m); 1675 (s, C=O); 1578 (s); 1520 (m); 1464 (w); 1335 (s); 822 (w, ArC-H).

m/z= Found: 253.18 (M+ 100%); 202 (13); 174 ((M-C_6H_8)+ 31); 142 (10); 109 (12); 61 (8). $C_{17}H_{19}NO$ requires 253.15.

Elemental Analysis= Found: $\underline{C}$ 80.3; $\underline{H}$ 8.4; $\underline{N}$ 5.5%.
$C_{17}H_{19}NO$ requires $\underline{C}$ 80.6; $\underline{H}$ 7.6; $\underline{N}$ 5.5%.

(158) 3.7mg, 0.5% (based on total starting material initially used).
δH (250MHz, CDCl$_3$) 7.67 (1H, m, ArC$_8$-$\underline{H}$); 7.17 (2H, m, ArC$_6$-$\underline{H}$, ArC$_7$-$\underline{H}$); 6.63 (1H, m, C$_{6'}$-$\underline{H}$); 6.41 (1H, m, C$_{5'}$-$\underline{H}$); 3.93 (1H, m, C$_{1'}$-$\underline{H}$); 3.53 (1H, dd, *J* 8.8, 2.2, C$_{3'}$-$\underline{H}_2$); 3.02 (1H, dt, *J* 16.7, 1.2, C$_{4'}$-$\underline{H}$); 2.80-2.40 (5H, m, C$_{3'}$-$\underline{H}_2$, C$_2$-$\underline{H}_2$, C$_4$-$\underline{H}_2$); 2.20-1.70 (4H, m, C$_{7'}$-$\underline{H}_2$, C$_{8'}$-$\underline{H}_2$); 1.50 (2H, m, C$_2$-$\underline{H}_2$).

δC (68MHz, CDCl$_3$) 199.21($\underline{C}$=O); 152.42 (Ar$\underline{C}_{quat}$); 138.00 (Ar$\underline{C}_{quat}$); 133.46 (C-$\underline{H}$); 133.11 (C-$\underline{H}$); 126.17 (C-$\underline{H}$); 124.32 (C-$\underline{H}$); 120.02 (C-$\underline{H}$); 55.29 ($\underline{C}_{3'}$-H$_2$); 51.47 ($\underline{C}_{1'}$-H); 38.90 ($\underline{C}$H$_2$); 31.28 ($\underline{C}_{4'}$-H); 27.67 ($\underline{C}$H$_2$); 26.77 ($\underline{C}$H$_2$); 23.32 ($\underline{C}$H$_2$); 22.79 ($\underline{C}$H$_2$).

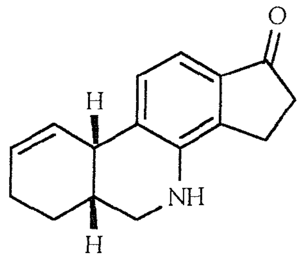
υ_{max}/cm^{-1} (CHCl$_3$) 2970 (s, C-H); 2890 (m); 1688 (s, C=O); 1592 (s); 1472 (m); 1365 (w); 1332 (w); 1298 (s); 803 (w); 746 (m); 710 (m).

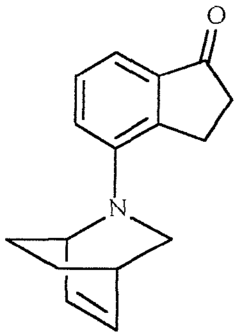
m/z= Found: 253.15 (M+ 100%); 225 (27); 190 (40); 174 (19); 162 (16); 117 (10); 93 (12); 61 (12). $C_{17}H_{19}NO$ requires 253.14.

Elemental Analysis= Found: $\underline{C}$ 80.3; $\underline{H}$ 8.3; $\underline{N}$ 5.5%.
$C_{17}H_{19}NO$ requires $\underline{C}$ 80.6; $\underline{H}$ 7.6; $\underline{N}$ 5.5%.

(5aα, 9aα)-1-Oxo-1,2,3,4,5,5a,7,9a-octahydro-6*H*-cyclopenta[*c*]-phenanthridine (159)

4-(2'-Aza-bicyclo-oct-5'-(2,2,2)en-yl)-1-indanone (160)





Trifluoroacetic acid (0.29g, 2.52mmol) in acetonitrile (2.0ml) was added to 4-amino-α-indanone (0.37g, 2.52mmol) dissolved in acetonitrile (10.0ml) to give a yellow solution of the amine. After 10min. of stirring under nitrogen, a mixture at 0°C of cyclohexadiene (0.20g, 2.53mmol) and formalin solution 37% (0.21g, 2.52mmol) in acetonitrile (5.0ml) was added to the former solution which turned dark brown. The reaction mixture was stirred under nitrogen at room temperature for a further 1h. The reaction mixture was added to saturated sodium bicarbonate solution (70ml) and was extracted with dichloromethane (3x80ml). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure to yield a brown oil. Flash column chromatography on silica gel (eluant petrol / ethyl acetate 90/10) isolated two compounds in one major fraction as a brown oil, 0.63g, 53%. Small scale preparative reverse phase HPLC using methanol and water afforded the pure title compounds in approximately 1:1 ratio.

(159) 2.8mg, 0.4% (based on total starting material initially used).
δH (250MHz, $CDCl_3$) 7.48 (1H, m, ArC_{11}-$\underline{H}$); 6.94 (1H, d, *J* 7.7, ArC_{10}-$\underline{H}$); 5.70 (1H, m, =C_9-$\underline{H}$-CH); 5.58 (1H, m, =C_8-$\underline{H}$-CH_2); 3.62 (1H, m, N-$\underline{H}$); 3.43 (1H, m, C_{9a}-$\underline{H}$-CH=); 3.24 (2H, m, C_5-$\underline{H}_2$-NH); 2.65 (4H, m, C_7-$\underline{H}_2$, C_2-$\underline{H}_2$); 2.26-1.78 (5H, m, C_6-$\underline{H}_2$-CH=, C_{5a}-$\underline{H}$-CH_2, C_3-$\underline{H}_2$).

δC (68MHz, $CDCl_3$) 207.35 ($\underline{C}$=O); 140.89 ($Ar\underline{C}_{quat}$-NH); 130.48 ($Ar\underline{C}_{quat}$); 130.30 (Ar$\underline{C}$-H); 128.67 ($Ar\underline{C}_{quat}$); 127.56 ($Ar\underline{C}_{quat}$); 126.88 ($\underline{C}$-H); 125.04 ($\underline{C}$-H); 115.34 ($\underline{C}$-H); 44.68 ($\underline{C}_{9a}$-H-CH=); 39.22 ($\underline{C}_5$-H_2-NH); 38.17 ($\underline{C}H_2$); 33.30 ($\underline{C}_{5a}$-H-CH_2); 24.44 ($\underline{C}H_2$); 22.93 ($\underline{C}H_2$); 21.86 ($\underline{C}H_2$).

υ_{max}/cm^{-1} ($CHCl_3$) 3420 (m, N-H); 3015 (w); 2939 (s, C-H); 2890 (w); 1692 (s, C=O); 1584 (m); 1518 (m); 1470 (w); 1350 (m); 1290 (m); 802 (w, ArC-H).

m/z= Found: 239.20 (M+ 100%); 188 (20); 160 (($MH-C_6H_8$)+ 25); 148 (16); 110 (12); 93 (10); 61 (8). $C_{16}H_{17}NO$ requires 239.13.

Elemental Analysis= Found: $\underline{C}$ 80.0; $\underline{H}$ 7.8; $\underline{N}$ 5.9%.
$C_{16}H_{17}NO$ requires $\underline{C}$ 80.3; $\underline{H}$ 7.2; $\underline{N}$ 5.9%.

(160) 4.1mg, 0.5% (based on total starting material initially used).
δH (250MHz, $CDCl_3$) 7.24 (2H, m, ArC_5-$\underline{H}$, ArC_7-$\underline{H}$); 7.04 (1H, m, ArC_6-$\underline{H}$); 6.64 (1H, m, $C_{6'}$-$\underline{H}$); 6.43 (1H, m, $C_{5'}$-$\underline{H}$); 4.25 (1H, m, $C_{1'}$-$\underline{H}$); 3.09 (1H, dd, *J* 8.7, 2.0, $C_{3'}$-$\underline{H}_2$); 3.09 (2H, m, $C_{3'}$-$\underline{H}_2$, $C_{4'}$-$\underline{H}$); 2.83-2.64 (4H, m, C_2-$\underline{H}_2$, C_3-$\underline{H}_2$); 2.19 (1H, m, $C_{7'}$-$\underline{H}_2$); 2.85-2.40 (3H, m, $C_{7'}$-$\underline{H}_2$, $C_{8'}$-$\underline{H}_2$).

δC (68MHz, $CDCl_3$) 207.70 ($\underline{C}$=O); 150.90 (Ar$\underline{C}_{quat}$); 145.22 (Ar$\underline{C}_{quat}$); 138.64 (Ar$\underline{C}_{quat}$); 133.48 (C-$\underline{H}$); 133.30 (C-$\underline{H}$); 128.40 (C-$\underline{H}$); 120.86 (C-$\underline{H}$); 114.32 (C-$\underline{H}$); 54.38 ($\underline{C}_{3'}$-H_2); 49.17 ($\underline{C}_{1'}$-H); 36.15 ($\underline{C}H_2$); 31.26 ($\underline{C}_{4'}$-H); 26.75 ($\underline{C}H_2$); 26.09 ($\underline{C}H_2$); 22.74 ($\underline{C}H_2$).

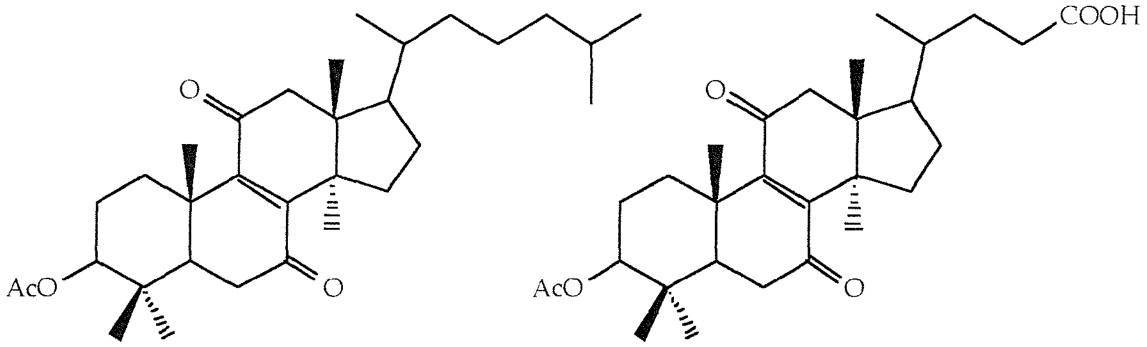
υ_{max}/cm^{-1} ($CHCl_3$) 2920 (m); 2900 (s, C-H); 2880 (s); 1705 (s, C=O); 1595 (s); 1482 (s); 1325 (m); 1294 (m); 762 (m, ArC-H); 705 (w).

m/z= Found: 239.22 (M+ 100%); 211 (15); 188 (13); 176 (18); 148 (20); 111 (12); 93 (12); 61 (16). $C_{16}H_{17}NO$ requires 239.13.

Elemental Analysis= Found: $\underline{C}$ 80.0; $\underline{H}$ 7.7; $\underline{N}$ 5.9%.
$C_{16}H_{17}NO$ requires $\underline{C}$ 80.3; $\underline{H}$ 7.2; $\underline{N}$ 5.9%.

3.3 LANOSTEROL SERIES

3β-Acetyloxy-5α-lanost-8-ene-7,11-dione 168) and 3β-acetyloxy-5α-lanost-8-ene-7,11-dione-24-carboxylic acid (169)



Isocholesteryl acetate was obtained by refluxing commercial lanosterol in acetic anhydride for 1h, allowing the product to crystallise and then washing the filtered product with cold methanol.[148] This starting material (4.69g, 10.0mmol) was dissolved in glacial acetic acid (140ml) and the solution warmed to 50°C. A solution of chromium trioxide (6.0g, 60mmol) in glacial acetid acid (50ml) was added dropwise with stirring. After stirring for 3h. at 50°C, the excess oxidising agent was quenched with methanol. The mixture was concentrated by evaporation of some solvent and water was then added yielding a thick green clay. This was dissolved in dichloromethane and the organic layer was dried and evaporated to yield a green crystalline solid. Flash column chromatography (eluant petroleum ether/ethyl acetate 5/1 - 1/5) gave the two products, 3β-acetyloxy-5α-lanost-8-ene-7,11-dione (168) (1.10g, 22%) as a yellow solid which was recrystallised from petroleum ether (mp 144°C, lit[147] 144 - 145°C); and 3β-acetyloxy-5α-lanost-8-ene-7,11-dione-24-carboxylic acid (169) (1.50g, 41%) as a yellow solid which was recrystallised from glacial acetic acid / water (mp 184 - 186°C, lit[149] 186 - 188°C).

3β-Acetyloxy-5α-lanost-8-ene-7,11-dione (168)

δH (270MHz, CDCl$_3$) 4.53 (1H, dd, *J* 11.0, 5.6, C_3-$\underline{H}$); 2.90 (1H, dt, *J* 13.7, 3.3, C_{12}-$\underline{H}$); 2.76 (1H, d, *J* 15.8, C_6-$\underline{H}$); 2.62 (1H, d, *J* 15.8, C_6-$\underline{H}$); 2.48 (1H, m, C_{12}-$\underline{H}$); 2.06 (3H, s, $C\underline{H}_3$-CO); 1.34 (3H, s, $C\underline{H}_3$); 1.17 (3H, s, $C\underline{H}_3$); 0.96 (3H, s, $C\underline{H}_3$); 0.89 (3H, s, $C\underline{H}_3$); 0.87 (3H, s, $C\underline{H}_3$); 0.86 (3H, s, $C\underline{H}_3$); 0.79 (3H, s, $C\underline{H}_3$).

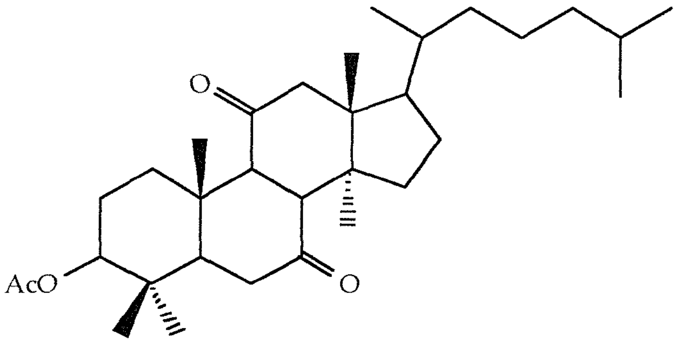
δC (68MHz, CDCl$_3$) 202.08 ($\underline{C}$=O); 201.53 ($\underline{C}$=O); 170.45 ($\underline{C}$=O); 151.61 ($\underline{C}$H=); 150.55 ($\underline{C}$H=); 79.21; 51.64; 50.14; 49.10; 49.02; 39.59; 39.44; 37.72; 36.22; 36.12; 33.77; 32.21; 27.99; 27.83; 27.38; 25.91; 24.97; 24.04; 22.91; 22.62; 21.20; 18.66; 17.56; 17.19; 16.81; 16.51.

3β-Acetyloxy-5α-lanost-8-ene-7,11-dione-24-carboxylic acid (169)

δH (360MHz, $CDCl_3$) 4.53 (1H, dd, *J* 11.2, 5.2, C_3-H); 2.88 (1H, dt, *J* 13.8, 3.7, C_{12}-H); 2.77 (1H, dd, *J* 15.8, 0.9, C_6-H); 2.59 (1H, d, *J* 15.8, C_6-H); 2.49 (1H, m, C_{12}-H); 2.03 (3H, s, CH_3-CO); 1.31 (3H, s, CH_3); 1.15 (3H, s, CH_3); 0.92 (3H, s, CH_3); 0.90 (3H, s, CH_3); 0.88 (3H, s, CH_3); 0.78 (3H, s, CH_3).

δC (68MHz, $CDCl_3$) 202.24 (C=O); 201.91 (C=O); 179.28 (C=O); 170.98 (C=O); 151.76 (CH=); 150.58 (CH=); 79.39 (C_3-H); 51.56; 50.11; 49.04; 48.90; 47.50; 39.63; 37.75; 35.72; 35.23; 33.76; 32.19; 31.11; 30.80; 27.83; 27.23; 25.91; 23.97; 21.28; 18.21; 17.61; 16.86; 16.59.

3β-Acetyloxy-5α-lanosta-7,11-dione



Zinc dust (10g) was added portionwise over 3h. to a solution of the dione (1.0g, 2.0mmol) in glacial acetic acid, which was simultaneously gradually warmed to approximately 100°C. The solution was not allowed to reach reflux point. The mixture was filtered and the zinc was washed thoroughly with hot acetic acid. The combined filtrates were poured into water and extracted with ether. The extracts were washed with sodium carbonate solution, then water, and evaporated. TLC analysis indicated the predominance of one compound. Flash column chromatography using petroleum ether / ethyl acetate as eluant isolated the required material (0.92g, 92%), mp 220-222°C, lit[175] 222-224°C.

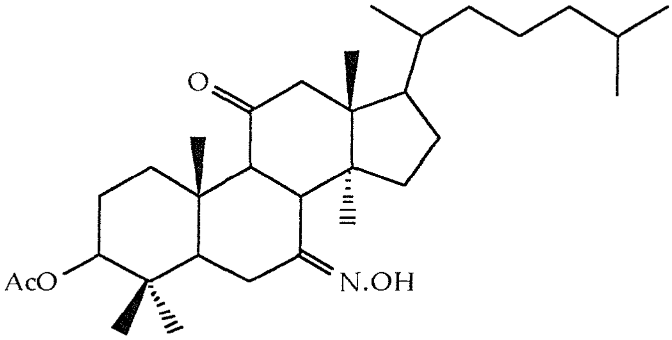
δH (270MHz, $CDCl_3$) 4.45 (1H, dd, *J* 10.8, 7.6, C_3-H); 2.84 (1H, dt, *J* 13.8, 3.5, C_{12}-H); 2.62 (1H, d, *J* 15.9, C_6-H); 2.56 (1H, d, *J* 16.0, C_6-H); 2.36 (1H, d, *J* 13.8, C_9-H); 2.33 (2H, m, C_{12}-H, C_8-H); 2.03 (3H, s, CH_3-CO); 1.28 (3H, s, CH_3); 1.19 (3H, s, CH_3); 0.88 (3H, s, CH_3); 0.85 (3H, s, CH_3); 0.84 (3H, s, CH_3); 0.82 (3H, s, CH_3); 0.81 (3H, s, CH_3); 0.70 (3H, s, CH_3).

δC (68MHz, $CDCl_3$) 209.62 (C=O); 209.06 (C=O); 170.88 (C=O); 80.02; 60.47; 53.18; 52.59; 52.48; 49.14; 48.71; 46.52; 39.51; 39.20; 38.27; 36.78; 36.37; 35.95; 35.78; 33.16;

28.72; 28.07; 27.77; 24.06; 23.74; 22.93; 22.65; 21.36; 18.54; 17.65; 16.27; 16.11; 13.82.

υ_{max}/cm^{-1} ($CHCl_3$) 3500-3200 (m), 1727 (s), 1687 (s), 1250 (m).
m/z= Found: 500 (M+ 100%); 480 (22); 469 (34); 441 (27); 378 (12); 248 (18).$C_{32}H_{52}O_4$ requires 500.

3β-Acetyloxy-5α-lanost-11-on-7-oxime (171)



The diketone (1.0g, 2.0mmol) was dissolved in ethanol (200ml) and hydroxylamine hydrochloride (2.5g) and pyridine (20ml) was added. The mixture was heated under reflux for 1h. The solution was evaporated to *ca* 40ml, dissolved in ether, and then washed with dilute H_2SO_4 and water. The organic layer was dried and evaporated to yield a white solid. Recrystallisation from ethyl acetate gave the monooxime (0.69g, 67%), mp 212-214°C, lit[176] 213-214°C.

δH (270MHz, $CDCl_3$) 7.45 (1H, br.s, O-$\underline{H}$); 4.49 (1H, t, *J* 8.1, C_3-$\underline{H}$); 3.43 (1H, dd, *J* 14.8, 2.8, C_6-$\underline{H}$); 2.84 (1H, dt, *J* 13.7, 3.5, C_{12}-$\underline{H}$); 2.73 (1H, m, C_6-$\underline{H}$); 2.62 (1H, d, *J* 13.7, C_9-$\underline{H}$); 2.38 (1H, d, *J* 13.7, C_8-$\underline{H}$); 2.05 (3H, s, $C\underline{H}_3$-CO); 1.29 (3H, s, $C\underline{H}_3$); 1.18 (3H, s, $C\underline{H}_3$); 0.92 (3H, s, $C\underline{H}_3$); 0.86 (3H, d, *J* 6.6, C_{26}-$C\underline{H}_3$); 0.86 (3H, d, *J* 6.6, C_{27}-$C\underline{H}_3$); 0.84 (3H, s, $C\underline{H}_3$); 0.73 (3H, s, $C\underline{H}_3$).

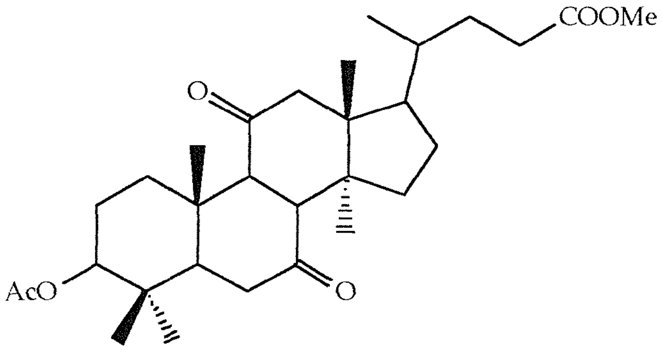
δC (68MHz, $CDCl_3$) 210.69 ($\underline{C}$=O); 171.09 (CH_3-$\underline{C}$=O); 159.49 ($\underline{C}$=N); 80.50 ($\underline{C}_3$-H); 61.06; 52.81; 52.00; 49.49; 49.24; 47.35; 45.36; 39.59; 38.51; 37.12; 36.42; 36.17; 36.11; 33.96; 28.75; 28.13; 24.16; 23.88; 22.98; 22.69; 21.45; 20.44; 18.62; 17.56; 16.34; 16.31; 13.95.

υ_{max}/cm^{-1} ($CHCl_3$) 3500 - 3200 (m), 2800 (m), 1728 (s), 1620 (s).
m/z= Found: 515 (M+ 100%); 482 (32); 456 (25); 435 (18); 374 (10); 237 (30).$C_{32}H_{53}NO_4$ requires 515.

(1) 3β-Hydroxy-5α-lanost-8-ene-7,11-dione-24-methyl ester

(2) 3β-Acetyloxy-5α-lanost-8-ene-7,11-dione-24-methyl ester (170)

(3) 3β-Acetyloxy-5α-lanosta-7,11-dione-24-methyl ester



(**1**) The dione (169) (1.0g, 2.05mmol) was added to methanol (50ml) and the solution warmed slightly to dissolve the compound. Concentrated sulfuric acid (1ml) was added and the solution heated under reflux for 3h. After cooling to room temperature, the solution was added to saturated sodium bicarbonate solution and extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulphate, filtered, and evaporated to give the 3-hydroxy-24-methyl ester as a yellow solid (0.92g, 98%), mp 137-139°C.

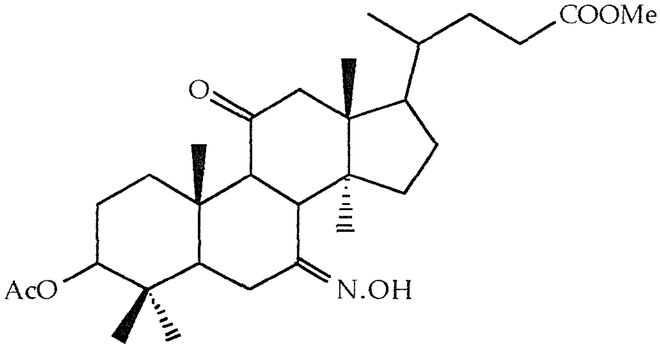
(**2**) The product (500mg, 1.09mmol) was added to acetic anhydride (30ml) and the mixture was warmed slightly to dissolve the compound. The solution was heated under reflux for 1h. and the solvent then evaporated to give the 3-acetyloxy-24-methyl ester (170) as a yellow solid (1.05g, 96%), mp 177-178°C, lit[177] 178-179°C.

(**3**) Zinc dust (10g) was added portionwise over 3h. to a solution of the dione (170) (1.0g, 2.0mmol) in glacial acetic acid, which was simultaneously gradually warmed to approximately 100°C. The solution was not allowed to reach reflux point. The mixture was filtered and the zinc was washed thoroughly with hot acetic acid. The combined filtrates were poured into water and extracted with ether. The extracts were washed with sodium carbonate solution, then water, and evaporated. TLC analysis indicated the predominance of one compound. Flash column chromatography using petroleum ether / ethyl acetate as eluant isolated the required material (0.80g, 80%), mp 259-262°C, lit[177] 260-265°C.

δH (270MHz, $CDCl_3$) 4.50 (1H, t, *J* 8.2 C_3-H); 3.67 (3H, s, $COOCH_3$); 2.85 (1H, dt, *J* 13.2, 3.5, C_{12}-H); 2.63 (2H, m, C_6-H_2); 2.35 (3H, m, C_{12}-H, C_8-H, C_9-H); 2.06 (3H, s, CH_3-CO); 1.29 (3H, s, CH_3); 1.24 (3H, s, CH_3); 0.92 (3H, s, CH_3); 0.86 (3H, s, CH_3); 0.85 (3H, s, CH_3); 0.72 (3H, s, CH_3).

δC (68MHz, $CDCl_3$) 209.38 (C=O); 208.93 (C=O); 174.50 (C=O); 170.89 (C=O); 79.98 (C_3-H); 60.38; 53.05; 52.48; 52.41; 51.61; 49.08; 48.46; 46.50; 39.19; 38.22; 36.74; 35.70; 33.06; 31.08; 28.55; 27.71; 23.68; 21.31; 18.07; 17.59; 16.28; 16.07; 13.78.

3β-Acetyloxy-5α-lanost-11-on-7-oxime-24-methyl ester (172)



The reduced diketone (1.0g, 2.0mmol) was dissolved in ethanol (200ml) and hydroxylamine hydrochloride (2.5g) and pyridine (20ml) was added. The mixture was heated under reflux for 1h. The solution was evaporated to *ca* 40ml, dissolved in ether, and then washed with dilute H_2SO_4 and water. The organic layer was dried and evaporated to yield a white solid. Recrystallisation from ethyl acetate gave the monooxime (0.87g, 84%), mp 218-220°C.

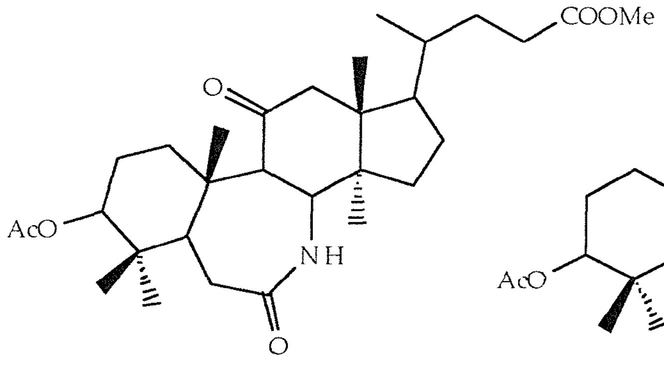
δH (270MHz, $CDCl_3$) 8.12 (1H, br.s, O-H); 4.50 (1H, t, *J* 8.0, C_3-H); 3.45 (1H, dd, *J* 14.9, 2.9, C_6-H); 2.82 (1H, dt, *J* 13.9, 2.8, C_{12}-H); 2.72 (1H, m, C_6-H); 2.62 (1H, d, *J* 13.7, C_9-H); 2.35 (1H, d, *J* 13.7, C_8-H); 2.07 (3H, s, CH_3-CO); 1.32 (3H, s, CH_3); 1.15 (3H, s, CH_3); 0.91 (3H, s, CH_3); 0.88 (3H, s, CH_3); 0.84 (3H, s, CH_3); 0.73 (3H, s, CH_3).

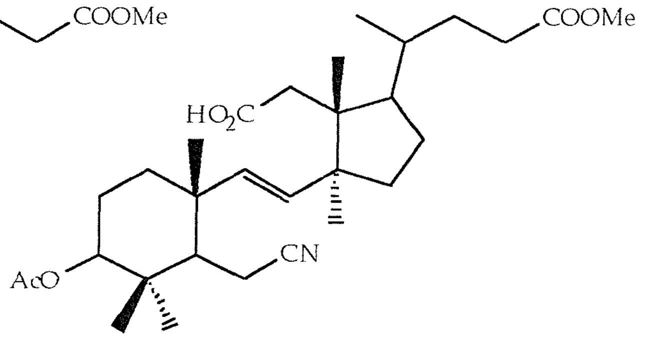
δC (68MHz, $CDCl_3$) 210.50 (C=O); 174.85 (C=O); 171.19 (CH_3-C=O); 159.07 (C=N); 80.51 (C_3-H); 61.00; 52.75; 51.92; 51.76; 49.44; 49.01; 47.37; 45.25; 38.48; 37.09; 36.11; 35.69; 33.92; 31.26; 31.17; 28.61; 28.12; 23.84; 21.46; 30.37; 18.17; 17.49; 16.32; 16.29; 13.91.

υ_{max}/cm^{-1} ($CHCl_3$) 3350 - 3180 (m), 2750 (m), 1735 (s), 1716 (s), 1375 (s), 1028 (m), 754 (m).

m/z= Found: 517 (M+ 65%); 502 (100); 451 (26); 440 (38); 384 (17); 226 (30); 250 (22). $C_{30}H_{47}NO_6$ requires 517.

3β-Acetyloxy-7a-aza-B-homo-5α-lanost-11-one-24-methyl ester (173b)





The oxime (100mg, 0.2mmol) was quickly dissolved with stirring in thionyl chloride (10ml) at -10°C and stirred for 20min. The light yellow solution was slowly added to 4M potassium hydroxide (100ml) at 90°C. After cooling, the mixture was extracted with ether and washed with dilute hydrochloric acid, saturated sodium bicarbonate solution and water. Flash column chromatography afforded the major product (173b) as a white solid (30mg, 30%), mp. 130-134°C, and (174) as a white solid (12mg, 12%), mp. 162-165°C.

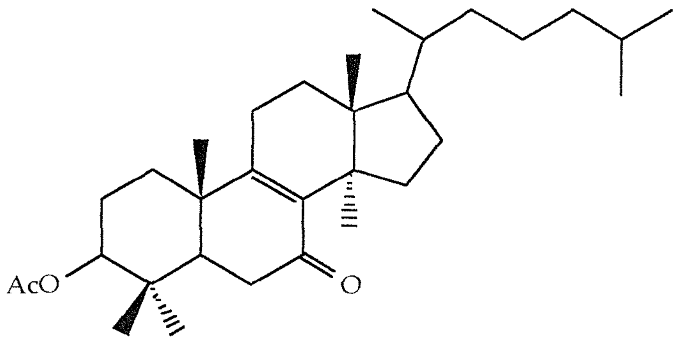
(173b)

δH (270MHz, $CDCl_3$) 5.60 (1H, br.s, N-$\underline{H}$); 4.43 (1H, dd, *J* 10.7, 4.6, C_3-$\underline{H}$); 3.65 (3H, s, $C\underline{H}_3$); 2.62 (2H, m, C_6-$\underline{H}$); 2.03 (3H, s, $C\underline{H}_3$-CO); 1.17 (3H, s, $C\underline{H}_3$); 1.09 (3H, s, $C\underline{H}_3$); 1.05 (3H, s, $C\underline{H}_3$); 1.03 (3H, s, $C\underline{H}_3$); 0.97 (3H, s, $C\underline{H}_3$); 0.89 (3H, s, $C\underline{H}_3$).
δC (68MHz, $CDCl_3$) 2116.68 ($\underline{C}$=O); 174.23 ($\underline{C}$=O); 170.47 (CH_3-$\underline{C}$=O); 79.32 ($\underline{C}_3$-H); 60.40; 56.35; 51.69; 51.33; 42.73; 40.47; 39.85; 39.51; 33.54; 32.85; 31.61; 31.17; 29.04; 28.33; 26.92; 23.28; 22.24; 21.33; 20.70; 20.28; 17.33; 13.69.
υ_{max}/cm^{-1} ($CHCl_3$) 3400 - 3200 (m), 2955 (s), 1732 (s), 1662 (s), 1465 (w), 1032 (m).
m/z= Found: 517 (M+ 65%); 502 (100); 470 (26); 458 (38); 429 (17); 379 (30); 312 (22); 272 (12); 238 (34). $C_{30}H_{47}NO_6$ requires 517.

(174)

δH (270MHz, $CDCl_3$) 5.63 (1H, dd, *J* 16.0, C_8-$\underline{H}$); 5.16 (1H, dd, *J* 16.0, C_9-$\underline{H}$); 4.56 (1H, dd, *J* 11.0, 5.4, C_3-$\underline{H}$); 2.45 (1H, d, *J* 13.6, $C\underline{H}_2$-CN); 2.32 (1H, d, *J* 13.6, $C\underline{H}_2$ -CN); 2.06 (3H, s, $C\underline{H}_3$-CO); 1.25 (3H, s, $C\underline{H}_3$); 1.10 (3H, s, $C\underline{H}_3$); 1.05 (3H, s, $C\underline{H}_3$); 1.02 (3H, s, $C\underline{H}_3$); 0.97 (3H, s, $C\underline{H}_3$); 0.96 (3H, s, $C\underline{H}_3$); 0.95 (3H, s, $C\underline{H}_3$).
δC (68MHz, $CDCl_3$) 178.82 ($\underline{C}$OOH); 175.61 (CH_3-$\underline{C}$=O); 172.29 ($\underline{C}OOCH_3$); 139.42 ($\underline{C}$H=); 136.78 ($\underline{C}$H=); 121.94 ($\underline{C}$N); 79.83 ($\underline{C}_3$-H); 51.08; 50.76; 50.29; 49.35; 43.44; 42.19; 39.98; 38.26; 36.31; 35.62; 32.34; 30.79; 30.02; 29.18; 26.42; 24.39; 23.68; 22.16; 19.97; 18.63; 18.29; 17.54; 14.58.
m/z= Found: 517 (M+ 100%); 500 (55); 458 (21); 418 (16); 301 (32); 266 (22); 216 (30). $C_{30}H_{47}NO_6$ requires 517.

3β-Acetyloxy-5α-lanost-8-en-7-one (175)



Lanosteryl acetate (1.0g, 2.1mmol) was dissolved in glacial acetic acid (140ml). A solution of sulfuric acid (0.6ml) in glacial acetic acid (5.0ml) was added dropwise with stirring, immediately followed by a solution of 30% hydrogen peroxide (5.0ml) in glacial acetic acid (5.0ml). The resulting solution was left stirring at room temperature overnight. The solution was then poured onto water and the resulting precipitate filtered and dried to give a white solid. Flash column chromatography (eluant petrol/ethyl acetate 10/90 - 0/100) yielded the 7-monoketone (175) as the major fraction (103mg, 10%) which was recrystallised from methanol, mp. 150 - 152°C, lit^{152} 150.5-152°C.

δH^{178} (270MHz, CDCl$_3$) 4.52 (1H, dd, *J* 11.4, 4.4, C$_3$-$\underline{H}$); 2.06 (3H, s, C$\underline{H}_3$-CO); 1.19 (3H, s, C$_{19}$-$\underline{H}_3$); 0.95 (3H, s, C$_{29}$-$\underline{H}_3$); 0.91 (3H, s, C$_{30}$-$\underline{H}_3$); 0.88 (3H, s, C$_{28}$-$\underline{H}_3$); 0.87 (3H, d, *J* 6.6, C$_{27}$-$\underline{H}_3$); 0.86 (3H, d, *J* 6.6, C$_{26}$-$\underline{H}_3$); 0.65 (3H, s, C$_{18}$-$\underline{H}_3$).

δC^{178} (68MHz, CDCl$_3$) 198.82 ($\underline{C}_7$=O); 170.91 (CH$_3$-$\underline{C}$O); 164.78 ($\underline{C}_9$=); 139.24 ($\underline{C}_8$=); 79.74 ($\underline{C}_3$); 50.01 ($\underline{C}_5$); 49.20 ($\underline{C}_{17}$); 47.93 ($\underline{C}_{14}$); 45.02 ($\underline{C}_{13}$); 39.75 ($\underline{C}_{10}$); 39.62 ($\underline{C}_{24}$); 37.89 ($\underline{C}_4$); 36.54 ($\underline{C}_{22}$); 34.64 ($\underline{C}_1$); 32.14 ($\underline{C}_{15}$); 30.25 ($\underline{C}_{12}$); 28.91 ($\underline{C}_{16}$); 28.13 ($\underline{C}_{25}$); 27.51 ($\underline{C}_{28}$); 25.17 ($\underline{C}_{30}$); 24.22 ($\underline{C}_{23}$); 23.99 ($\underline{C}_2$); 23.84 ($\underline{C}_{11}$); 22.98 ($\underline{C}_{27}$); 22.69 ($\underline{C}_{26}$); 21.36 ($\underline{C}$H$_3$-CO); 18.95 ($\underline{C}_{21}$); 18.58 ($\underline{C}_{19}$); 16.51 ($\underline{C}_{29}$); 15.93 ($\underline{C}_{18}$).

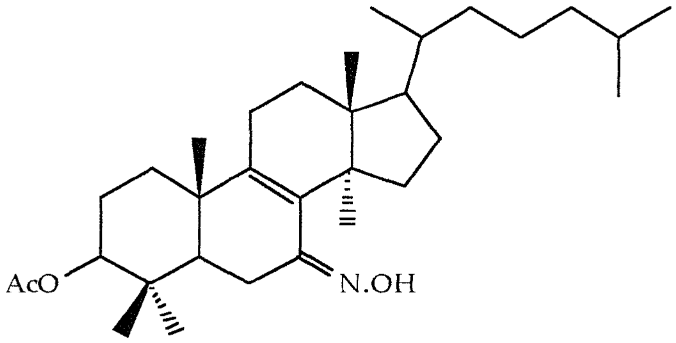
υ_{max}/cm^{-1} (CHCl$_3$) 3400 - 3200 (m), 2955 (w), 1724 (s), 1654 (s), 1388 (s), 1582 (m), 1466 (m), 1023 (m), 757 (s).
m/z= Found: 484 (M$^+$ 100%); 469 (32); 433 (45); 397 (26); 352 (38); 310 (42); 251 (16); 208 (19). C$_{32}$H$_{52}$O$_3$ requires 484.

The 11-monoketone (176) was obtained as a minor fraction (33mg, 3%) and recrystallised from methanol, mp 164 - 165°C.
δH (270MHz, CDCl$_3$) 4.49 (1H, t, *J* 8.4 C$_3$-$\underline{H}$); 3.00 (1H, dt, *J* 13.7, 3.2, C$_7$-$\underline{H}$); 2.64

(1H, d, *J* 16.6, C_{12}-$\underline{H}$); 2.45 (1H, d, *J* 16.4, C_{12}-$\underline{H}$); 2.02 (3H, s, $C\underline{H}_3$-CO); 1.13 (3H, s, $C\underline{H}_3$); 1.10 (3H, s, $C\underline{H}_3$); 0.88 (3H, s, $C\underline{H}_3$); 0.86 (3H, s, $C\underline{H}_3$); 0.83 (3H, s, $C\underline{H}_3$); 0.82 (3H, s, $C\underline{H}_3$); 0.79 (3H, s, $C\underline{H}_3$).

δC (68MHz, $CDCl_3$) 199.27 ($\underline{C}_7$=O); 171.03 (CH_3-$\underline{C}$O); 164.22 ($\underline{C}_9$=); 139.50 ($\underline{C}_8$=); 80.68 ($\underline{C}_3$); 52.06; 52.00; 51.74; 50.35; 47.40; 39.55; 38.07; 37.62; 36.29; 34.19; 31.30; 29.96; 29.81; 28.40; 28.09; 27.14; 25.91; 24.37; 24.14; 22.93; 22.65; 21.41; 19.12; 18.57; 17.39; 16.90; 16.77.

3β-Acetyloxy-5α-lanost-8-en-7-oxime (177)



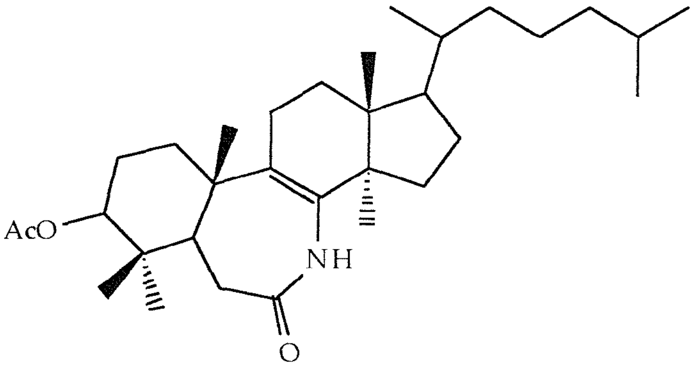
The monoketone (175) (100mg, 0.2mmol) was dissolved in ethanol (20ml) and pyridine (1.0ml) was added. Hydroxylamine hydrochloride (140mg) was added to the solution with stirring. The solution was refluxed for 80h. and then evaporated to *ca* 5ml. The residue was dissolved in ether and washed with dilute sulfuric acid and water. The organic layer was dried, filtered and the solvent evaporated to yield a pale yellow solid. Flash column chromatography (eluant petrol/ethyl acetate 10/90 - 50/50) gave the monooxime (64mg, 62%), mp. 134-136°C.

δH (270MHz, $CDCl_3$) 4.50 (1H, dd, *J* 11.0, 4.4, C_3-$\underline{H}$); 3.17 (1H, dd, *J* 17.3, 3.9, C_6-$\underline{H}$); 2.06 (3H, s, $C\underline{H}_3$-CO); 1.03 (3H, s, C_{19}-$\underline{H}_3$); 0.98 (3H, s, C_{29}-$\underline{H}_3$); 0.95 (3H, s, C_{30}-$\underline{H}_3$); 0.92 (3H, s, C_{21}-$\underline{H}_3$); 0.90 (3H, s, C_{28}-$\underline{H}_3$); 0.87 (3H, d, *J* 6.6, C_{27}-$\underline{H}_3$); 0.86 (3H, d, *J* 6.6, C_{26}-$\underline{H}_3$); 0.71 (3H, s, C_{18}-$\underline{H}_3$).

δC (68MHz, $CDCl_3$) 171.16 (CH_3-$\underline{C}$O); 157.96 ($\underline{C}$=N); 149.87 ($\underline{C}_9$=); 133.58 ($\underline{C}_8$=); 80.48 ($\underline{C}_3$); 49.78; 47.63; 46.22; 40.08; 39.12; 38.78; 37.92; 34.36; 33.69; 31.86; 29.02; 28.77; 28.45; 26.34; 24.89; 23.94; 23.41; 23.20; 22.63; 21.16; 19.83; 18.92; 17.38; 16.87.

υ_{max}/cm^{-1} ($CHCl_3$) 3400 - 3200 (m), 2945 (w), 1789 (s), 1386 (s), 902 (m), 826 (m).
m/z= Found: 499 (M+ 100%); 456 (21); 440 (46); 368 (31); 312 (18); 284 (16); 231 (27).
$C_{32}H_{53}NO_3$ requires 499.

3β-Acetyloxy-7a-aza-B-homo-5α-lanost-8-one (178)



The oxime (100mg, 0.2mmol) was quickly dissolved with stirring in thionyl chloride (10ml) at -10°C and stirred for 20min. The light yellow solution was slowly added to 4M potassium hydroxide (100ml) at 90°C. After cooling, the mixture was extracted with ether and washed with dilute hydrochloric acid, saturated sodium bicarbonate solution and water. Flash column chromatography afforded the product (178) as a white solid (48mg, 48%), which was recrystallised from methanol, mp. 130-134°C.

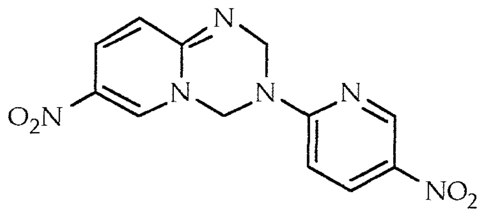
δH (270MHz, $CDCl_3$) 6.32 (1H, s, N-H); 4.46 (1H, dd, *J* 10.6, 4.3, C_3-$\underline{H}$); 2.48 (1H, dd, *J* 14.5, 5.8, C_6-$\underline{H}$); 2.26 (3H, m, C_6-$\underline{H}$, C_{11}-$\underline{H}_2$); 2.03 (3H, s, $C\underline{H}_3$-CO); 1.25 (3H, s, $C\underline{H}_3$); 1.03 (3H, s, $C\underline{H}_3$); 0.99 (3H, s, $C\underline{H}_3$); 0.93 (3H, s, $C\underline{H}_3$); 0.90 (3H, s, $C\underline{H}_3$); 0.85 (3H, s, $C\underline{H}_3$); 0.83 (3H, s, $C\underline{H}_3$); 0.75 (3H, s, $C\underline{H}_3$).

δC (68MHz, $CDCl_3$) 176.28 ($\underline{C}_7$=O); 170.96 (CH_3-$\underline{C}$O); 133.41 ($\underline{C}_9$=); 126.21 ($\underline{C}_8$=); 79.89 ($\underline{C}_3$); 52.87; 50.66; 39.58 ($\underline{C}H_2$); 36.42; 36.37 ($\underline{C}H_2$); 35.85 ($\underline{C}H_2$); 34.17 ($\underline{C}H_2$); 30.92 ($\underline{C}H_2$); 30.38 ($\underline{C}H_2$); 28.43; 28.13; 28.09 ($\underline{C}H_2$); 24.20 ($\underline{C}H_2$); 24.14; 24.09 ($\underline{C}H_2$); 23.54 ($\underline{C}H_2$); 22.96; 22.67; 21.38; 20.99; 18.66; 17.17; 16.31.

υ_{max}/cm^{-1} ($CHCl_3$) 3350 - 3300 (m), 2885 (w), 1789 (s), 1529 (s), 1382 (s), 914 (m).
m/z= Found: 499 (M+ 100%); 456 (28); 439 (25); 329 (31); 298 (21); 272 (11); 216 (32).
$C_{32}H_{53}NO_3$ requires 499.

3.4 CYCLIC AMIDINES SERIES

3,4-Dihydro-7-nitro-3-(5-nitro-2-pyridyl)-2*H*-pyrido[1,2-*a*][1,3,5]triazine (187)

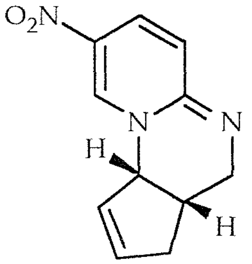


2-Amino-5-nitropyridine (1.39g, 10mmol) was added to acetonitrile (28.6ml) containing two equivalents of trifluoroacetic acid (2.28g, 20mmol) to give a 0.35M amine concentration. To this turbid yellow solution was added with stirring a heterogeneous mixture of indene (2.32g, 20mmol) and 37% formalin solution (1.63ml, 20mmol). The mixture was stirred at room temperature under nitrogen for 30min and poured into sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x100ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to give the adduct (187) as a yellow solid (2.54g, 84%). Recrystallisation of (187) from acetonitrile gave a yellow powder (mp. 294-296°C).

δH(270MHz, DMSO) 9.05 (1H, d, *J* 2.7, ArC$_{6'}$-$\underline{\text{H}}$) 8.88 (1H, d, *J* 2.7, ArC$_{6}$-$\underline{\text{H}}$); 8.41 (1H, dd, *J* 9.5, 2.9, ArC$_{4'}$-$\underline{\text{H}}$); 7.45 (1H, dd, *J* 10.2, 2.7, ArC$_{8}$-$\underline{\text{H}}$); 7.35 (1H, d, *J* 9.5, ArC$_{3'}$-$\underline{\text{H}}$); 6.18 (1H, d, *J* 10.2, ArC$_{9}$-$\underline{\text{H}}$); 5.92(2H, br.s, N-C$\underline{\text{H}}_2$-N); 5.41 (2H, br.s, N-C$\underline{\text{H}}_2$-N).

δC(68MHz, DMSO) 159.95 (Ar$\underline{\text{C}}_{2'}$-N); 146.84 (Ar$\underline{\text{C}}_{9a}$=N); 145.63 (Ar$\underline{\text{C}}_{6'}$-H); 140.52 (Ar$\underline{\text{C}}_{6}$-H); 137.31 (Ar$\underline{\text{C}}_{5'}$-NO$_2$); 134.12 (Ar$\underline{\text{C}}_{4'}$-H); 127.95 (Ar$\underline{\text{C}}_{7}$-NO$_2$); 126.90 (Ar$\underline{\text{C}}_{8}$-H); 120.84 (Ar$\underline{\text{C}}_{9}$-H); 108.52 (Ar$\underline{\text{C}}_{3'}$-H); 61.84 (N-$\underline{\text{C}}H_2$-N); 61.46(N-$\underline{\text{C}}H_2$-N).

(3aα, 10aα)-3,3a,4,10a-Tetrahydro-8-nitrocyclopenta[*e*]pyrido[1,2-*a*] pyrimidine (184)



2-Amino-5-nitropyridine (1.00g, 7.19mmol) was added to acetonitrile (72ml) containing two equivalents of trifluoroacetic acid (1.64g) to give a 0.1M solution of the amine. To this yellow suspension was added with stirring a heterogeneous mixture at 0°C of cyclopentadiene (4.75g, 10eq.) and 37% formalin solution (1.17ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). It was then extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a dark brown oil. This was washed with petroleum ether which was then decanted. The residue was purified using flash column chromatography on alumina (eluant 100/0 - 60/40 ethyl acetate/methanol) to give the adduct as a yellow oil (1.37g, 88%).

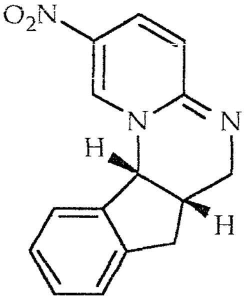
δH (270MHz) 8.31 (1H, d, *J* 2.3, ArC$_9$-H); 7.49 (1H, dd, *J* 10.2, 2.3, ArC$_7$-H); 6.50 (1H, d, *J* 10.2, ArC$_6$-H); 6.10 (1H, m, =CH); 5.99 (1H, m, =CH); 4.91 (1H, d, *J* 6.6, CH-N); 3.63 (1H, dd, *J* 15.3, 5.4, CH$_2$-N); 3.10 (1H, dd, *J* 15.3, 9.3, CH$_2$-N); 2.73 (1H, m, CH$_2$-CH); 2.59 (1H, m, CH-CH$_2$); 2.28 (1H, d, *J* 16.6, CH$_2$-CH).

δC (68MHz) 149.67 (ArC$_{5a}$=N); 140.78 (ArC$_9$-H); 135.69 (=CH); 131.96 (=CH'); 129.53 (ArC$_8$-NO$_2$); 126.13 (ArC$_7$-H); 122.92 (ArC$_6$-H); 67.52 (CH-N); 45.74 (CH$_2$-N); 36.89 (CH$_2$-CH); 32.02 (CH-CH$_2$).

υ_{max}/cm^{-1} (CHCl$_3$) 3085 (w); 2940 (br. m); 2850 (w, C-H); 1649 (s, C=N, C=C); 1600 (m); 1570 (m, C-CAr); 1499 (m, C-CAr, NO$_2$); 1324 (s, NO$_2$); 1276 (s, ArC-N).

m/z= Found: 217 (M$^+$ 45%); 277 ((M-HCN)$^+$ 2); 152 (80); 124 (7); 106 (17); 78 (14); 66 ((M-C$_6$H$_5$N$_3$O$_2$)$^+$ 100). C$_{11}$H$_{11}$N$_3$O$_2$ requires 217.

(6aα, 11bα)-6,6a,7,11b-Tetrahydro-2-nitroindeno[2,1-*e*]pyrido[1,2-*a*] pyrimidine (215)



2-Amino-5-nitropyridine (1.00g, 7.19mmol) was added to acetonitrile (72ml) containing two equivalents of trifluoroacetic acid (2.43g) to give a 0.1M solution of the amine. To this yellow suspension was added with stirring a heterogeneous mixture at 0°C of indene (8.35g, 10eq.) and 37% formalin solution (1.17ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). It was then extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a black oil. This was washed with petroleum ether which was then decanted. The residue was purified using flash column chromatography on alumina (eluant 100/0 - 0/100 ethyl acetate/methanol) to give the adduct as a brown oil (1.34g, 57%). Recrystallisation from ethyl acetate gave brown crystals (mp. 127 - 130°C).

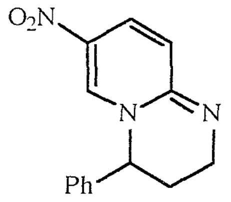
δH (270MHz) 8.47 (1H, d, *J* 2.7, ArC$_1$-$\underline{H}$); 7.47 (1H, dd, *J* 10.3, 2.7, ArC$_3$-$\underline{H}$); 7.29 (4H, m, ArC-$\underline{H}$); 6.42 (1H, d, *J* 10.3, ArC$_4$-$\underline{H}$); 5.30 (1H, d, *J* 6.0, C$\underline{H}$-N); 3.70 (1H, ddd, *J* 16.4, 5.4, 1.2, C$\underline{H}_2$-N); 3.19 (1H, dd, *J* 16.0, 6.2, C$\underline{H}_2$-CH); 2.98 (1H, dd, *J* 16.3, 9.4, C$\underline{H}_2$-N); 2.77 (1H, d, *J* 16.0, C$\underline{H}_2$-CH); 2.75 (1H, m, C$\underline{H}$-CH$_2$).

δC (68MHz) 147.73 (Ar$\underline{C}_{4a}$=N); 141.04 (Ar$\underline{C}$); 140.70 (Ar$\underline{C}$); 140.50 (Ar$\underline{C}_1$-H); 129.68 (Ar$\underline{C}_2$-NO$_2$); 129.47 (Ar$\underline{C}$-H); 127.35 (Ar$\underline{C}$-H); 126.79 (Ar$\underline{C}$-H); 125.82 (Ar$\underline{C}$-H); 123.39 (Ar$\underline{C}$-H); 123.30 (Ar$\underline{C}$-H); 65.93 ($\underline{C}$H-N); 45.50 ($\underline{C}$H$_2$-N); 34.81 ($\underline{C}$H$_2$-CH); 33.17 ($\underline{C}$H-CH$_2$).

υ_{max}/cm^{-1} (CHCl$_3$) 3010 (w); 1660 (m, C=N, C=C); 1634 (m); 1589 (m); 1504 (m); 1352 (s, C-NO$_2$); 1080 (s); 800 (s).

m/z= Found: 267.1010 (M+ 30%); 152 ((M-C$_9$H$_7$)+ 29); 128 (17); 116 ((M-C$_6$H$_5$N$_3$O$_2$)+ 100); 115 (40). $C_{15}H_{13}N_3O_2$ requires 267.1008.

3,4-Dihydro-7-nitro-4-phenyl-2*H*-pyrido[1,2-*a*]pyrimidine (189)



2-Amino-5-nitropyridine (1.00g, 7.19mmol) was added to acetonitrile (72ml) containing two equivalents of trifluoroacetic acid (1.64g) to give a 0.1M solution of the amine. To this yellow suspension was added with stirring a heterogeneous mixture at 0°C of styrene (7.49g, 10eq.) and 37% formalin solution (1.17ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). It was then extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a black oil. This was washed with petroleum ether which was then decanted. The residue was purified using flash column chromatography on alumina (eluant 100/0 - 0/100 ethyl acetate/methanol) to give the adduct as a brown oil (0.95g, 52%). The cycloadduct decomposed during attempted recrystallisations.

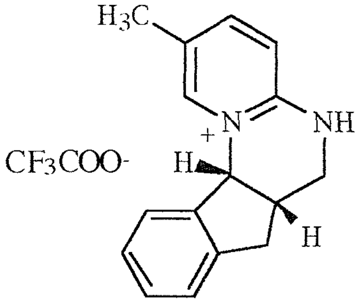
δH (270MHz) 8.04 (1H, d, *J* 2.5, ArC_6-$\underline{H}$); 7.48 (1H, dd, *J* 10.2, 2.5, ArC_8-$\underline{H}$); 7.42 - 7.25 (3H, m, Ar-$\underline{H}$); 7.15 (2H, m, Ar-$\underline{H}$); 6.53 (1H, d, *J* 10.2, ArC_9-$\underline{H}$); 5.19 (1H, m, C$\underline{H}$-N); 3.58 (1H, br d, *J* 16.8, C$\underline{H}_2$-N); 3.28 (1H, ddd, *J* 16.8, 10.6, 4.3, C$\underline{H}_2$-N); 2.25 (1H, m, C$\underline{H}_2$); 2.10 (1H, m, C$\underline{H}_2$).

δC (68MHz) 147.80 (Ar$\underline{C}_{9a}$=N); 140.41 (Ar$\underline{C}_6$-H); 139.44 (Ar$\underline{C}$); 129.48 (2xAr$\underline{C}$-H); 128.86 (Ar$\underline{C}_8$-H); 126.53 (Ar$\underline{C}$-H); 125.95 (2xAr$\underline{C}$-H); 122.83 (Ar$\underline{C}_9$-H); 63.45 ($\underline{C}$H-CH$_2$); 40.75 ($\underline{C}$H$_2$-N); 27.43 ($\underline{C}$H$_2$-CH).

υ_{max}/cm^{-1} (CHCl$_3$) 3010 (w); 1660 (m, C=N, C=C); 1634 (m); 1589 (m); 1504 (m); 1352 (s, C-NO$_2$); 1080 (s); 800 (s).

m/z= Found: 255.1009 (M$^+$ 73%); 228 ((M-HCN)$^+$ 10); 208 (5); 164 (11); 124 (16); 115 (9); 104 ((M-$C_6H_5N_3O_2$)$^+$ 100). $C_{14}H_{13}N_3O_2$ requires 255.1008.

(6aα, 11bα)-6,6a,7,11b-Tetrahydro-2-methylindeno[2,1-*e*]pyrido[1,2-*a*] pyrimidine, mono(trifluoroacetate) (219a)



2-Amino-5-methylpicoline (1.00g, 9.25mmol) was added to acetonitrile (93ml) containing two equivalents of trifluoroacetic acid (2.11g) to give a 0.1M solution of the amine. To this clear solution was added with stirring a heterogeneous mixture at 0°C of indene (10.74g, 10eq.) and 37% formalin solution (1.50ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a pale yellow oil. The oil was washed with petroleum ether and the solvent was carefully decanted to yield a cream solid. Recrystallisation of the solid from ethanol / toluene gave a white powder (1.67g, 76%), (m.p. 195 - 207°C (dec.)).

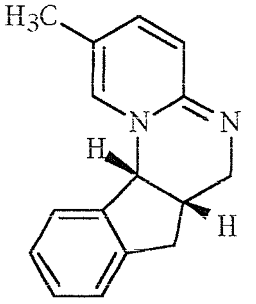
δH(270MHz) 11.16 (1H, s, N-$\underline{H}$); 7.52 (1H, s, ArC$_1$-$\underline{H}$); 7.43 - 7.19 (6H, m, ArC-$\underline{H}$); 5.58 (1H, d, *J* 5.4, C$\underline{H}$-N); 3.63 (1H, dt, *J* 12.4, 4.0, C$\underline{H}_2$-NH); 3.23 (1H, dd, *J* 15.9, 5.5, C$\underline{H}_2$-CH); 3.02 - 2.82 (2H, m, C$\underline{H}_2$-NH, C$\underline{H}$-CH$_2$); 2.79 (1H, d, *J* 15.9, C$\underline{H}_2$-CH); 2.23 (3H, s, C$\underline{H}_3$).

δC(68MHz) 150.95 (Ar$\underline{C}_{4a}$-NH); 142.35 (Ar$\underline{C}$-H); 139.89 ($\underline{C}_{quat}$); 139.76 ($\underline{C}_{quat}$); 134.75 (Ar$\underline{C}$-H); 129.88 (Ar$\underline{C}$-H); 127.49 (Ar$\underline{C}$-H); 126.93 (Ar$\underline{C}$-H); 123.39 (Ar$\underline{C}$-H); 122.02 ($\underline{C}_{quat}$-CH$_3$); 117.42 (Ar$\underline{C}$-H); 66.01 ($\underline{C}$H-N); 38.83 ($\underline{C}$H$_2$-NH); 34.39 ($\underline{C}$H$_2$-CH); 33.17 ($\underline{C}$H-CH$_2$); 17.32 ($\underline{C}$H$_3$).

υ_{max}/cm^{-1} (CHCl$_3$) 3450 (m, N-H); 3018 (w, Ar-H); 2937 (m); 1690 (s, C=C, C=N); 1598 (m); 831 (w, Ar-H); 766 (s, Ar-H).

m/z= Found: 237.1388 (M+ 32%); 236 (66); 121 ((M-C_9H_8)+ 95); 116 ((M-$C_7H_9N_2$)+ 100); 93 (57); 65 (23); 45 (15). $C_{16}H_{17}N_2$ requires 237.1392.

(6aα, 11bα)-6,6a,7,11b-Tetrahydro-2-methylindeno[2,1-*e*]pyrido[1,2-*a*] pyrimidine (219b)



The salt (100mg) was added to dichloromethane (100ml) and the mixture heated gently until all the solid had dissolved. 2M sodium hydroxide (100ml) was added and the mixture stirred at room temperature for one minute. The organic layer was separated, dried, and the solvent evaporated to yield a yellow oil, (92mg, 92%).

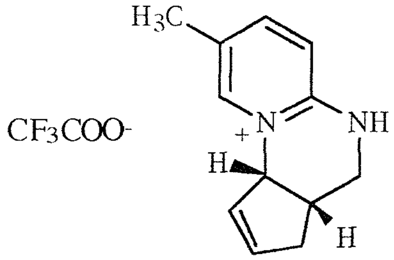
δH (270MHz) 7.32 - 7.13 (4H, m, ArC-H); 6.80 (1H, s, ArC$_1$-H); 6.62 (1H, dd, *J* 9.5, 1.9, ArC$_3$-H); 6.40 (1H, d, *J* 9.5, ArC$_4$-H); 5.04 (1H, d, *J* 6.0, CH-N); 3.49 (1H, dd, *J* 15.1, 4.8, CH$_2$-N); 3.14 (1H, dd, *J* 15.7, 6.1, CH$_2$-CH); 2.80 (1H, dd, *J* 15.1, 10.5, CH$_2$-N); 2.65 (1H, d, *J* 15.7, CH$_2$-CH); 2.56 (1H, m, CH-CH$_2$); 1.98 (3H, s, CH$_3$).

δC (68MHz) 150.26 (ArC$_{4a}$=N); 143.76 (C$_{quat}$); 140.52 (C$_{quat}$); 135.25 (ArC-H); 133.89 (ArC-H); 128.21 (ArC-H); 126.40 (ArC-H); 126.30 (ArC-H); 123.85 (ArC-H); 123.26 (ArC-H); 112.06 (ArC$_{quat}$-CH$_3$); 64.24 (CH-N); 45.19 (CH$_2$-N); 34.57 (CH$_2$-CH); 32.54 (CH-CH$_2$); 17.12 (CH$_3$).

υ_{max}/cm^{-1} (CHCl$_3$) 3031 (w, Ar-H); 2895 (s); 2883 (w); 1680 (m, C=C); 1585 (m); 835 (s, Ar-H); 761 (s, Ar-H).

m/z= Found: 236.1320 (M$^+$ 30%); 120 ((M-C$_9$H$_8$)$^+$ 95); 115 ((M-C$_7$H$_9$N$_2$)$^+$ 100); 92 (41); 48 (25). C$_{16}$H$_{16}$N$_2$ requires 236.1314.

(3aα, 10aα)-3,3a,4,10a-Tetrahydro-8-methylcyclopenta[*e*]pyrido[1,2-*a*] pyrimidine, mono(trifluoroacetate) (221)



2-Amino-5-methylpicoline (1.00g, 9.25mmol) was added to acetonitrile (93ml) containing two equivalents of trifluoroacetic acid (2.11g) to give a 0.1M solution of the amine. To this clear solution was added with stirring a heterogeneous mixture at 0°C of cyclopentadiene (6.11g, 10eq.) and 37% formalin solution (1.50ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a dark yellow oil. The oil was washed with petroleum ether and the solvent was carefully decanted. The residue was purified using flash column chromatography on alumina (eluant ethyl acetate / methanol 100/0 - 50/50) to give the adduct as a pale yellow oil (0.73g, 42%).

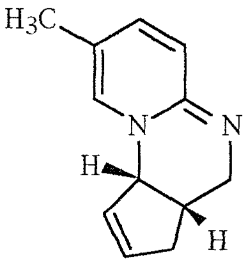
δH(270MHz) 9.89 (1H, s, N-$\underline{H}$); 7.40 (1H, s, ArC$_9$-$\underline{H}$); 7.14 (1H, d, *J* 8.6, ArC$_6$-$\underline{H}$); 6.95 (1H, d, *J* 8.6, ArC$_7$-$\underline{H}$); 5.71 (2H, m, C$\underline{H}$=C$\underline{H}$); 5.03 (1H, m, C$\underline{H}$-N); 3.25 (1H, dt, *J* 13.1, 4.3, C$\underline{H}_2$-NH); 2.63 (1H, m, C$\underline{H}$-CH$_2$); 2.49 (1H, m, C$\underline{H}_2$-CH); 2.05 (1H, d, *J* 14.8, C$\underline{H}_2$-CH); 1.91 (3H, s, C$\underline{H}_3$).

δC(68MHz) 151.27 (Ar$\underline{C}_{5a}$-NH); 142.01 ($\underline{C}$-H); 135.17 ($\underline{C}$-H); 134.59 ($\underline{C}$-H); 129.83 ($\underline{C}$-H); 122.34 ($\underline{C}_{quat}$); 115.76 ($\underline{C}$-H); 66.98 ($\underline{C}$H-N); 38.51 ($\underline{C}$H$_2$-NH); 35.62 ($\underline{C}$H$_2$-CH); 32.19 ($\underline{C}$H-CH$_2$); 16.40 ($\underline{C}$H$_3$).

υ_{max}/cm^{-1} (CHCl$_3$) 3445 (m, N-H); 3025 (w, Ar-H); 2915 (s); 1680 (m, C=C, C=N); 1568 (m, N-H); 847 (w, Ar-H); 828 (s, Ar-H).

m/z= Found: 187.1246 (M+ 28%); 186 (46); 122 ((M-C$_5$H$_5$)$^+$ 95); 66 ((M-C$_7$H$_9$N$_2$)$^+$ 100). C$_{12}$H$_{15}$N$_2$ requires 187.1235.

(3aα, 10aα)-3,3a,4,10a-Tetrahydro-8-methylcyclopenta[*e*]pyrido[1,2-*a*] pyrimidine (223)



The salt (100mg) was added to dichloromethane (100ml) and the mixture heated gently until all the solid had dissolved. 2M sodium hydroxide (100ml) was added and the mixture stirred at room temperature for one minute. The organic layer was separated, dried, and the solvent evaporated to yield a dark yellow oil, (87mg, 87%).

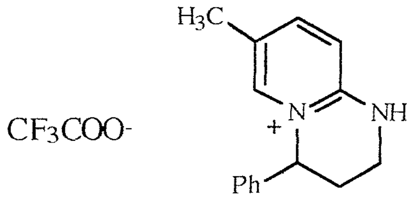
δH(270MHz) 7.58 (1H, s, ArC$_9$-$\underline{H}$); 7.34 (1H, d, *J* 9.7, ArC$_6$-$\underline{H}$); 6.82 (1H, d, *J* 9.7, ArC$_7$-$\underline{H}$); 5.91 (1H, m, =C$\underline{H}$); 5.63 (1H, m, =C$\underline{H}$); 4.88 (1H, m, C$\underline{H}$-N); 3.14 (1H, dd, *J* 15.2, 4.9, C$\underline{H}_2$-N); 3.97 (1H, dd, *J* 15.2, 9.3, C$\underline{H}_2$-N); 2.41 (1H, m, C$\underline{H}$-CH$_2$); 2.26 (1H, m, C$\underline{H}_2$-CH); 2.01 (1H, d, *J* 14.8, C$\underline{H}_2$-CH); 1.86 (3H, s, C$\underline{H}_3$).

δC(68MHz) 150.05 (Ar$\underline{C}_{5a}$=N); 143.10 ($\underline{C}$-H); 134.28 ($\underline{C}$-H); 132.93 ($\underline{C}$-H); 127.34 ($\underline{C}$-H); 119.77 ($\underline{C}$-H); 118.25 ($\underline{C}_{quat}$); 64.73 ($\underline{C}$H-N); 42.15 ($\underline{C}$H$_2$-N); 35.31 ($\underline{C}$H$_2$-CH); 31.05 ($\underline{C}$H-CH2); 16.18 ($\underline{C}$H$_3$).

υ_{max}/cm^{-1} (CHCl$_3$) 3020 (w, Ar-H); 2945 (w); 2852 (w); 1665 (m, C=C, C=N); 1592 (m); 1570 (m); 842 (w); 821 (s).

m/z= Found: 186 (M$^+$ 43%); 171 (46); 121 ((M-C$_5$H$_5$)$^+$ 95); 66 ((M-C$_7$H$_8$N$_2$)$^+$ 100). C$_{12}$H$_{14}$N$_2$ requires 186.

3,4-Dihydro-7-methyl-4-phenyl-2*H*-pyrido[1,2-*a*]pyrimidine, mono(trifluoroacetate) (222)



2-Amino-5-methylpicoline (1.00g, 9.25mmol) was added to acetonitrile (93ml) containing two equivalents of trifluoroacetic acid (2.11g) to give a 0.1M solution of the amine. To this clear solution was added with stirring a heterogeneous mixture at 0°C of styrene (9.63g, 10eq.) and 37% formalin solution (1.50ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a dark yellow oil. The oil was washed with petroleum ether and the solvent was carefully decanted. The residue was purified using flash column chromatography on alumina (eluant ethyl acetate / methanol 100/0 - 50/50) to give the adduct as a yellow oil (1.12g, 54%).

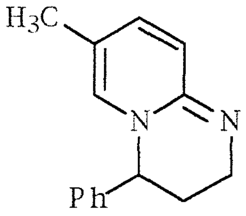
δH(270MHz) 11.03 (1H, s, N-$\underline{H}$); 7.34 - 7.25 (5H, m, ArC-$\underline{H}$); 7.13 (1H, s, ArC$_6$-$\underline{H}$); 6.94 (2H, m, ArC$_8$-$\underline{H}$, ArC$_9$-$\underline{H}$); 5.58 (1H, s, C$\underline{H}$-N); 3.45 (1H, m, C$\underline{H}_2$-NH); 3.06 (1H, td, *J* 12.5, 4.4, C$\underline{H}_2$-NH); 2.33 (1H, m, C$\underline{H}_2$-CH); 2.18 (1H, m, C$\underline{H}_2$-CH); 2.01 (3H, s, C$\underline{H}_3$).

δC(68MHz) 151.21 (Ar$\underline{C}_{9a}$-NH); 142.71 (Ar$\underline{C}$-H); 138.26 ($\underline{C}_{quat}$); 135.12 (Ar$\underline{C}$-H); 129.31 (2xAr$\underline{C}$-H); 128.79 (Ar$\underline{C}$-H); 125.55 (2xAr$\underline{C}$-H); 121.88 ($\underline{C}_{quat}$-CH$_3$); 116.41 (Ar$\underline{C}$-H); 62.79 ($\underline{C}$H-N); 34.31 ($\underline{C}$H$_2$-NH); 25.80 ($\underline{C}$H$_2$-CH); 16.84 ($\underline{C}$H$_3$).

υ_{max}/cm^{-1} (CHCl$_3$) 3450 (m, N-H); 3035 (w, Ar-H); 2900 (s); 1682 (m, C=N); 1594 (m); 840 (s); 750 (s).

m/z= Found: 225.1398 (M+ 36%); 224 (52); 121 ((M-C$_8$H$_8$)$^+$ 80); 104 ((M-C$_7$H$_9$N$_2$)$^+$ 100). C$_{15}$H$_{17}$N$_2$ requires 225.1392.

3,4-Dihydro-7-methyl-4-phenyl-2*H*-pyrido[1,2-*a*]pyrimidine (224)



The salt (100mg) was added to dichloromethane (100ml) and the mixture heated gently until all the solid had dissolved. 2M sodium hydroxide (100ml) was added and the mixture stirred at room temperature for one minute. The organic layer was separated, dried, and the solvent evaporated to yield a yellow oil, (94mg, 94%).

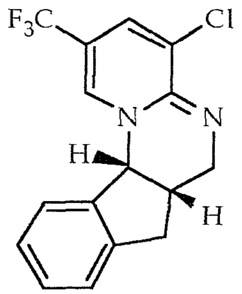
δH(270MHz) 7.31 - 7.25 (3H, m, ArC-H); 7.10 (2H, m, ArC-H); 6.93(1H, s, ArC-H); 6.82 (2H, m, ArC-H); 5.41 (1H, s, CH-N); 3.32 (1H, d, *J* 15.6, CH_2-N); 2.98 (1H, dd, *J* 15.5, 4.6, CH_2-N); 2.23 (1H, m, CH_2-CH); 2.02 (1H, m, CH_2-CH); 1.97 (3H, s, CH_3).

δC(68MHz) 148.29 (ArC_{9a}=N); 140.16 (ArC-H); 138.73 (C_{quat}); 133.28 (ArC-H); 128.63 (ArC-H); 128.31 (ArC-H); 127.07 (ArC-H); 124.56 (2xArC-H); 122.79 (ArC-H); 116.78 (C_{quat}-CH_3); 60.54 (CH-N); 38.36 (CH_2-N); 25.01 (CH_2-CH); 16.14 (CH_3).

υ_{max}/cm^{-1} ($CHCl_3$) 3025 (w); 2910 (s); 2895 (s); 1672, 1661 (m, C=N, C=C); 1582 (m); 760 (s); 752 (s).

m/z= Found: 224 (M^+ 58%); 209 (22); 120 ($(M-C_8H_8)^+$ 49); 104 ($(M-C_7H_8N_2)^+$ 100). $C_{15}H_{16}N_2$ requires 224.

(6aα, 11bα)-4-Chloro-6,6a,7,11b-tetrahydro-2-(trifluoromethyl)-indeno[1,2-*e*]pyrido [1,2-*a*]pyrimidine (225)



2-Amino-3-chloro-5-(trifluoromethyl)-pyridine (1.00g, 5.09mmol) was added to acetonitrile (51ml) containing two equivalents of trifluoroacetic acid (1.16g) to give a 0.1M solution of the amine, and the mixture was stirred at room temperature for 10 min.. To this clear solution was added with stirring a heterogeneous mixture at 0°C of indene (5.19g, 10eq.) and 37% formalin solution (0.83ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a yellow oil. The oil was washed with petroleum ether and the solvent was carefully decanted. The residue was purified using flash column chromatography on silica (eluant ethyl acetate) to give the adduct as a yellow solid (1.45g, 88%). Recrystallisation from ethyl acetate gave yellow crystals, mp. 134 - 135°C.

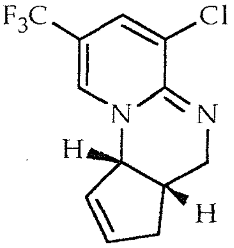
δH(270MHz) 7.32 (1H, s, ArC$_1$-$\underline{H}$); 7.23 - 7.08 (4H, m, ArC-$\underline{H}$); 7.00 (1H, s, ArC$_3$-$\underline{H}$); 5.08 (1H, d, *J* 6.0, C$\underline{H}$-N); 3.66 (1H, dd, *J* 16.0, 5.3, C$\underline{H}_2$-N); 3.05 (1H, dd, *J* 15.6, 6.0, C$\underline{H}_2$-CH); 2.83 (1H, dd, *J* 16.0, 10.1, C$\underline{H}_2$-N); 2.63 (1H, d, *J* 15.6, C$\underline{H}_2$-CH); 2.54 (1H, m, C$\underline{H}$-CH$_2$).

δC(68MHz) 144.84 (Ar$\underline{C}_{4a}$=N); 141.94 ($\underline{C}_{quat}$); 140.09 ($\underline{C}_{quat}$); 135.62 (Ar$\underline{C}_1$-H); 128.75 (Ar$\underline{C}$-H); 128.22 ($\underline{C}_{quat}$); 126.69 (Ar$\underline{C}$-H); 126.49 (Ar$\underline{C}$-H); 125.75 (Ar$\underline{C}_3$-H); 122.80 (Ar$\underline{C}$-H); 65.45 ($\underline{C}$H-N); 45.73 ($\underline{C}$H$_2$-N); 34.44 ($\underline{C}$H$_2$-CH); 32.36 ($\underline{C}$H-CH$_2$).

υ_{max}/cm^{-1} (CHCl$_3$) 3018 (m, Ar-H); 2949 (m, CH$_2$); 1660 (s, C=N, C=C); 1615 (s); 1316 (s); 1220 (s); 864 (m, Ar-H); 762 (s).

m/z= Found: 324.0640 (M$^+$ 30%); 211(12); 209 ((M-C$_9$H$_7$)$^+$ 33); 128 (15); 116 ((M-C$_7$H$_4$ClF$_3$N$_2$)$^+$ 100); 115 (41). C$_{16}$H$_{12}$ClF$_3$N$_2$ requires 324.0641.

(3aα, 10aα)-6-Chloro-3,3a,4,10a-tetrahydro-8-(trifluoromethyl)-cyclopenta[*e*]pyrido [1,2-*a*]pyrimidine (226)



2-Amino-3-chloro-5-(trifluoromethyl)-pyridine (1.00g, 5.09mmol) was added to acetonitrile (51ml) containing two equivalents of trifluoroacetic acid (1.16g) to give a 0.1M solution of the amine, and the mixture was stirred at room temperature for 10 min.. To clear solution was added with stirring a heterogeneous mixture at 0°C of cyclopentadiene (3.36g, 10eq.) and 37% formalin solution (0.83ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a yellow oil. The oil was washed with petroleum ether and the solvent was carefully decanted. The residue was purified using flash column chromatography on silica (eluant ethyl acetate) to give the adduct as a yellow solid (1.26g, 90%). Recrystallisation from ethyl acetate gave yellow crystals, mp. 122 - 124°C.

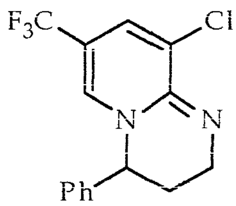
δH(270MHz) 7.00 (1H, s, ArC$_9$-$\underline{H}$); 6.68 (1H, s, ArC$_7$-$\underline{H}$); 5.59 (2H, m, C$\underline{H}$=C$\underline{H}$); 4.49 (1H, d, *J* 5.2, C$\underline{H}$-N); 3.55 (1H, dd, *J* 14.8, 5.2, C$\underline{H}_2$-N); 2.96 (1H, dd, *J* 14.8, 9.8, C$\underline{H}_2$-N); 2.34 (1H, m, C$\underline{H}_2$-CH); 2.05 (1H, m, C$\underline{H}$-CH$_2$); 1.84 (1H, d, *J* 16.2, C$\underline{H}_2$ -CH).

δC(68MHz) 147.67 (Ar$\underline{C}_{5a}$=N); 135.25 (Ar$\underline{C}_9$-H); 134.23 (=$\underline{C}$H); 131.58 (=$\underline{C}$H); 127.73 ($\underline{C}_{quat}$); 125.66 (Ar$\underline{C}_7$-H); 66.18 ($\underline{C}$H-N); 46.29 ($\underline{C}$H$_2$-N); 36.84 ($\underline{C}$H$_2$-CH); 31.98 ($\underline{C}$H-CH$_2$).

υ_{max}/cm^{-1} (CHCl$_3$) 3030 (w, Ar-H); 2850 (m, C-H); 1680 (m, C=N, C=C); 1602 (s); 1253 (s); 848 (m, Ar-H); 883 (m); 773 (s).

m/z= Found: 274.0490 (M+ 43%); 211 (34); 209 ((M-C$_5$H$_5$)$^+$ 100); 196 (7); 181 (15); 66 ((M-C$_7$H$_4$ClF$_3$N$_2$)$^+$ 88). C$_{12}$H$_{10}$ClF$_3$N$_2$ requires 274.0485.

9-Chloro-3,4-dihydro-4-phenyl-7-(trifluoromethyl)-2*H*-pyrido[1,2-*a*] pyrimidine (227)



2-Amino-3-chloro-5-(trifluoromethyl)-pyridine (1.00g, 5.09mmol) was added to acetonitrile (51ml) containing two equivalents of trifluoroacetic acid (1.16g) to give a 0.1M solution of the amine, and the mixture was stirred at room temperature for 10 min.. To this clear solution was added with stirring a heterogeneous mixture at 0°C of styrene (5.30g, 10eq.) and 37% formalin solution (0.83ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a yellow oil. The oil was washed with petroleum ether and the sovent was carefully decanted. The residue was purified using flash column chromatography on silica (eluant ethyl acetate) to give the adduct as a yellow solid (1.11g, 70%). Recrystallisation from ethyl acetate gave yellow crystals, mp. 128 - 129°C.

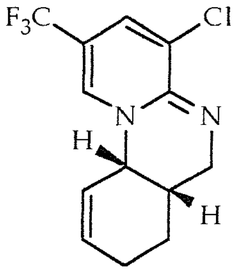
δH(270MHz) 7.24 (3H, m, ArC-$\underline{H}$); 7.00 (4H, m, ArC-$\underline{H}$); 5.09 (1H, s, C$\underline{H}$-N); 3.53 (1H, br. d, *J* 16.4, C$\underline{H}_2$-N); 3.17 (1H, ddd, *J* 16.4, 11.3, 4.6, C$\underline{H}_2$-N); 2.00 (2H, m, C$\underline{H}_2$ -CH).

δC(68MHz) 145.66 (Ar$\underline{C}_{9a}$=N); 140.05 ($\underline{C}_{quat}$); 135.79 (Ar$\underline{C}_6$-H); 128.90 (2xAr$\underline{C}$-H); 128.10 (Ar$\underline{C}$-H); 127.51 ($\underline{C}_{quat}$); 126.64 (Ar$\underline{C}$-H); 125.49 (2xAr$\underline{C}$-H); 62.85 ($\underline{C}$H-N); 39.82 ($\underline{C}H_2$-N); 26.66 ($\underline{C}H_2$-CH).

υ_{max}/cm^{-1} ($CHCl_3$) 3017 (s, Ar-H); 2959 (s); 1659 (s, C=C, C=N); 1608 (s); 1335 (s); 1220 (s); 874 (m, Ar-H); 761 (s); 700 (s).

m/z= Found: 312.0638 (M^+ 38%); 277 ($(M-Cl)^+$ 11); 181 (11); 104 ($(M-C_7H_4ClF_3N_2)^+$ 100); 70 (10). $C_{15}H_{12}ClF_3N_2$ requires 312.0641.

(6aα, 10aα)-4-Chloro-6a,7,8,10a-tetrahydro-2-(trifluoromethyl)-6*H*-pyrido[1,2-*a*] quinazoline (228)



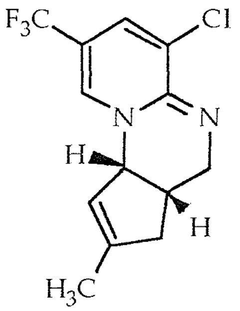
2-Amino-3-chloro-5-(trifluoromethyl)-pyridine (1.00g, 5.09mmol) was added to acetonitrile (51ml) containing two equivalents of trifluoroacetic acid (1.16g) to give a 0.1M solution of the amine, and the mixture was stirred at room temperature for 10 min.. To this clear solution was added with stirring a heterogeneous mixture at 0°C of cyclohexadiene (4.08g, 10eq.) and 37% formalin solution (0.83ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a yellow oil. The oil was washed with petroleum ether and the solvent was carefully decanted. The residue was purified using flash column chromatography on silica (eluant ethyl acetate) to give the adduct as a yellow solid (1.25g, 85%). Recrystallisation from ethyl acetate gave yellow crystals, mp. 134 - 135°C.

δH(270MHz) 7.04 (1H, s, ArC$_3$-$\underline{H}$); 6.93 (1H, s, ArC$_1$-$\underline{H}$); 5.78 (1H, m, =C$\underline{H}$-CH); 5.51 (1H, m, =C$\underline{H}$-CH$_2$); 4.29 (1H, s, C$\underline{H}$-N); 3.40 (2H, m, C$\underline{H}_2$-N); 2.11 (1H, m, C$\underline{H}$-CH); 2.02 (2H, m, C$\underline{H}_2$-CH$_2$); 1.73 (2H, m, C$\underline{H}_2$-CH).

υ_{max}/cm^{-1} (CHCl$_3$) 3038 (w, Ar-H); 2852 (m, C-H); 1670 (m, C=N, C=C); 1600 (s); 1239 (s); 853 (m, Ar-H); 770 (s).

m/z= Found: 288.0647 (M$^+$ 48%); 211 (25); 209 ((M-C$_6$H$_7$)$^+$ 70); 180 (12); 80 ((M-C$_7$H$_4$ClF$_3$N$_2$)$^+$ 100); 79 (45). C$_{13}$H$_{12}$ClF$_3$N$_2$ requires 288.0641.

(3aα, 10aα)-6-Chloro-2-methyl-3,3a,4,10a-tetrahydro-8-(trifluoromethyl)-cyclopenta[*e*]pyrido[1,2-*a*]pyrimidine (229)



2-Amino-3-chloro-5-(trifluoromethyl)-pyridine (1.00g, 5.09mmol) was added to acetonitrile (51ml) containing two equivalents of trifluoroacetic acid (1.16g) to give a 0.1M solution of the amine, and the mixture stirred at room temperature for 10 min.. To this white solution was added with stirring a heterogeneous mixture at 0°C of methylcyclopentadiene (4.08g, 10eq.) and 37% formalin solution (0.83ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a brown oil. The oil was washed with petroleum ether and the solvent was carefully decanted. The residue was purified using flash column chromatography on silica (eluant ethyl acetate) to give the adduct as an orange oil (0.06g, 4%).

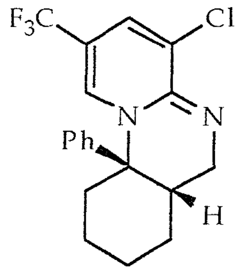
δH(270MHz) 7.20 (1H, s, ArC$_9$-H); 7.04 (1H, s, ArC$_7$-H); 5.49 (1H, s, =CH); 4.72 (1H, m, CH-N); 3.61 (1H, dd, *J* 15.2, 5.4, CH$_2$-N); 3.08 (1H, dd, *J* 15.2, 10.2, CH$_2$-N); 2.53 (2H, m, CH-CH$_2$, CH$_2$-CH); 2.06 (1H, d, *J* 15.8, CH$_2$-CH); 1.75 (3H, s, CH$_3$).

δC(68MHz) 147.39 (ArC$_{5a}$=N); 145.65 (ArC$_6$); 134.82 (ArC$_9$-H); 127.94 (C$_{quat}$-CH$_3$); 125.97 (ArC$_7$-H); 124.89 (=CH); 67.37 (CH-N); 46.92 (CH$_2$-N); 40.99 (CH$_2$-CH); 33.21 (CH-CH$_2$); 16.93 (CH$_3$).

υ_{max}/cm^{-1} (CHCl$_3$) 3020 (M, Ar-H); 2889 (s); 1652 (m, C=C, C=N); 1598 (s); 1238 (s); 856 (w, Ar-H); 760 (s).

m/z= Found: 288 (M$^+$ 51%); 273 (100); 209 (22); 198 (21); 153 (15); 80 ((M-C$_7$H$_4$ClF$_3$N$_2$)$^+$ 35). C$_{13}$H$_{12}$ClF$_3$N$_2$ requires 288.

(6aα, 10aα)-4-Chloro-6a,7,8,9,10,10a-hexahydro-10a-phenyl-2-(trifluoromethyl)-6*H*-pyrido[1,2-*a*]quinazoline (231)



2-Amino-3-chloro-5-(trifluoromethyl)-pyridine (1.00g, 5.09mmol) was added to acetonitrile (51ml) containing two equivalents of trifluoroacetic acid (1.16g) to give a 0.1M solution of the amine, and the mixture stirred at room temperature for 10 min.. To this clear solution was added with stirring a heterogeneous mixture at 0°C of 1-phenylcyclohexene (4.03g, 5eq.) and 37% formalin solution (0.83ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a yellow oil. The oil was washed with petroleum ether and the solvent was carefully decanted. The residue was purified using flash column chromatography on silica (eluant ethyl acetate) to give the adduct as a yellow solid (1.11g, 70%). Recrystallisation from ethyl acetate gave yellow crystals, mp. 128 - 129°C.

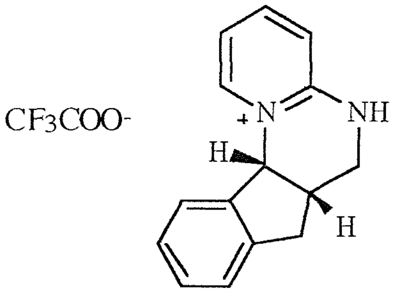
δH(270MHz) 7.25 (4H, m, ArC-$\underline{H}$); 7.11 (1H, s, ArC$_1$-$\underline{H}$); 6.97 (2H, m, ArC$_3$-$\underline{H}$, ArC-$\underline{H}$); 3.24 (1H, d, *J* 16.6, C$\underline{H}_2$-N); 3.06 (1H, dd, *J* 16.6, 4.4, C$\underline{H}_2$-N); 2.38 - 1.16 (9H, m, C$\underline{H}_2$, C$\underline{H}$).

δC(68MHz) 144.84 (Ar$\underline{C}_{5a}$=N); 144.51 ($\underline{C}_{quat}$); 131.91 (Ar$\underline{C}$-H); 129.19 (2xAr$\underline{C}$-H); 128.53 ($\underline{C}_{quat}$); 127.75 (Ar$\underline{C}$-H); 125.68 (Ar$\underline{C}$-H); 124.28 (2xAr$\underline{C}$-H); 66.88 ($\underline{C}_{quat}$-Ph); 36.89 ($\underline{C}H_2$); 38.02 ($\underline{C}H_2$); 36.89 ($\underline{C}H_2$); 26.56 ($\underline{C}$H); 25.21 ($\underline{C}H_2$); 21.03 ($\underline{C}H_2$).

υ_{max}/cm^{-1} ($CHCl_3$) 3020 (s, Ar-H); 2954 (s); 2892 (s); 1650 (s, C=C, C=N); 1610 (s); 1336 (s); 1220 (s, C-F); 880 (w, Ar-H); 752 (s); 699 (s); 670 (s).

m/z= Found: 366.1122 (M+ 34%); 289 ((M-C_6H_5)+ 22); 210 (12); 208 ((M-$C_{12}H_{14}$)+ 53); 180 (18); 158 ((M-$C_7H_4ClF_3N_2$)+ 100); 78 (8). $C_{19}H_{18}ClF_3N_2$ requires 366.1111.

(6aα, 11bα)-6,6a,7,11b-Tetrahydroindeno[2,1-*e*]pyrido[1,2-*a*]pyrimidine, mono(trifluoroacetate) (232)



2-Aminopyridine (1.00g, 10.64mmol) was added to acetonitrile (106ml) containing two equivalents of trifluoroacetic acid (2.43g) to give a 0.1M solution of the amine. To this pale yellow solution was added with stirring a heterogeneous mixture at 0°C of indene (12.34g, 10eq.) and 37% formalin solution (1.72ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). It was then extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a cream solid. This was washed with petroleum ether which was then decanted. Recrystallisation of the solid from ethyl acetate / ethanol gave large clear crystals (2.08g, 88%), (m.p. 180 - 193°C (dec.)).

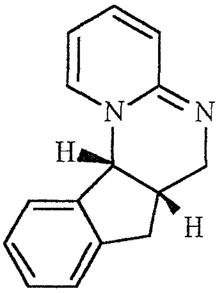
δH (270MHz) 11.27 (1H, s, N-H); 7.81 (1H, d, *J* 6.6, ArC$_1$-H); 7.43 (2H, m, ArC$_2$-H, ArC$_3$-H); 7.22 (4H, m, ArC-H); 6.72 (1H, t, *J* 6.7, ArC$_4$-H); 5.67 (1H, d, *J* 5.7, CH-N); 3.61 (1H, dd, *J* 12.9, 4.6, CH$_2$-NH); 3.22 (1H, dd, *J* 15.9, 5.7, CH$_2$-CH); 2.96 (1H, m, CH-CH$_2$); 2.88 (1H, dd, *J* 13.0, 9.8, CH$_2$-NH); 2.76 (1H, d, *J* 15 8, CH$_2$-CH).

δC (68MHz) 152.22 (ArC$_{4a}$-NH); 139.78 (ArC$_1$-H); 139.65 (ArC); 137.76 (ArC-H); 129.88 (ArC-H); 127.52 (ArC-H); 126.89 (ArC-H); 123.39 (ArC-H); 117.53 (ArC-H); 112.19 (ArC-H); 66.13 (CH-N); 38.80 (CH$_2$-NH); 34.38 (CH$_2$-CH); 33.01 (CH-CH$_2$).

υ_{max}/cm^{-1} (CHCl$_3$) 3018 (m, Ar-H); 2850 (w); 2399 (w); 1678 (s, C=C, C=N); 1597 (m); 1521 (w); 758 (s).

m/z= Found: 223.1238 (M$^+$ 100%); 129 (13); 107 ((M-C$_9$H$_8$)$^+$ 58); 116 (16); 92 (8). C$_{15}$H$_{15}$N$_2$ requires 223.1235.

(6aα, 11bα)-6,6a,7,11b-Tetrahydroindeno[2,1-*e*]pyrido[1,2-*a*]pyrimidine (233)



The salt (100mg) was dissolved in dichloromethane (100ml) and 2M sodium hydroxide (100ml) added and the mixture stirred at room temperature for one minute. The organic layer was separated, dried, and the solvent evaporated to yield a yellow oil, (90mg, 90%).

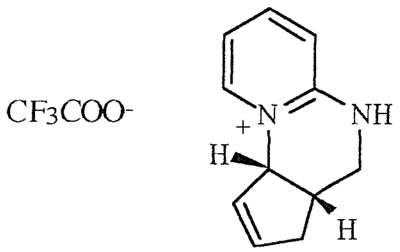
δH (270MHz) 7.27 (4H, m, ArC-H); 6.99 (1H, dt, *J* 7.2, 0.8, 0.8, ArC$_1$-H); 6.71 (1H, ddd, *J* 9.5, 6.2, 1.7, ArC$_2$-H); 6.39 (1H, d, *J* 9.5, ArC$_3$-H); 6.18 (1H, t, *J* 6.5, ArC$_4$-H); 5.76 (1H, d, *J* 6.2, CH-N); 3.52 (1H, ddd, *J* 15.3, 5.4, 1.4, CH$_2$-N); 3.14 (1H, dd, *J* 15.6, 6.0, CH$_2$-CH); 2.81 (1H, dd, *J* 15.3, 10.4, CH$_2$-N); 2.66 (1H, d, *J* 15.6, CH$_2$ -CH); 2.59 (1H, m, CH-CH$_2$).

δC (68MHz) 150.63 (ArC$_{4a}$=N); 143.7 (ArC); 140.57 (ArC); 137.14 (ArC-H); 131.89 (ArC-H); 128.33 (ArC-H); 126.50 (ArC-H); 126.39 (ArC-H); 124.36 (ArC-H); 123.28 (ArC-H); 103.18 (ArC-H); 64.41 (CH-N); 45.34 (CH$_2$-N); 34.83 (CH$_2$-CH); 32.48 (CH-CH$_2$).

υ_{max}/cm^{-1} (CHCl$_3$) 3020 (w); 1671, 1652 (m, C=N, C=C); 1628 (m); 1589 (m); 1503 (m); 980 (m); 800 (m); 753, 740 (s, Ar-H).

m/z= Found: 222.1150 (M$^+$ 48%); 116 ((M-C$_6$H$_6$N$_2$)$^+$ 100); 107 ((M-C$_9$H$_7$)$^+$ 39); 98 (27); 76 (30). C$_{15}$H$_{14}$N$_2$ requires 222.1157.

(3aα, 10aα)-3,3a,4,10a-Tetrahydrocyclopenta[*e*]pyrido[1,2-*a*]pyrimidine, mono(trifluoroacetate) (234)



2-Aminopyridine (1.00g, 10.64mmol) was added to acetonitrile (106ml) containing two equivalents of trifluoroacetic acid (2.43g) to give a 0.1M solution of the amine. To this pale yellow solution was added with stirring a heterogeneous mixture at 0°C of cyclopentadiene (7.02g, 10eq.) and 37% formalin solution (1.72ml, 2eq). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). It was then extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a pale yellow oil. This was washed with petroleum ether which was then decanted. The residue was purified using flash column chromatography on silica gel (eluant 100/0 - 50/50 ethyl acetate/methanol) to give the title adduct as a clear oil (0.79g, 46%).

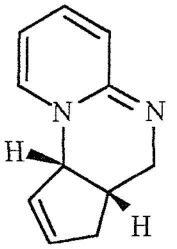
δH (270MHz) 10.92 (1H, s, N-$\underline{H}$); 7.67 (1H, d, *J* 6.0, ArC$_9$-$\underline{H}$); 7.52 (1H, ddd, *J* 9.1, 6.8, 1.5, ArC$_8$-$\underline{H}$); 7.39 (1H, m, ArC$_7$-$\underline{H}$); 6.73 (1H, ddd, *J* 6.8, 6.8, 1.4, ArC$_6$-$\underline{H}$); 6.12 (1H, m, =C$\underline{H}$); 6.06 (1H, m, =C$\underline{H}$); 5.29 (1H, d, *J* 6.9, C$\underline{H}$-NH); 3.58 (1H, ddd, *J* 13.3, 5.3, 3.8, C$\underline{H}_2$-NH); 3.13 (1H, ddd, *J* 13.3, 8.5, 1.4, C$\underline{H}_2$-N); 2.73-2.98 (2H, m, C$\underline{H}_2$ -CH, C$\underline{H}$-CH$_2$); 2.34 (1H, d, *J* 16.0, C$\underline{H}_2$-CH).

δC (68MHz) 153.28 (Ar$\underline{C}_{5a}$-NH); 139.69 (Ar$\underline{C}_9$-H); 137.26 (Ar$\underline{C}_7$-H); 135.97 (=$\underline{C}$H); 130.11 (=$\underline{C}$H); 117.18 (Ar$\underline{C}_8$-H); 112.71 (Ar$\underline{C}_6$-H); 67.64 ($\underline{C}$H-N); 38.99 ($\underline{C}$H$_2$-N); 36.21 ($\underline{C}$H$_2$-CH); 32.54 ($\underline{C}$H-CH$_2$).

υ_{max}/cm^{-1} (CHCl$_3$) 3350 (w); 3025 (m, Ar-H); 2850 (w, C-H); 2399 (w); 1650 (s, C=C, C=N); 1600 (m); 1530 (m); 828 (s).

m/z= Found: 173.1076 (M+ 100%); 108 ((M-C$_5$H$_5$)$^+$ 58); 78 (22); 66 (21). C$_{11}$H$_{13}$N$_2$ requires 173.1079.

(3aα, 10aα)-3,3a,4,10a-Tetrahydrocyclopenta[*e*]pyrido[1,2-*a*] pyrimidine (186)



The salt (100mg) was dissolved in dichloromethane (100ml) and 2M sodium hydroxide (100ml) added and the mixture stirred at room temperature for one minute. The organic layer was separated, dried, and the solvent evaporated to yield a dark yellow oil, (86mg, 86%).

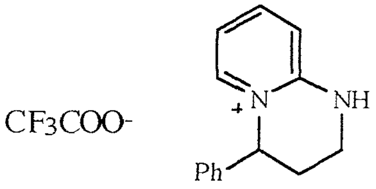
δH (270MHz) 7.60 (1H, d, *J* 6.8, ArC$_9$-$\underline{H}$); 7.40 (2H, m, ArC$_7$-$\underline{H}$, ArC$_8$-$\underline{H}$); 6.62 (1H, m, ArC$_6$-$\underline{H}$); 6.10 (1H, m, =C$\underline{H}$); 6.02 (1H, m, =C$\underline{H}$); 5.18 (1H, s, C$\underline{H}$-N); 3.59 (1H, dd, *J* 13.5, 5.3, C$\underline{H_2}$-N); 3.12 (1H, dd, *J* 13.5, 8.8, C$\underline{H_2}$-N); 2.90-2.70 (2H, m, C$\underline{H_2}$-C=, C$\underline{H}$-CH$_2$); 2.34 (1H, d, *J* 16.0, C$\underline{H_2}$-C=).

δC (68MHz) 153.38 (Ar$\underline{C}_{5a}$=N); 138.85 (Ar$\underline{C}_9$-H); 136.80 (Ar$\underline{C}_7$-H); 135.88 (=$\underline{C}$H); 130.31 (=$\underline{C}$H); 118.18 (Ar$\underline{C}_8$-H); 111.73 (Ar$\underline{C}_6$-H); 67.54 ($\underline{C}$H-N); 39.66 ($\underline{C}$H$_2$-N); 36.42 ($\underline{C}$H$_2$-CH); 31.99 ($\underline{C}$H-CH$_2$).

υ_{max}/cm^{-1} (CHCl$_3$) 3000 (m, Ar-H); 2860 (w, C-H); 1685 (s, C=C, C=N); 1600 (m); 1470 (m); 839 (s).

m/z= Found: 172 (M+ 42%); 149 (12); 123 (12); 107 ((M-C$_5$H$_5$)$^+$ 100); 94 (22); 79 (61); 66 ((M-C$_6$H$_6$N$_2$)$^+$ 24). C$_{11}$H$_{13}$N$_2$ requires 172.

3,4-Dihydro-4-phenyl-2*H*-pyrido[1,2-*a*]pyrimidine, mono(trifluoroacetate) (235)



2-Aminopyridine (1.00g, 10.64mmol) was added to acetonitrile (106ml) containing two equivalents of trifluoroacetic acid (2.43g) to give a 0.1M solution of the amine. To this pale yellow solution was added with stirring a heterogeneous mixture at 0°C of styrene (11.07g, 10eq.) and 37% formalin solution (1.72ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). It was then extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a pale yellow oil. This was washed with petroleum ether which was then carefully decanted. The residue was purified using flash column chromatography on silical gel (eluant 100/0 - 30/70 ethyl acetate/methanol) to give the adduct as a clear oil (0.81g, 36%).

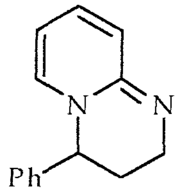
δH (270MHz) 11.30 (1H, s, N-$\underline{H}$); 7.78 (1H, d, *J* 6.5, ArC$_6$-$\underline{H}$); 7.34 (3H, m, ArC-$\underline{H}$); 7.23 (4H, m, ArC-$\underline{H}$); 6.68 (1H, t, *J* 6.8, ArC$_9$-$\underline{H}$); 5.73 (1H, d, *J* 5.8, C$\underline{H}$-N); 3.57 (1H, d, *J* 16.6, C$\underline{H}_2$-NH); 3.26 (1H, dd, *J* 16.6, 10.4, C$\underline{H}_2$-NH); 2.34 (1H, m, C$\underline{H}_2$); 2.12 (1H, m, C$\underline{H}_2$).

δC(68MHz) 152.82 (Ar$\underline{C}_{9a}$-NH); 138.88 (Ar$\underline{C}_6$-H); 138.27 ($\underline{C}_{quat}$); 137.25 (Ar$\underline{C}$-H); 129.83 (Ar$\underline{C}$-H); 128.28 (2Ar$\underline{C}$-H); 126.94 (Ar$\underline{C}$-H); 125.86 (2Ar$\underline{C}$-H); 123.15 (Ar$\underline{C}$-H); 65.73 ($\underline{C}$H-N); 38.92 ($\underline{C}$H$_2$-NH); 27.29 ($\underline{C}$H$_2$-CH).

υ_{max}/cm^{-1} (CHCl$_3$) 3452 (m, N-H); 3020 (m, Ar-H); 2903 (s); 1668 (s, C=C, C=N); 1546 (w); 1503 (m); 902 (s); 881 (m); 756 (s); 748 (s).

m/z= Found: 211.1248 (M$^+$ 47%); 183 (11); 107 ((M-C$_8$H$_8$)$^+$ 73); 104 ((M-C$_6$H$_7$N$_2$)$^+$ 100); 77 (32). C$_{14}$H$_{15}$N$_2$ requires 211.1235.

3,4-Dihydro-4-phenyl-2*H*-pyrido[1,2-*a*]pyrimidine (196)



The salt (100mg) was dissolved in dichloromethane (100ml) and 2M sodium hydroxide (100ml) added and the mixture stirred at room temperature for one minute. The organic layer was separated, dried, and the solvent evaporated to yield a yellow oil, (85mg, 85%).

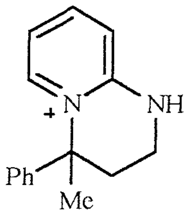
δH (270MHz) 7.31-7.21 (3H, m, ArC-$\underline{H}$); 7.10 (2H, m, Ar-H); 6.82 (1H, m, ArC$_6$-$\underline{H}$); 6.68 (1H, dd, *J* 9.4, 6.0, ArC$_7$-$\underline{H}$); 6.38 (1H, d, *J* 9.4, ArC$_8$-$\underline{H}$); 6.31 (1H, t, *J* 6.4, ArC$_9$-$\underline{H}$); 5.62 (1H, m, C$\underline{H}$-N); 3.52 (1H, d, *J* 15.7, C$\underline{H}_2$-N); 3.07 (1H, ddd, *J* 15.7, 9.5, 3.6, C$\underline{H}_2$-N); 2.21 (1H, m, C$\underline{H}_2$); 2.08 (1H, m, C$\underline{H}_2$).

δC (68MHz) 147.82 (Ar$\underline{C}_{9a}$=N); 140.74 (Ar$\underline{C}_6$-H); 139.22 (Ar$\underline{C}$); 130.67 (Ar$\underline{C}$-H); 128.73 (Ar$\underline{C}$-H); 128.63 (Ar$\underline{C}$-H); 127.34 (Ar$\underline{C}$-H); 125.85 (2Ar$\underline{C}$-H); 123.91 (Ar$\underline{C}$-H); 122.93 (Ar$\underline{C}$-H); 62.25 ($\underline{C}$H-N); 40.39 ($\underline{C}$H$_2$-N); 26.29 ($\underline{C}$H$_2$-CH).

υ_{max}/cm^{-1} (CHCl$_3$) 3025 (m); 2905 (m); 1652, 1640 (m, C=N, C=C); 1592 (s); 1378 (w); 762 (s, Ar-H); 740 (s, Ar-H).

m/z= Found: 210.1167 (M$^+$ 82%); 113 (22); 112 (28); 104 ((M-C$_6$H$_6$N$_2$)$^+$ 100); 83 (17); 76 (10). C$_{14}$H$_{14}$N$_2$ requires 210.1157.

3,4-Dihydro-4-methyl-4-phenyl-2*H*-pyrido[1,2-*a*]pyrimidine, mono(trifluoroacetate) (236)



2-Aminopyridine (1.00g, 10.64mmol) was added to acetonitrile (106ml) containing two equivalents of trifluoroacetic acid (2.43g) to give the amine as a 0.1M solution. To this pale yellow solution was added with stirring a heterogeneous mixture at 0°C of α-methylstyrene (12.56g, 10eq.) and 37% formalin solution (1.73ml, 2eq). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). It was then extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a pale yellow oil. This was washed with petroleum ether which was then decanted. The residue was purified using flash column chromatography on silical gel (eluant 100/0 - 30/70 ethyl acetate/methanol) to give the title adduct as a clear oil (0.79g, 46%).

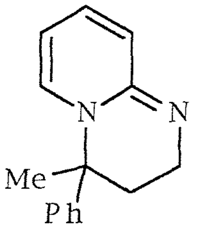
δH (270MHz) 11.21 (1H, s, N-$\underline{H}$); 7.51 (2H, m, Ar-$\underline{H}$); 7.39 (4H, m, Ar-$\underline{H}$); 7.09 (2H, m, Ar-$\underline{H}$); 6.61 (1H, m, ArC$_9$-$\underline{H}$); 3.58 (1H, m, C$\underline{H}_2$-NH); 3.32 (1H, m, C$\underline{H}_2$-NH); 2.45 (1H, m, C$\underline{H}_2$-C$_{quat}$); 2.27 (1H, m, C$\underline{H}_2$-C$_{quat}$); 2.05 (3H, s, C$\underline{H}_3$).

δC (68MHz) 153.05 (Ar$\underline{C}_{9a}$-NH); 141.60 ($\underline{C}_{quat}$); 139.65 (Ar$\underline{C}$-H); 134.30 (Ar$\underline{C}$-H); 129.61 (2xAr$\underline{C}$-H); 128.98 (Ar$\underline{C}$-H); 125.19 (2xAr$\underline{C}$-H); 122.34 (Ar$\underline{C}$-H); 119.97 (Ar$\underline{C}$-H); 65.80 ($\underline{C}_{quat}$-CH$_3$); 35.57 ($\underline{C}$H$_2$-NH); 34.70 ($\underline{C}$H$_2$-C$_{quat}$); 27.43 ($\underline{C}$H$_3$).

υ_{max}/cm^{-1} (CHCl$_3$) 3452 (m, N-H); 3020 (m, Ar-H); 2903 (s); 1668 (s, C=C, C=N); 1546 (w); 1503 (m); 902 (s); 881 (m); 756 (s); 748 (s).

m/z= Found: 225.1399 (M$^+$ 100%); 147 (5); 131 (8); 107 ((M-C$_9$H$_{10}$)$^+$ 95); 91 (7); 78 (13). C$_{15}$H$_{17}$N$_2$ requires 225.1392.

3,4-Dihydro-4-methyl-4-phenyl-2*H*-pyrido[1,2-*a*]pyrimidine (237)



The salt (100mg) was dissolved in dichloromethane (100ml) and 2M sodium hydroxide (100ml) added and the mixture stirred at room temperature for one minute. The organic layer was separated, dried, and the solvent evaporated to yield a dark yellow oil, (92mg, 92%).

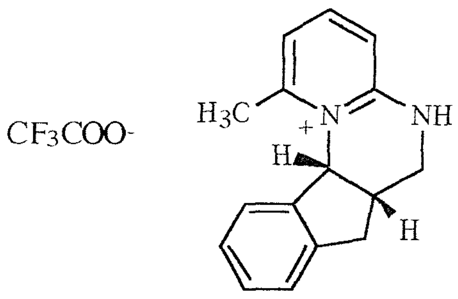
δH (270MHz) 7.78 (1H, d, *J* 6.6, ArC$_6$-H); 7.52 (2H, m, Ar-H); 7.32 (2H, m, ArC$_8$-H, ArC$_7$-H); 7.19 (3H, m, Ar-H); 6.52 (1H, m, ArC$_9$-H); 3.79 (1H, dd, *J* 12.8, 4.5, CH$_2$-N); 3.48 (1H, d, *J* 12.8, CH$_2$-N); 2.35 (1H, dd, *J* 13.8, 4.5, CH$_2$-C$_{quat}$); 2.04 (1H, m, CH$_2$-C$_{quat}$); 1.89 (3H, s, CH$_3$).

δC (68MHz) 150.28 (ArC$_{9a}$=N); 140.50 (C$_{quat}$); 139.58 (ArC$_6$-H); 135.80 (ArC-H); 136.76 (2xArC-H); 128.83 (ArC-H); 125.19 (2xArC-H); 121.42 (ArC-H); 119.99 (ArC-H); 63.64 (C$_{quat}$-CH$_3$); 38.76 (CH$_2$-N); 34.42 (CH$_2$-C$_{quat}$); 31.69 (CH$_3$).

υ_{max}/cm^{-1} (CHCl$_3$) 2982 (m); 2940 (w, C-H); 1649 (s, C=C, C=N); 1597 (m); 1570 (m); 1307 (m); 839 (s).

m/z= Found: 224 (M$^+$ 39%); 209 ((M-CH$_3$)$^+$ 100); 153 (12); 147 (28); 123 (22); 86 (16); 62 (23). $C_{15}H_{16}N_2$ requires 224.

(6aα, 11bα)-6,6a,7,11b-Tetrahydro-1-methylindeno[2,1-*e*]pyrido[1,2-*a*] pyrimidine, mono(trifluoroacetate) (238)



2-Amino-6-methylpicoline (1.00g, 9.25mmol) was added to acetonitrile (93ml) containing two equivalents of trifluoroacetic acid (2.11g) to give a 0.1M solution of the amine. To this clear solution was added with stirring a heterogeneous mixture at 0°C of indene (10.74g, 10eq.) and 37% formalin solution (1.50ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a yellow oil. The oil was washed with petroleum ether and the solvent was carefully decanted to yield a cream solid. Recrystallisation of the solid from ethanol / toluene gave a white powder (1.36g, 62%), (m.p. 198 - 210°C (dec.)).

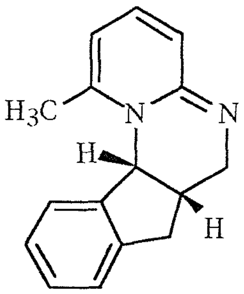
δH(270MHz) 7.38 - 7.11 (5H, m, ArC-$\underline{\mathrm{H}}$); 6.84 (1H, d, *J* 7.5, ArC-$\underline{\mathrm{H}}$); 6.57 (1H, d, *J* 7.5, ArC-$\underline{\mathrm{H}}$); 5.77 (1H, d, *J* 5.4, C$\underline{\mathrm{H}}$-N); 3.53 (1H, dt, *J* 14.1, 5.2, C$\underline{\mathrm{H}}_2$-NH); 3.28 (1H, dd, *J* 15.7, 5.0, C$\underline{\mathrm{H}}_2$-NH); 2.85 (1H, m, C$\underline{\mathrm{H}}$-CH$_2$); 2.68 (2H, m, C$\underline{\mathrm{H}}_2$-CH); 2.60 (3H, s, C$\underline{\mathrm{H}}_3$).

δC(68MHz) 152.43 (Ar$\underline{\mathrm{C}}_{4a}$-NH); 145.87 ($\underline{\mathrm{C}}_{\mathrm{quat}}$); 139.69 ($\underline{\mathrm{C}}_{\mathrm{quat}}$); 139.42 (Ar$\underline{\mathrm{C}}$-H); 139.19 ($\underline{\mathrm{C}}_{\mathrm{quat}}$); 129.39 (Ar$\underline{\mathrm{C}}$-H); 127.28 (Ar$\underline{\mathrm{C}}$-H); 122.92 (Ar$\underline{\mathrm{C}}$-H); 115.05 (Ar$\underline{\mathrm{C}}$-H); 113.12 (Ar$\underline{\mathrm{C}}$-H); 61.98 ($\underline{\mathrm{C}}$H-N); 38.31 ($\underline{\mathrm{C}}H_2$-NH); 34.42 ($\underline{\mathrm{C}}H_2$-CH); 32.36 ($\underline{\mathrm{C}}$H-CH$_2$); 19.69 ($\underline{\mathrm{C}}H_3$).

υ_{max}/cm^{-1} (CHCl$_3$) 3450 (m, N-H); 3020 (w, Ar-H); 2938 (m); 1688 (s, C=C); 1580 (m); 745 (s, Ar-H); 801 (s, Ar-H).

m/z= Found: 237.1380 (M$^+$ 32%); 235 (58); 121 ((M-C$_9$H$_8$)$^+$ 88); 116 ((M-C$_7$H$_9$N$_2$)$^+$ 100); 93 (48); 73 (28); 44 (13). C$_{16}$H$_{17}$N$_2$ requires 237.1392.

(6aα, 11bα)-6,6a,7,11b-Tetrahydro-1-methylindeno[2,1-*e*]pyrido[1,2-*a*] pyrimidine (239)



The salt (100mg) was added to dichloromethane (100ml) and the mixture heated gently until all the solid had dissolved. 2M sodium hydroxide (100ml) was added and the mixture stirred at room temperature for one minute. The organic layer was separated, dried, and the solvent evaporated to yield a yellow oil, (87mg, 87%).

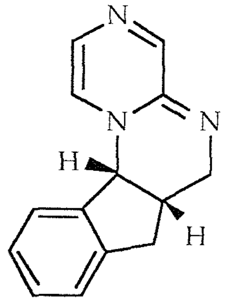
δH (270MHz) 7.26 - 7.08 (3H, m, ArC-$\underline{\mathrm{H}}$); 7.01 (1H, d, *J* 7.3, ArC-$\underline{\mathrm{H}}$); 6.66 (1H, d, *J* 9.4, 6.6, ArC$_3$-$\underline{\mathrm{H}}$); 6.33 (1H, d, *J* 9.4, ArC$_4$-$\underline{\mathrm{H}}$); 5.68 (1H, d, *J* 6.6, ArC$_2$-$\underline{\mathrm{H}}$); 5.34 (1H, d, *J* 5.6, C$\underline{\mathrm{H}}$-N); 3.46 (1H, ddd, *J* 15.5, 5.6, 1.4, C$\underline{\mathrm{H}}_2$-N); 3.14 (1H, dd, *J* 15.5, 5.2, C$\underline{\mathrm{H}}_2$-CH); 2.66 (1H, dd, *J* 15.5, 11.0, C$\underline{\mathrm{H}}_2$-N); 2.60 (1H, d, *J* 15.5, C$\underline{\mathrm{H}}_2$-CH); 2.49 (1H, m, C$\underline{\mathrm{H}}$-CH$_2$); 2.32 (3H, s, C$\underline{\mathrm{H}}_3$).

δC (68MHz) 150.69 (Ar$\underline{\mathrm{C}}_{4a}$=N); 144.04 ($\underline{\mathrm{C}}_{\mathrm{quat}}$); 143.71 ($\underline{\mathrm{C}}_{\mathrm{quat}}$); 140.34 ($\underline{\mathrm{C}}_{\mathrm{quat}}$); 132.29 (Ar$\underline{\mathrm{C}}$-H); 128.11 (Ar$\underline{\mathrm{C}}$-H); 126.72 (Ar$\underline{\mathrm{C}}$-H); 126.49 (Ar$\underline{\mathrm{C}}$-H); 123.56 (Ar$\underline{\mathrm{C}}$-H); 121.89 (Ar$\underline{\mathrm{C}}$-H); 104.64 (Ar$\underline{\mathrm{C}}$-H); 60.30 ($\underline{\mathrm{C}}$H-N); 44.30 ($\underline{\mathrm{C}}H_2$-N); 34.97 ($\underline{\mathrm{C}}H_2$-CH); 32.51 ($\underline{\mathrm{C}}$H-CH$_2$); 19.62 ($\underline{\mathrm{C}}H_3$).

υ_{max}/cm^{-1} (CHCl$_3$) 3020 (w, Ar-H); 2898 (s); 1683 (m, C=C); 1580 (m); 745 (s, Ar-H); 800 (s, Ar-H).

m/z= Found: 236.1328 (M$^+$ 41%); 120 ((M-C$_9$H$_8$)$^+$ 95); 115 ((M-C$_7$H$_9$N$_2$)$^+$ 100); 88 (34); 47 (31). C$_{16}$H$_{16}$N$_2$ requires 236.1314.

(6aα, 11bα)-6,6a,7,11b-Tetrahydroindeno[2,1-*e*]pyrazino[1,2-*a*]pyrimidine (240)



2-Aminopyrazine (1.00g, 10.52mmol) was added to acetonitrile (95ml) containing two equivalents of trifluoroacetic acid (2.40g) to give a 0.1M solution of the amine. To this clear solution was added with stirring a heterogeneous mixture at 0°C of indene (12.21g, 10eq.) and 37% formalin solution (1.71ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a brown oil. The oil was washed with petroleum ether and the solvent was carefully decanted. The residue was purified using flash column chromatography on alumina (eluant ethyl acetate / methanol 100/0 - 0/100) to give the adduct as a dark yellow oil (1.03g, 44%).

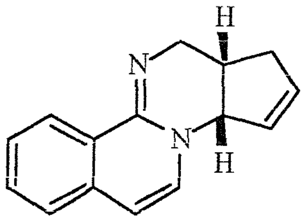
δH(270MHz) 7.73 (1H, s, C_4-$\underline{H}$); 7.22 - 7.08 (4H, m, ArC-$\underline{H}$); 6.70 (1H, d, *J* 4.7, C_2-$\underline{H}$); 6.65 (1H, d, *J* 4.7, C_1-$\underline{H}$); 4.90 (1H, d, *J* 6.2, C$\underline{H}$-N); 3.49 (1H, dd, *J* 16.0, 5.2, C$\underline{H}_2$-N); 3.03 (1H, dd, *J* 15.8, 6.2, C$\underline{H}_2$-CH); 2.75 (1H, dd, *J* 16.0, 9.7, C$\underline{H}_2$-N); 2.57 (1H, d, *J* 15.8, C$\underline{H}_2$-CH); 2.45 - 2.39 (1H, m, C$\underline{H}$-CH_2).

δC(68MHz) 153.07 ($\underline{C}_4$-H); 145.42 ($\underline{C}_{4a}$=N); 142.66 ($\underline{C}_{quat}$); 140.23 ($\underline{C}_{quat}$); 128.67 ($\underline{C}$-H); 128.08 ($\underline{C}$-H); 126.67 ($\underline{C}$-H); 126.47 ($\underline{C}$-H); 123.26 ($\underline{C}$-H); 119.50 ($\underline{C}$-H); 63.42 ($\underline{C}$H -N); 45.37 ($\underline{C}H_2$-N); 34.68 ($\underline{C}H_2$-CH); 32.09 ($\underline{C}$H-CH_2).

υ_{max}/cm^{-1} ($CHCl_3$) 3015 (m, Ar-H); 2890 (s); 1654 (m, C=C, C=N); 1598 (m); 828 (m, Ar-H); 824 (s); 754 (s, Ar-H).

m/z= Found: 223.1951 (M^+ 33%); 189 (9); 157 (11); 116 ((M-$C_5H_5N_3$)$^+$ 100); 107 ((M-C_9H_8)$^+$ 58); 68 (10). $C_{14}H_{13}N_3$ requires 223.1940.

(3aα, 12aα)-1,3a,12,12a-Tetrahydrocyclopenta[5,6]pyrimido[2,1-*a*] isoquinoline (242)



1-Aminoisoquinoline (1.00g, 6.94mmol) was added to acetonitrile (69ml) containing two equivalents of trifluoroacetic acid (1.58g) to give a 0.1M solution of the amine. To this light brown suspension was added with stirring a heterogeneous mixture at 0°C of cyclopentadiene (4.58g, 10eq.) and 37% formalin solution (1.13ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a brown oil. The oil was washed with petroleum ether and the solvent was carefully decanted. The residue was purified using flash column chromatography on alumina (eluant ethyl acetate / methanol 100/0 - 50/50) to give the adduct as a yellow oil (0.35g, 23%).

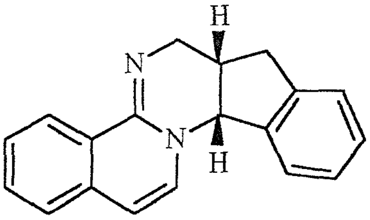
δH(270MHz) 8.30 (1H, dt, *J* 8.1, 0.7, ArC$_6$-$\underline{H}$); 7.40 (1H, td, *J* 7.4, 1.4, ArC-$\underline{H}$); 7.29 (2H, m, ArC-$\underline{H}$); 6.67 (1H, d, *J* 7.4, ArC$_{10}$-$\underline{H}$); 6.05 (1H, m, *J* 7.4, ArC$_{11}$-$\underline{H}$); 5.91 (2H, m, C$\underline{H}$=C$\underline{H}$); 4.65 (1H, m, C$\underline{H}$-N); 3.60 (1H, ddd, *J* 14.3, 5.4, 0.8, C$\underline{H}_2$-N); 3.05 (1H, dd, *J* 14.3, 10.2, C$\underline{H}_2$-N); 2.66 (1H, m, C$\underline{H}_2$-CH); 2.42 (1H, m, C$\underline{H}$-CH$_2$); 2.21 (1H, br. d, *J* 16.4, C$\underline{H}_2$-CH).

δC(68MHz) 150.59 (Ar$\underline{C}_{5a}$=N); 133.76 ($\underline{C}_{quat}$); 132.99 ($\underline{C}$H); 132.49 ($\underline{C}$H); 131.76 ($\underline{C}$H); 130.32 ($\underline{C}$H); 128.01 ($\underline{C}_{quat}$); 126.66 ($\underline{C}$H); 125.45 ($\underline{C}$H); 125.39 ($\underline{C}$H); 103.77 (Ar$\underline{C}_{11}$-H); 65.85 ($\underline{C}$H-N); 46.78 ($\underline{C}$H$_2$-N); 36.94 ($\underline{C}$H$_2$-CH); 32.05 ($\underline{C}$H-CH$_2$).

υ_{max}/cm^{-1} (CHCl$_3$) 3033 (w); 3005 (w); 2945 (m); 2852 (m, C-H); 1628 (m, C=C, C=N); 1620 (m); 1215 (s); 1485 (s, C-CAr); 752 (s, Ar-H).

m/z= Found: 222.1166 (M$^+$ 36%); 194 (20); 157 ((M-C$_5$H$_5$)$^+$ 100); 142 (13); 66 ((M-C$_{10}$H$_8$N$_2$)$^+$ 57). C$_{15}$H$_{14}$N$_2$ requires 222.1157.

(6aα, 11bα)-6,6a,7,11b-Tetrahydroindeno[2',1':5,6]pyrimido[2,1-*a*] isoquinoline (243)



1-Aminoisoquinoline (1.00g, 6.94mmol) was added to acetonitrile (69ml) containing two equivalents of trifluoroacetic acid (1.58g) to give a 0.1M solution of the amine. To this light brown suspension was added with stirring a heterogeneous mixture at 0°C of indene (8.06g, 10eq.) and 37% formalin solution (1.13ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a yellow oil. The oil was washed with petroleum ether and the solvent was carefully decanted. The residue was purified using flash column chromatography on alumina (eluant ethyl acetate / methanol 100/0 - 50/50) to give the adduct as a yellow oil (0.68g, 36%).

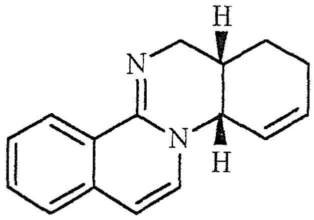
δH(270MHz) 8.30 (1H, d, *J* 8.1, ArC$_4$-$\underline{H}$); 7.37 (1H, td, *J* 7.5, 1.5, ArC-$\underline{H}$); 7.32 - 7.08 (6H, m, ArC-$\underline{H}$); 6.80 (1H, d, *J* 7.4, ArC$_{14}$-$\underline{H}$); 6.06 (1H, d, *J* 7.5, ArC$_{13}$-$\underline{H}$); 5.02 (1H, d, *J* 6.0, C$\underline{H}$-N); 3.69 (1H, ddd, *J* 15.7, 5.4, 1.6, C$\underline{H}_2$-N); 3.10 (1H, dd, *J* 15.8, 6.0, C$\underline{H}_2$-CH); 2.93 (1H, dd, *J* 15.7, 10.4, C$\underline{H}_2$-N); 2.65 (1H, d, *J* 15.8, C$\underline{H}_2$-CH); 2.57 (1H, m, C$\underline{H}$-CH$_2$).

δC(68MHz) 148.40 (Ar$\underline{C}_{4b}$=N); 144.15 ($\underline{C}_{quat}$); 140.47 ($\underline{C}_{quat}$); 133.92 ($\underline{C}_{quat}$); 133.05 (Ar$\underline{C}$-H); 130.33 (Ar$\underline{C}$-H); 128.18 (Ar$\underline{C}$-H); 126.60 (Ar$\underline{C}$-H); 126.54 (Ar$\underline{C}$-H); 126.31 (Ar$\underline{C}$-H); 125.59 (Ar$\underline{C}$-H); 125.46 (Ar$\underline{C}$-H); 123.46 (Ar$\underline{C}$-H); 103.30 (Ar$\underline{C}_{13}$-H); 64.46 ($\underline{C}$H-N); 45.96 ($\underline{C}$H$_2$-N); 34.85 ($\underline{C}$H$_2$-CH); 32.67 ($\underline{C}$H-CH$_2$).

υ_{max}/cm^{-1} (CHCl$_3$) 3045 (w); 3030 (w); 3010 (w); 2940 (m); 2845 (m, C-H); 1630 (m, C=C, C=N); 1615 (m); 1505 (m); 1488 (s, C-CAr); 762 (s, Ar-H).

m/z= Found: 272.1320 (M$^+$ 44%); 256 (21); 203 (15); 130 (8); 156 ((M-C$_9$H$_8$)$^+$ 100); 116 ((M-C$_{10}$H$_8$N$_2$)$^+$ 48); 70 (10). C$_{19}$H$_{16}$N$_2$ requires 272.1314.

(6aα, 10aα)-6,6a,7,10a-Tetrahydro-6*H*-isoquino[2,1-*a*]quinazoline (245)



1-Aminoisoquinoline (1.00g, 6.94mmol) was added to acetonitrile (69ml) containing two equivalents of trifluoroacetic acid (1.58g) to give a 0.1M solution of the amine. To this light brown suspension was added with stirring a heterogeneous mixture at 0°C of cyclohexadiene (5.56g, 10eq.) and 37% formalin solution (1.13ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a brown oil. The oil was washed with petroleum ether and the solvent was carefully decanted. The residue was purified using flash column chromatography on alumina (eluant ethyl acetate / methanol 100/0 - 50/50) to give the adduct as a yellow oil (0.08g, 5%).

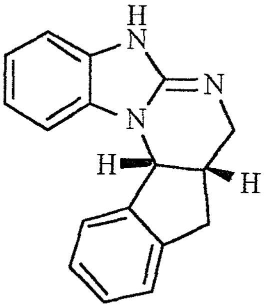
δH(270MHz) 8.30 (1H, d, *J* 8.1, ArC4-H); 7.72 - 7.11 (3H, m, ArC-H); 6.55 (1H, d, *J* 7.3, ArC13-H); 6.01 (1H, d, *J* 7.3, ArC12-H); 5.73 (2H, m, CH=CH); 4.24 (1H, s, CH-N); 3.51 (2H, m, CH_2-N); 2.21 (1H, m, CH-CH_2); 2.08 (2H, m, CH_2); 1.85 (2H, m, CH_2).

δC(68MHz) 148.20 (C_{quat}); 134.16 (C_{quat}); 131.84 (C-H); 130.34 (C-H); 129.09 (C-H); 128.07 (C_{quat}); 127.15 (C-H); 126.62 (C-H); 125.75 (C-H); 125.45 (C-H); 103.51 (ArC12-H); 56.94 (CH-N); 44.99 (CH_2-N); 27.40 (CH-CH_2); 23.05 (CH_2); 21.00 (CH_2).

υ_{max}/cm^{-1} ($CHCl_3$) 3038 (w, Ar-H); 3010 (w); 2850 (m, C-H); 1642 (s, C=C); 1603 (s); 1510 (s).

m/z= Found: 236.1324 (M^+ 44%); 202 (22); 183 (13); 156 ($(M-C_6H_7)^+$ 100); 80 ($(M-C_{10}H_8N_2)^+$ 37); 61 (11). $C_{16}H_{16}N_2$ requires 236.1314.

(7aα, 12bα)-7,7a,8,12b-Tetrahydroindeno[2',1':5,6]pyrimido[2,1-*b*] benzimidazole (246)



2-Aminobenzimidazole (1.00g, 7.52mmol) was added to acetonitrile (75ml) containing two equivalents of trifluoroacetic acid (1.71g) to give a 0.1M solution of the amine. To this white suspension was added with stirring a heterogeneous mixture at 0°C of indene (8.72g, 10eq.) and 37% formalin solution (1.23ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a brown oil. The oil was washed with petroleum ether and the solvent was carefully decanted. The residue was purified using flash column chromatography on silica (eluant 100/0 - 0/100 ethyl acetate/methanol) to give the adduct as a dark yellow oil (0.22g, 11%).

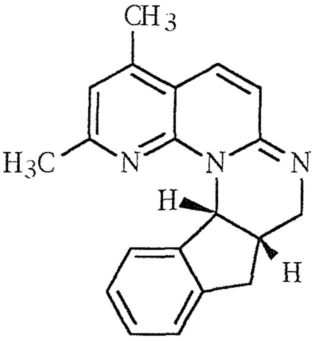
δH (270MHz, DMSO) 7.45 - 7.35 (4H, m, ArC-$\underline{H}$); 7.32 - 7.02 (4H, m, ArC-$\underline{H}$); 5.28 (1H, d, *J* 5.8, C$\underline{H}$-N); 3.74 (1H, dd, *J* 10.8, 5.04, C$\underline{H}_2$-N); 2.98 (1H, dd, *J* 15.1, 7.2, C$\underline{H}_2$-CH); 2.83 (1H, d, *J* 10.8, C$\underline{H}_2$-N); 2.59 (1H, d, *J* 15.1, C$\underline{H}_2$-CH); 2.48 (1H, m, C$\underline{H}$-CH$_2$).

δC (68MHz, DMSO) 158.74 ($\underline{C}_{5a}$=N); 144.41 ($\underline{C}_{quat}$); 144.17 ($\underline{C}_{quat}$); 142.81 ($\underline{C}_{quat}$); 141.36 ($\underline{C}_{quat}$); 128.43 (Ar$\underline{C}$-H); 127.97 (Ar$\underline{C}$-H); 126.67 (Ar$\underline{C}$-H); 124.87 (Ar$\underline{C}$-H); 124.72 (Ar$\underline{C}$-H);124.18 (Ar$\underline{C}$-H); 122.86 (Ar$\underline{C}$-H); 119.37 (Ar$\underline{C}$-H); 62.31 ($\underline{C}$H-N); 52.02 ($\underline{C}$H$_2$-N); 45.34 ($\underline{C}$H$_2$-CH); 32.78 ($\underline{C}$H-CH$_2$).

υ_{max}/cm^{-1} (CHCl$_3$) 3458 (w, N-H); 3008 (m, Ar-H); 2910 (m); 2890 (s); 1645 (m, C=C, C=N); 1552 (m); 775 (s, Ar-H); 765 (s, Ar-H).

m/z= Found: 261 (M+ 22%); 238 (10); 192 (15); 145 ((M-C_9H_8)$^+$ 100); 116 ((M-$C_8H_7N_3$)$^+$ 36); 92 (11). $C_{17}H_{15}N_3$ requires 261.

(8aα, 13bα)-8,8a,9,13b-Tetrahydro-2,4-dimethylindeno[2',1':5,6] pyrimido[1,2-*a*][1,8]naphthyridine (248)



2-Amino-5,7-dimethylnaphthyridine (1.00g, 9.25mmol) was added to acetonitrile (108ml) containing two equivalents of trifluoroacetic acid (2.11g) to give a 0.1M solution of the amine. To this brown suspension was added with stirring a heterogeneous mixture at 0°C of indene (6.71g, 10eq.) and 37% formalin solution (1.50ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a brown oil. The oil was washed with petroleum ether and the solvent was carefully decanted. The residue was purified using flash column chromatography on alumina (eluant ethyl acetate / methanol 100/0 - 50/50) to give the adduct as a yellow oil (0.83g, 48%).

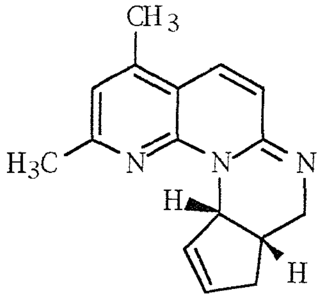
δH(270MHz) 7.27 (1H, d, *J* 9.8, C_6-$\underline{H}$); 7.22 - 6.91 (4H, m, ArC-$\underline{H}$); 6.71 (1H, s, C_3-$\underline{H}$); 6.60 (1H, d, *J* 9.8, C_5-$\underline{H}$); 6.44 (1H, d, *J* 5.8, C$\underline{H}$-N); 6.04 (1H, br. s, N-$\underline{H}$); 3.58 (1H, dd, *J* 15.7, 5.3, C$\underline{H}_2$-N); 3.23 (1H, dd, *J* 15.5, 5.6, C$\underline{H}_2$-CH); 2.85 (1H, dd, *J* 15.7, 11.3, C$\underline{H}_2$-N); 2.65 (1H, d, *J* 15.5, C$\underline{H}_2$-CH); 2.52 (1H, m, C$\underline{H}$-CH_2); 2.39 (3H, s, C$\underline{H}_3$); 2.37 (3H, s, $\underline{C}H_3$).

δC(68MHz) 157.50 ($\underline{C}_{quat}$); 150.32 ($\underline{C}_{quat}$); 150.20 ($\underline{C}_{quat}$); 144.80 ($\underline{C}_{quat}$); 144.33 ($\underline{C}_{quat}$); 140.21 ($\underline{C}_{quat}$); 127.57 ($\underline{C}$-H); 127.49 ($\underline{C}$-H); 126.08 ($\underline{C}$-H); 125.78 ($\underline{C}$-H); 124.21 ($\underline{C}$-H); 119.32 ($\underline{C}$-H); 58.18 ($\underline{C}$H-N); 45.16 ($\underline{C}H_2$-N); 35.03 ($\underline{C}H_2$-CH); 32.18 ($\underline{C}H_3$); 24.53 ($\underline{C}$H-CH_2); 17.97 ($\underline{C}H_3$).

υ_{max}/cm^{-1} ($CHCl_3$) 3017 (m, Ar-H); 2930 (m); 2922 (m); 1642 (s, C=C, C=N); 1584 (s); 1443 (m); 1347 (m); 755 (s).

m/z= Found: 301.1582 (M^+ 32%); 286 (14); 185 ((M-$C_9H_8)^+$ 31); 116 ((M-$C_{11}H_{11}N_3)^+$ 100). $C_{20}H_{19}N_3$ requires 301.1579.

(8aα, 11aα)-8,8a,9,11a-Tetrahydro-2,4-dimethylcyclopenta[5,6]pyrimido[1,2-*a*][1,8]naphthyridine (249)



2-Amino-5,7-dimethylnaphthyridine (1.00g, 9.25mmol) was added to acetonitrile (108ml) containing two equivalents of trifluoroacetic acid (2.11g) to give a 0.1M solution of the amine. To this brown suspension was added with stirring a heterogeneous mixture at 0°C of cyclopentadiene (6.11g, 10eq.) and 37% formalin solution (1.50ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a brown oil. The oil was washed with petroleum ether and the solvent was carefully decanted. The residue was purified using flash column chromatography on alumina (eluant ethyl acetate / methanol 100/0 - 50/50) to give the adduct as a yellow oil (0.73g, 34%).

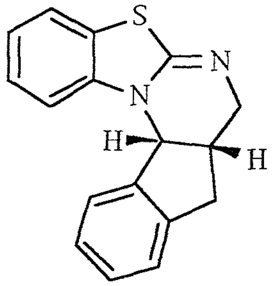
δH(270MHz) 7.20 (1H, d, *J* 9.9, $C_6\text{-}\underline{H}$); 6.64 (1H, s, $C_3\text{-}\underline{H}$); 6.53 (1H, d, *J* 9.9, $C_5\text{-}\underline{H}$); 6.21 (1H, m, $=C\underline{H}$); 5.85 (1H, m, $=C\underline{H}$); 5.50 (1H, m, $C\underline{H}\text{-}N$); 4.80 (1H, br. s, $N\text{-}\underline{H}$); 3.47 (1H, dd, *J* 14.9, 4.6, $C\underline{H}_2\text{-}N$); 3.02 (1H, d, *J* 14.9, 10.6, $C\underline{H}_2\text{-}N$); 2.69 (1H, m, $C\underline{H}\text{-}CH_2$); 2.43 (3H, s, $C\underline{H}_3$); 2.37 (1H, m, $C\underline{H}_2\text{-}CH$); 2.33 (3H, s, $C\underline{H}_3$); 2.13 (1H, d, *J* 15.8, $C\underline{H}_2\text{-}CH$).

δC(68MHz) 156.69 ($\underline{C}_{quat}$); 151.55 ($\underline{C}_{quat}$); 150.33 ($\underline{C}_{quat}$); 143.84 ($\underline{C}_{quat}$); 135.07 ($\underline{C}\text{-}H$); 130.46 ($\underline{C}\text{-}H$); 126.90 ($\underline{C}\text{-}H$); 124.00 ($\underline{C}\text{-}H$); 118.54 ($\underline{C}\text{-}H$); 112.42 ($\underline{C}_{quat}$); 60.48 ($\underline{C}H\text{-}N$); 45.77 ($\underline{C}H_2\text{-}N$); 35.98 ($\underline{C}H_2\text{-}CH$); 30.85 ($\underline{C}H_3$); 24.36 ($\underline{C}H\text{-}CH_2$); 17.71 ($\underline{C}H_3$).

υ_{max}/cm^{-1} ($CHCl_3$) 3028 (w, Ar-H); 2920 (m); 2911 (m); 2885 (m); 1643 (s, C=C, C=N); 1582 (s); 1547 (s); 846 (m, Ar-H); 753 (s, Ar-H).

m/z= Found: 251.1433 (M^+ 35%); 236 (14); 186 ($(M-C_5H_5)^+$ 20); 151 (12);102 (18); 66 ($(M-C_{11}H_{11}N_3)^+$ 100). $C_{16}H_{17}N_3$ requires 251.1423.

(7aα, 12bα)-7,7a,8,12b-Tetrahydroindeno[2',1':5,6]pyrimido[2,1-*b*] benzothiazole (251)



2-Aminobenzothiazole (1.00g, 6.66mmol) was added to acetonitrile (67ml) containing two equivalents of trifluoroacetic acid (1.52g) to give a 0.1M solution of the amine. To this white suspension was added with stirring a heterogeneous mixture at 0°C of indene (7.73g, 10eq.) and 37% formalin solution (1.08ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a pale yellow oil. The oil was washed with petroleum ether and the solvent was carefully decanted. The residue was purified using flash column chromatography on silica (eluant 100/0 - 50/50 ethyl acetate/methanol) to give the adduct as a cream solid (1.67g, 90%). Recrystallisation from ethyl acetate gave a cream powder, mp. 129 - 132°C.

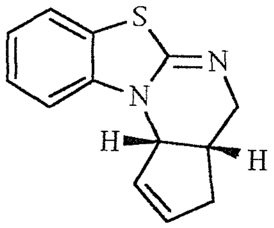
δH (270MHz) 7.31 - 7.04 (8H, m, ArC-H); 5.35 (1H, d, *J* 6.0, CH-N); 3.59 (1H, dd, *J* 14.7, 4.9, CH_2-N); 3.26 (1H, dd, *J* 15.8, 6.2, CH_2-CH); 2.88 (1H, dd, *J* 14.7, 11.4, CH_2-N); 2.66 (1H, d, *J* 15.8, CH_2-CH); 2.58 (1H, m, CH-CH_2).

δC (68MHz) 157.46 (C_{5a}=N); 143.13 (C_{quat}); 141.81 (C_{quat}); 140.58 (C_{quat}); 128.42 (ArC-H); 126.95 (ArC-H); 126.30 (ArC-H); 126.04 (ArC-H); 124.50 (ArC-H); 122.71 (C_{quat}); 122.14 (ArC-H); 121.95 (ArC-H); 108.13 (ArC-H); 60.46 (CH-N); 48.02 (CH_2-N); 34.51 (CH_2-CH); 31.45 (CH-CH_2).

υ_{max}/cm^{-1} ($CHCl_3$) 3008 (m, Ar-H); 2890 (s); 1683 (m, C=C, C=N); 1595 (s);1492 (m); 762 (s, Ar-H); 750 (s, Ar-H).

m/z= Found: 278.0872 (M^+ 43%); 162 (($M-C_9H_8$)$^+$ 100); 148 (17); 130 (($M-C_8H_6N_2S$)$^+$ 54); 113 (16); 98 (18). $C_{17}H_{14}N_2S$ requires 278.0878.

(3aα, 11aα)-3,3a,4,11a-Tetrahydrocyclopenta[5,6]pyrimido[2,1-*b*] benzothiazole (252)



2-Aminobenzothiazole (1.00g, 6.66mmol) was added to acetonitrile (67ml) containing two equivalents of trifluoroacetic acid (1.52g) to give a 0.1M solution of the amine. To this white suspension was added with stirring a heterogeneous mixture at 0°C of cyclopentadiene (4.40g, 10eq.) and 37% formalin solution (1.08ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a dark brown oil. The oil was washed with petroleum ether and the solvent was carefully decanted. The residue was purified using flash column chromatography on silica (eluant 100/0 - 50/50 ethyl acetate/methanol) to give the adduct as a light brown oil (1.34g, 88%).

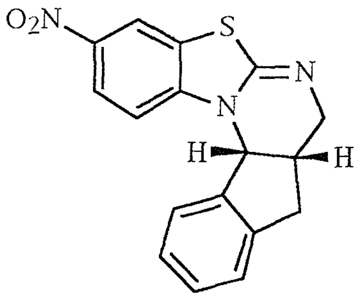
δH (270MHz) 7.00 (1H, d, *J* 7.2, ArC$_{10}$-H); 6.93 (1H, t, *J* 7.3, ArC$_9$-H); 6.75 (1H, t, *J* 7.8, ArC$_8$-H); 6.54 (1H, d, *J* 7.8, ArC$_7$-H); 5.72 (2H, m, CH=CH); 4.48 (1H, d, *J* 5.8, CH-N); 3.27 (1H, dd, *J* 15.2, 5.0, CH$_2$-N); 2.75 (1H, dd, *J* 15.2, 9.4, CH$_2$-N); 2.42 (1H, m, CH$_2$-CH); 2.15 (1H, m, CH$_2$-CH); 1.87 (1H, d, *J* 15.2, CH$_2$-CH).

δC (68MHz) 158.23 (C$_{quat}$=N); 141.58 (ArC$_{quat}$-N); 133.43 (C-H); 130.74 (C-H); 125.97 (C-H); 123.19 (ArC$_{quat}$-S); 122.55 (ArC-H); 122.03 (ArC-H); 108.67 (ArC-H); 61.54 (CH-N); 48.32 (CH$_2$-N); 34.42 (CH$_2$-CH); 30.03 (CH-CH$_2$).

υ_{max}/cm^{-1} (CHCl$_3$) 3005 (m, Ar-H); 2886 (s); 1680 (s, C=C, C=N); 1598 (s); 1490 (m); 762 (s, Ar-H).

m/z= Found: 228.0728 (M$^+$ 33%); 163 ((M-C$_5$H$_5$)$^+$ 100); 149 (16); 121 (18); 80 ((M-C$_8$H$_6$N$_2$S)$^+$ 45); 68 (8). C$_{13}$H$_{12}$N$_2$S requires 228.0721.

(7aα, 12bα)-7,7a,8,12b-Tetrahydro-3-nitroindeno[2',1':5,6]pyrimido[2,1-*b*] benzothiazole (253)



2-Amino-6-nitrobenzothiazole (1.00g, 5.12mmol) was added to acetonitrile (51ml) containing two equivalents of trifluoroacetic acid (1.17g) to give a 0.1M solution of the amine. To this yellow suspension was added with stirring a heterogeneous mixture at 0°C of indene (5.95g, 10eq.) and 37% formalin solution (0.83ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a dark orange oil. The oil was washed with petroleum ether and the solvent was carefully decanted. The residue was purified using flash column chromatography on alumina (eluant 100/0 - 30/70 ethyl acetate/methanol) to give the adduct as a yellow foam (1.01g,72%). Recrystallisation from ethyl acetate/toluene gave a yellow solid, mp. 130 -140°C (dec.).

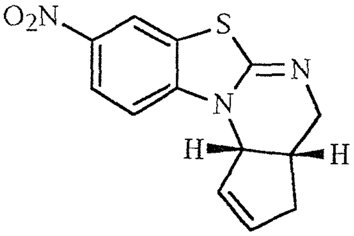
δH (270MHz) 8.20 (2H, m, ArC$_2$-$\underline{\text{H}}$, ArC$_4$-$\underline{\text{H}}$); 7.33 - 7.18 (4H, m, ArC-$\underline{\text{H}}$); 7.11 (1H, d, *J* 9.5, ArC$_1$-$\underline{\text{H}}$); 5.46 (1H, d, *J* 6.4, C$\underline{\text{H}}$-N); 3.68 (1H, ddd, *J* 15.1, 5.4, 1.2, C$\underline{\text{H}}_2$-N); 3.30 (1H, dd, *J* 15.9, 6.1, C$\underline{\text{H}}_2$-CH); 2.91 (1H, dd, *J* 15.1, 11.4, C$\underline{\text{H}}_2$-N); 2.73 (1H, br. d, *J* 15.8, C$\underline{\text{H}}_2$-CH); 2.70 (1H, m, C$\underline{\text{H}}$-CH$_2$).

δC (68MHz) 155.92 ($\underline{\text{C}}_{5a}$=N); 146.60 ($\underline{\text{C}}_{\text{quat}}$); 142.81 ($\underline{\text{C}}_{\text{quat}}$); 141.76 ($\underline{\text{C}}_{\text{quat}}$); 140.58 ($\underline{\text{C}}_{\text{quat}}$); 129.00 (Ar$\underline{\text{C}}$-H); 127.29 (Ar$\underline{\text{C}}$-H); 126.69 (Ar$\underline{\text{C}}$-H); 124.11 (Ar$\underline{\text{C}}$-H); 123.29 (Ar$\underline{\text{C}}$-H); 117.89 (Ar$\underline{\text{C}}$-H); 107.05 (Ar$\underline{\text{C}}$-H); 60.82 ($\underline{\text{C}}$H-N); 48.03 ($\underline{\text{C}}H_2$-N); 34.47 ($\underline{\text{C}}H_2$-CH); 32.02 ($\underline{\text{C}}$H-CH$_2$).

υ_{max}/cm^{-1} (CHCl$_3$) 3012 (w, Ar-H); 2910 (s, C-H)); 1660 (m, C=N, C=C); 1643 (m, C=C, C=N); 1521 (s, C-NO$_2$); 1310 (s, C-NO$_2$); 850 (s, ArC-H).

m/z= Found: 323.0734 (M+ 38%); 256 (11); 207 ((M-C$_9$H$_8$)+ 17); 128 (28); 130 (28); 116 ((M-C$_8$H$_5$N$_3$O$_2$S)+ 100); 115 (32); 69 (39). C$_{17}$H$_{13}$N$_3$O$_2$S requires 323.0729.

(3aα, 11aα)-3,3a,4,11a-Tetrahydro-8-nitrocyclopenta[5,6]pyrimido[2,1-*b*] benzothiazole (254)



2-Amino-6-nitrobenzothiazole (1.00g, 5.12mmol) was added to acetonitrile (51ml) containing two equivalents of trifluoroacetic acid (1.17g) to give a 0.1M solution of the amine. To this yellow suspension was added with stirring a heterogeneous mixture at 0°C of cyclopentadiene (3.39g, 10eq.) and 37% formalin solution (0.83ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a dark orange oil. The oil was washed with petroleum ether and the solvent was carefully decanted. The residue was purified using flash column chromatography on alumina (eluant 100/0 - 30/70 ethyl acetate/methanol) to give the adduct as a yellow oil (1.01g, 72%).

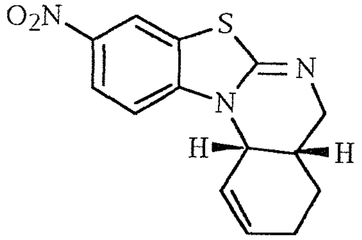
δH (270MHz) 8.15 (2H, m, ArC$_7$-$\underline{H}$, ArC$_9$-$\underline{H}$); 6.87 (1H, d, *J* 8.7, ArC$_{10}$-$\underline{H}$); 6.07 (2H, m, C$\underline{H}$=C$\underline{H}$); 4.90 (1H, d, *J* 5.2, C$\underline{H}$-N); 3.61 (1H, dd, *J* 14.7, 5.6, C$\underline{H}_2$-N); 3.09 (1H, dd, *J* 14.7, 10.6, C$\underline{H}_2$-N); 2.75 (1H, m, C$\underline{H}_2$-CH); 2.55 (1H, m, C$\underline{H}$-CH$_2$); 2.21 (1H, br. d, *J* 16.6, C$\underline{H}_2$-CH).

δC (68MHz) 157.21 ($\underline{C}_{5a}$=N); 146.17 ($\underline{C}_{quat}$); 142.66 ($\underline{C}_{quat}$); 134.72 (=$\underline{C}$H); 129.45 (=$\underline{C}$H); 124.17 ($\underline{C}_{quat}$); 123.03 (Ar$\underline{C}$-H); 117.67 (Ar$\underline{C}$-H); 107.21 (Ar$\underline{C}$-H); 62.33 ($\underline{C}$H-N); 48.79 ($\underline{C}$H$_2$-N); 35.76 ($\underline{C}$H$_2$-CH); 30.59 ($\underline{C}$H-CH$_2$).

υ_{max}/cm^{-1} (CHCl$_3$) 3010 (w, Ar-H); 2900 (s); 1652 (m, C=N, C=C); 1640 (m, C=C, C=N); 1532 (s, C-NO$_2$); 1302 (s, C-NO$_2$).

m/z= Found: 273.0579 (M$^+$ 40%); 208 ((M-C$_5$H$_5$)$^+$ 100); 196 (17); 80 (21); 66 ((M-C$_8$H$_5$N$_3$O$_2$S)$^+$ 73); 103 (16). C$_{17}$H$_{15}$N$_3$O$_2$S requires 273.0572.

(4aα, 12aα)-3,4a,5,12a-Tetrahydro-9-nitro-4*H*-benzothiazolo[3,2-*a*] quinazoline (255)



2-Amino-6-nitrobenzothiazole (1.00g, 5.12mmol) was added to acetonitrile (51ml) containing two equivalents of trifluoroacetic acid (1.17g) to give a 0.1M solution of the amine. To this yellow suspension was added with stirring a heterogeneous mixture at 0°C of cyclohexadiene (4.11g, 10eq.) and 37% formalin solution (0.83ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml).The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a dark orange oil. The oil was washed with petroleum ether and the solvent was carefully decanted. The residue was purified using flash column chromatography on alumina (eluant 100/0 - 30/70 ethyl acetate/methanol) to give the adduct as a yellow foam (0.93g, 63%). The cycloadduct decomposed during attempted recrystallisations.

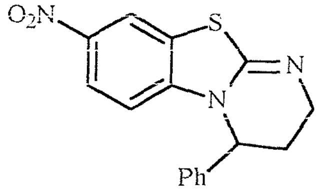
δH (270MHz) 8.13 (1H, m, ArC$_8$-$\underline{H}$, ArC$_{10}$-$\underline{H}$); 6.82 (1H, d, *J* 8.7, ArC$_{11}$-$\underline{H}$); 5.90 (1H, dd, *J* 10.2, 2.5, =C$\underline{H}$-CH$_2$); 4.68 (1H, d, *J* 2.5, C$\underline{H}$-N); 3.48 (2H, d, *J* 8.7, C$\underline{H}_2$-N); 2.30 (1H, m, C$\underline{H}$-CH); 2.10 - 1.92 (4H, m, C$\underline{H}_2$-C$\underline{H}_2$).

δC (68MHz) 155.40 ($\underline{C}_{6a}$=N); 145.10 (Ar$\underline{C}_9$-NO$_2$); 142.32 ($\underline{C}_{quat}$-N); 130.40 (Ar$\underline{C}_{11}$-H); 124.24 ($\underline{C}_{quat}$-S); 123.26 (Ar$\underline{C}$-H); 123.07 (Ar$\underline{C}$-H); 117.76 (=$\underline{C}$H-CH); 106.20 (=$\underline{C}$H-CH$_2$); 52.13 ($\underline{C}$H-N); 46.55 ($\underline{C}$H$_2$-N); 26.58 ($\underline{C}$H-CH); 22.92 ($\underline{C}$H$_2$); 20.51 ($\underline{C}$H$_2$).

υ_{max}/cm^{-1} (CHCl$_3$) 3012 (m); 2900 (s, CH$_2$); 1650 (m, C=N, C=C); 1640 (m, C=C); 1600 (s); 1510 (s, C-NO$_2$); 1315 (s, C-NO$_2$); 820 (s, ArC-H).

m/z= Found: 287.0721 (M+ 55%); 208 ((M-C$_6$H$_7$)+ 71); 179 ((M-C$_7$H$_{10}$N)+ 13); 80 ((M-C$_8$H$_5$N$_3$O$_2$S)+ 100); 79 (48). C$_{14}$H$_{13}$N$_3$O$_2$S requires 287.0729.

3,4-Dihydro-8-nitro-4-phenyl-2*H*-pyrimido[2,1-*b*]benzothiazole (256)



2-Amino-6-nitrobenzothiazole (1.00g, 5.12mmol) was added to acetonitrile (51ml) containing two equivalents of trifluoroacetic acid (1.17g) to give a 0.1M solution of the amine. To this yellow suspension was added with stirring a heterogeneous mixture at 0°C of styrene (5.34g, 10eq.) and 37% formalin solution (0.83ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a dark orange oil. The oil was washed with petroleum ether and the solvent was carefully decanted. The residue was purified using flash column chromatography on alumina (eluant 100/0 - 30/70 ethyl acetate/methanol) to give the adduct as a yellow foam (0.76g, 48%). Recrystallisation from ethyl acetate / toluene gave a yellow solid, mp. 90 - 100°C (dec.).

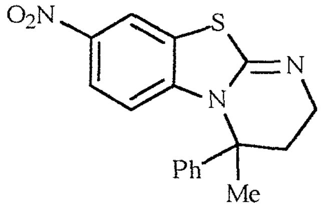
δH (270MHz) 8.16 (1H, d, *J* 2.3, ArC$_9$-H̲); 7.94 (1H, dd, *J* 8.8, 2.3, ArC$_7$-H̲); 7.38 - 7.17 (5H, m, ArC-H̲); 6.51 (1H, d, *J* 8.8, ArC$_6$-H̲); 5.32 (1H, d, *J* 5.6, CH̲-N); 3.58 (1H, br. d, *J* 15.8, CH̲$_2$-N); 3.29 (1H, ddd, *J* 15.8, 12.4, 3.7, CH̲$_2$-N); 2.33 (1H, m, CH̲$_2$-CH); 2.09 (1H, m, CH̲$_2$-CH).

δC (68MHz) 156.52 (C̲$_{10a}$=N); 145.07 (C̲$_{quat}$); 142.68 (C̲$_{quat}$); 139.26 (C̲$_{quat}$); 129.38 (2xArC̲-H); 128.47 (ArC̲-H); 125.71 (2xArC̲-H); 123.03 (ArC̲-H); 117.73 (ArC̲-H); 107.47 (ArC̲-H); 56.42 (C̲H-N); 41.54 (C̲H$_2$-N); 27.50 (C̲H$_2$-CH).

υ_{max}/cm^{-1} (CHCl$_3$) 3015 (w, Ar-H); 2910 (s); 1655 (m, C=N); 1590 (s); 1512 (s, C-NO$_2$); 1315 (s, C-NO$_2$); 817 (s, Ar-H); 753 (s, Ar-H).

m/z= Found: 311.0739 (M$^+$ 100%); 284 (15); 207 ((M-C$_8$H$_8$)$^+$ 14); 195 (23); 122 (10); 104 ((M-C$_8$H$_5$N$_3$O$_2$S)$^+$ 73); 78 (7). C$_{16}$H$_{13}$N$_3$O$_2$S requires 311.0729.

3,4-Dihydro-4-methyl-8-nitro-4-phenyl-2*H*-pyrimido[2,1-*b*]benzothiazole (257)



2-Amino-6-nitrobenzothiazole (1.00g, 5.12mmol) was added to acetonitrile (51ml) containing two equivalents of trifluoroacetic acid (1.17g) to give a 0.1M solution of the amine. To this yellow suspension was added with stirring a heterogeneous mixture at 0°C of α-methylstyrene (6.05g, 10eq.) and 37% formalin solution (0.83ml, 2eq.). The mixture was stirred at reflux for 1h., allowed to cool to room temperature and poured into saturated sodium bicarbonate solution (100ml). The solution was extracted with dichloromethane (5x50ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated to yield a dark orange oil. The oil was washed with petroleum ether and the solvent was carefully decanted. The residue was purified using flash column chromatography on alumina (eluant 100/0 - 30/70 ethyl acetate/methanol) to give the adduct as a yellow foam (1.07g, 64%). Recrystallisation from ethyl acetate / toluene gave a yellow powder, mp. 108 - 120°C (dec.).

δH (270MHz) 8.10 (1H, d, *J* 2.3, ArC$_9$-$\underline{\mathrm{H}}$); 7.69 (1H, dd, *J* 9.1, 2.3, ArC$_7$-$\underline{\mathrm{H}}$); 7.39 - 7.28 (5H, m, ArC-$\underline{\mathrm{H}}$); 6.05 (1H, d, *J* 9.1, ArC$_6$-$\underline{\mathrm{H}}$); 3.57 (2H, m, C$\underline{\mathrm{H}}_2$-N); 2.07 (2H, m, C$\underline{\mathrm{H}}_2$-C$_{\mathrm{quat}}$); 2.01 (3H, s, C$\underline{\mathrm{H}}_3$).

δC (68MHz) 156.87 ($\underline{\mathrm{C}}_{10\mathrm{a}}$=N); 144.17 ($\underline{\mathrm{C}}_{\mathrm{quat}}$); 142.89 ($\underline{\mathrm{C}}_{\mathrm{quat}}$); 141.86 ($\underline{\mathrm{C}}_{\mathrm{quat}}$); 129.32 (2xAr$\underline{\mathrm{C}}$-H); 128.04 (Ar$\underline{\mathrm{C}}$-H); 125.34 (Ar$\underline{\mathrm{C}}$-H); 124.11 ($\underline{\mathrm{C}}_{\mathrm{quat}}$-S); 121.58 (Ar$\underline{\mathrm{C}}$-H); 117.23 (Ar$\underline{\mathrm{C}}$-H); 111.40 (Ar$\underline{\mathrm{C}}$-H); 63.04 ($\underline{\mathrm{C}}_{\mathrm{quat}}$-CH$_2$); 43.45 ($\underline{\mathrm{C}}H_2$-N); 39.42 ($\underline{\mathrm{C}}H_2$-C$_{\mathrm{quat}}$); 23.26 ($\underline{\mathrm{C}}H_3$).

υ_{max}/cm^{-1} (CHCl$_3$) 3020 (m, Ar-H); 2909 (s); 2888 (m); 1658 (m, C=N); 1620 (m); 1503 (m); 1315 (s, C-NO$_2$); 830 (s, Ar-H); 744 (s, Ar-H).

m/z= Found: 325.0890 (M$^+$ 100%); 310 ((M-CH$_3$)$^+$ 15); 208 ((M-C$_9$H$_9$)$^+$ 52); 195 (44); 130 (28); 118 ((M-C$_8$H$_5$N$_3$O$_2$S)$^+$ 62); 103 (16). C$_{17}$H$_{15}$N$_3$O$_2$S requires 325.0885.

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4.0 REFERENCES

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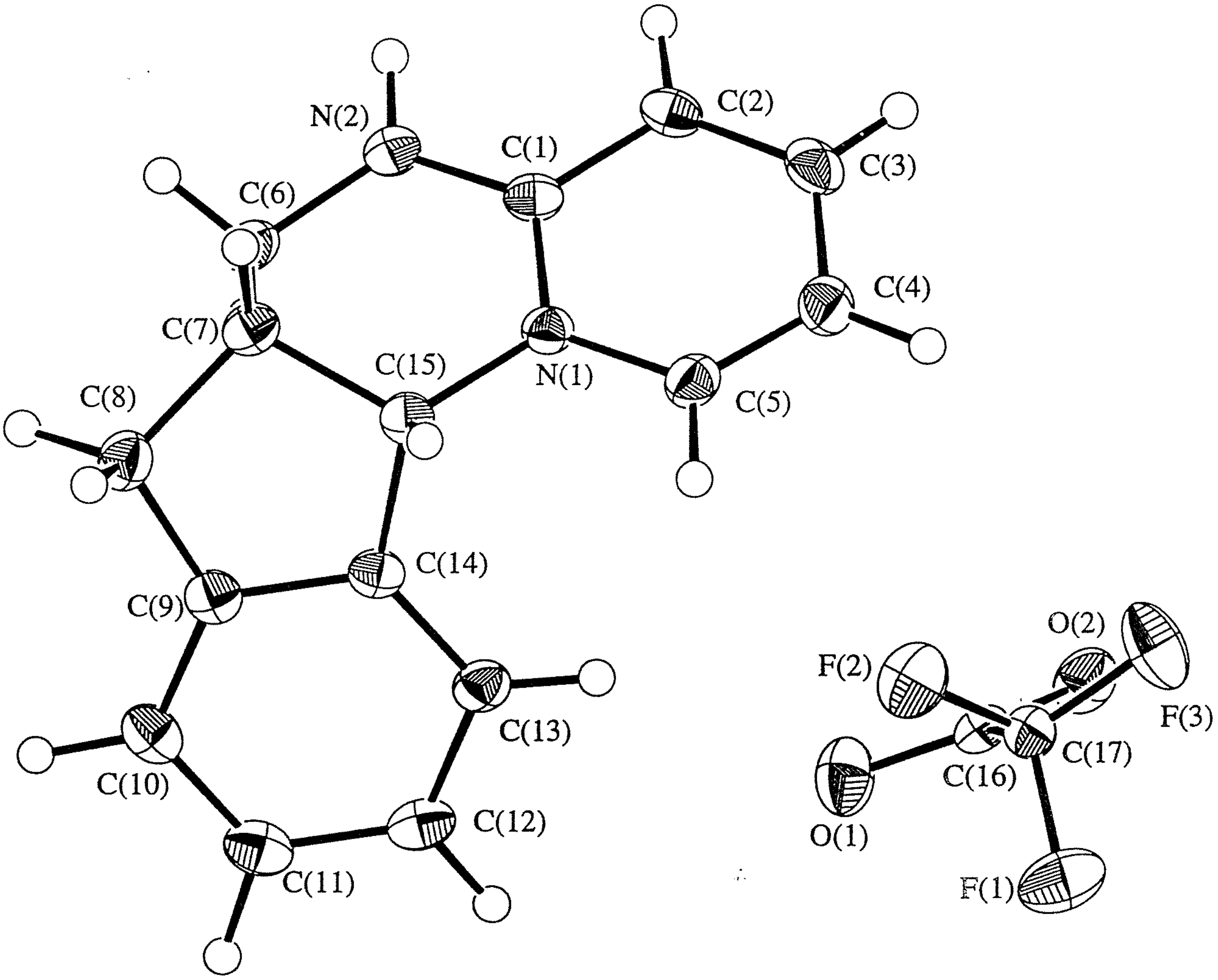
APPENDIX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O(1)
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Experimental

Data Collection

A colourlessblock block crystal of $C_{17}H_{15}N_2O_2F_3$ having approximate dimensions of 0.50 x 0.40 x 0.30 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated Mo-Kα radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $36.84 < 2\theta < 42.78°$ corresponded to a primitive monoclinic cell with dimensions:

$$a = 10.859(3)\ Å$$
$$b = 12.316(3)\ Å \qquad \beta = 104.48(2)°$$
$$c = 11.413(2)\ Å$$
$$V = 1477.8(6)\ Å^3$$

For Z = 4 and F.W. = 336.31, the calculated density is 1.51 g/cm^3. The systematic absences of:

$$h0l:\ h+l \neq 2n$$
$$0k0:\ k \neq 2n$$

uniquely determine the space group to be:

$$P2_1/n\ (\#14)$$

The data were collected at a temperature of 150 ± 1°C using the ω-2θ scan technique to a maximum 2θ value of 50.0°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.22° with a take-off angle of 6.0°. Scans of $(0.84 + 0.35 \tan \theta)°$ were made at a speed of 16.0°/min (in omega). The weak reflections ($I < 15.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm and the crystal to detector distance was 400 mm, The computer-controlled slits were set to 9.0 mm (horizontal) and 13.0 mm (vertical).

Data Reduction

Of the 2884 reflections which were collected, 2735 were unique ($R_{int} = 0.038$). The intensities of three representative reflection were measured after every 150 reflections. No decay correction was applied.

The linear absorption coefficient, μ, for Mo-Kα radiation is 1.3 cm^{-1}. Azimuthal scans of several reflections indicated no need for an absorption correction. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques[2]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[3] was based on 2164 observed reflections ($I > 3.00\sigma(I)$) and 217 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.042$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2/\Sigma wFo^2)]} = 0.051$$

The standard deviation of an observation of unit weight[4] was 3.01. The weighting scheme was based on counting statistics and included a factor (p = 0.011) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin\theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.33 and -0.25 $e^-/\mathring{A}^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[5]. Anomalous dispersion effects were included in Fcalc[6]; the values for Δf' and Δf" were those of Creagh and McAuley[7]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[8]. All calculations were performed using the teXsan[9] crystallographic software package of Molecular Structure Corporation.

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(3) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

where $w = \frac{1}{\sigma^2(Fo)} = \frac{4Fo^2}{\sigma^2(Fo^2)}$

$\sigma^2(Fo^2) = \frac{S^2(C+R^2B)+(pFo^2)^2}{Lp^2}$

S = Scan rate

C = Total integrated peak count

R = Ratio of scan rime to background counting time

B = Total background count

Lp = Lorentz-polarization factor

p = p-factor

(4) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2/(No - Nv)}$$

where: No = number of observations

Nv = number of variables

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(9) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{17}H_{15}N_2O_2F_3$
Formula Weight	336.31
Crystal Color, Habit	colourlessblock, block
Crystal Dimensions	0.50 X 0.40 X 0.30 mm
Crystal System	monoclinic
Lattice Type	Primitive
No. of Reflections Used for Unit Cell Determination (2θ range)	25 (36.8 - 42.8°)
Omega Scan Peak Width at Half-height	0.22°
Lattice Parameters	$a = 10.859(3) Å$
	$b = 12.316(3) Å$
	$c = 11.413(2) Å$
	$\beta = 104.48(2)°$
	$V = 1477.8(6) Å^3$
Space Group	$P2_1/n$ (#14)
Z value	4
D_{calc}	1.511 g/cm^3
F_{000}	696.00
μ(MoKα)	1.25 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC7S
Radiation	MoKα ($\lambda = 0.71069$ Å) graphite monochromated
Attenuator	Zr foil (factors = 1.00, 8.59, 8.59, 8.59)
Take-off Angle	6.0°
Detector Aperture	9.0 mm horizontal 13.0 mm vertical
Crystal to Detector Distance	400 mm
Temperature	150.0°C
Scan Type	ω-2θ
Scan Rate	16.0°/min (in ω) (up to 4 scans)
Scan Width	$(0.84 + 0.35 \tan \theta)°$
$2\theta_{max}$	50.0°
No. of Reflections Measured	Total: 2884 Unique: 2735 ($R_{int} = 0.038$)
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELXS86)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\lvert Fo\rvert - \lvert Fc\rvert)^2$
Least Squares Weights	$\frac{1}{\sigma^2(Fo)} = \frac{4Fo^2}{\sigma^2(Fo^2)}$
p-factor	0.011
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I>3.00\sigma(I)$)	2164
No. Variables	217
Reflection/Parameter Ratio	9.97
Residuals: R; Rw	0.042 ; 0.051

Goodness of Fit Indicator	3.01
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.33 $e^-/\mathring{A}^3$
Minimum peak in Final Diff. Map	-0.25 $e^-/\mathring{A}^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
F(1)	0.2525(1)	0.5614(1)	0.6925(1)	4.20(4)
F(2)	0.2056(1)	0.6955(1)	0.5694(1)	3.58(3)
F(3)	0.2416(1)	0.7224(1)	0.7595(1)	4.50(4)
O(1)	0.4537(2)	0.6501(2)	0.5900(1)	3.54(4)
O(2)	0.4887(2)	0.7198(1)	0.7773(1)	3.11(4)
N(1)	0.3060(2)	0.9458(1)	0.3254(2)	1.96(4)
N(2)	0.4099(2)	1.0781(1)	0.2388(2)	2.33(4)
C(1)	0.3680(2)	1.0428(2)	0.3322(2)	2.07(4)
C(2)	0.3883(2)	1.1040(2)	0.4410(2)	2.36(5)
C(3)	0.3512(2)	1.0635(2)	0.5374(2)	2.63(5)
C(4)	0.2883(2)	0.9619(2)	0.5288(2)	2.60(5)
C(5)	0.2651(2)	0.9072(2)	0.4227(2)	2.37(5)
C(6)	0.4078(2)	1.0117(2)	0.1335(2)	2.36(5)
C(7)	0.2867(2)	0.9440(2)	0.0995(2)	2.17(4)
C(8)	0.3034(2)	0.8528(2)	0.0117(2)	2.49(5)
C(9)	0.3704(2)	0.7647(2)	0.0963(2)	2.09(4)
C(10)	0.4378(2)	0.6754(2)	0.0709(2)	2.46(5)
C(11)	0.4860(2)	0.6017(2)	0.1634(2)	2.66(5)
C(12)	0.4684(2)	0.6171(2)	0.2792(2)	2.57(5)
C(13)	0.4020(2)	0.7073(2)	0.3048(2)	2.23(5)
C(14)	0.3538(2)	0.7804(2)	0.2123(2)	1.99(4)
C(15)	0.2719(2)	0.8808(2)	0.2116(2)	2.01(4)
C(16)	0.4234(2)	0.6806(2)	0.6818(2)	2.18(5)
C(17)	0.2806(2)	0.6661(2)	0.6761(2)	2.32(5)

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(1)	0.4458	1.1784	0.4470	4.7715
H(2)	0.3665	1.1080	0.6234	4.7715
H(3)	0.2668	0.9274	0.6056	4.7715
H(4)	0.2184	0.8335	0.4088	4.7715
H(5)	0.4498	1.1533	0.2435	4.7715
H(6)	0.4147	1.0624	0.0659	4.7715
H(7)	0.4822	0.9597	0.1460	4.7715
H(8)	0.2035	0.9839	0.0576	4.7715
H(9)	0.3536	0.8787	-0.0514	4.7715
H(10)	0.2197	0.8253	-0.0396	4.7715
H(11)	0.4392	0.6641	-0.0189	4.7715
H(12)	0.5318	0.5292	0.1429	4.7715
H(13)	0.5002	0.5587	0.3437	4.7715
H(14)	0.3895	0.7198	0.3933	4.7715
H(15)	0.1710	0.8654	0.1916	4.7715

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
F(1)	0.0480(9)	0.0361(8)	0.078(1)	-0.0134(7)	0.0204(8)	0.0129(8)
F(2)	0.0347(8)	0.0557(9)	0.0418(8)	0.0016(7)	0.0027(6)	0.0076(7)
F(3)	0.0511(9)	0.075(1)	0.0525(10)	0.0042(8)	0.0279(8)	-0.0204(8)
O(1)	0.0426(10)	0.060(1)	0.0368(10)	0.0055(8)	0.0192(8)	0.0030(9)
O(2)	0.0406(10)	0.0377(10)	0.0371(10)	-0.0137(7)	0.0046(8)	0.0032(8)
N(1)	0.0249(9)	0.0226(9)	0.0282(10)	0.0013(7)	0.0091(7)	0.0014(7)
N(2)	0.035(1)	0.0227(9)	0.033(1)	-0.0030(8)	0.0113(8)	0.0015(8)
C(1)	0.022(1)	0.023(1)	0.033(1)	0.0055(9)	0.0062(9)	0.0013(9)
C(2)	0.026(1)	0.025(1)	0.038(1)	0.0068(9)	0.0066(10)	-0.0035(10)
C(3)	0.034(1)	0.034(1)	0.034(1)	0.0127(10)	0.010(1)	-0.003(1)
C(4)	0.035(1)	0.035(1)	0.032(1)	0.010(1)	0.0150(10)	0.002(1)
C(5)	0.030(1)	0.030(1)	0.033(1)	0.0042(10)	0.0136(10)	0.006(1)
C(6)	0.035(1)	0.026(1)	0.030(1)	-0.0036(9)	0.0112(10)	0.0039(9)
C(7)	0.026(1)	0.028(1)	0.027(1)	-0.0002(9)	0.0046(9)	0.0023(9)
C(8)	0.035(1)	0.033(1)	0.026(1)	-0.003(1)	0.0060(9)	0.0002(10)
C(9)	0.024(1)	0.026(1)	0.030(1)	-0.0067(9)	0.0062(9)	-0.0028(9)
C(10)	0.027(1)	0.032(1)	0.036(1)	-0.0063(10)	0.0100(10)	-0.007(1)
C(11)	0.029(1)	0.027(1)	0.046(1)	-0.0019(10)	0.009(1)	-0.005(1)
C(12)	0.031(1)	0.024(1)	0.042(1)	-0.0036(9)	0.007(1)	0.003(1)
C(13)	0.027(1)	0.025(1)	0.032(1)	-0.0049(9)	0.0071(9)	0.0013(9)
C(14)	0.022(1)	0.023(1)	0.030(1)	-0.0055(8)	0.0070(9)	-0.0008(9)
C(15)	0.026(1)	0.024(1)	0.027(1)	-0.0020(9)	0.0063(9)	-0.0007(9)
C(16)	0.033(1)	0.022(1)	0.029(1)	-0.0010(9)	0.0091(10)	0.0063(9)
C(17)	0.036(1)	0.026(1)	0.029(1)	-0.0016(10)	0.0119(10)	-0.0019(10)

Table 2. Anisotropic Displacement Parameters (continued)

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Bond Lengths(Å)

atom	atom	distance	atom	atom	distance
F(1)	C(17)	1.348(3)	F(2)	C(17)	1.335(2)
F(3)	C(17)	1.330(3)	O(1)	C(16)	1.233(3)
O(2)	C(16)	1.240(3)	N(1)	C(1)	1.364(3)
N(1)	C(5)	1.380(3)	N(1)	C(15)	1.491(3)
N(2)	C(1)	1.331(3)	N(2)	C(6)	1.450(3)
C(1)	C(2)	1.422(3)	C(2)	C(3)	1.358(3)
C(3)	C(4)	1.417(3)	C(4)	C(5)	1.353(3)
C(6)	C(7)	1.523(3)	C(7)	C(8)	1.546(3)
C(7)	C(15)	1.540(3)	C(8)	C(9)	1.512(3)
C(9)	C(10)	1.391(3)	C(9)	C(14)	1.393(3)
C(10)	C(11)	1.391(3)	C(11)	C(12)	1.395(3)
C(12)	C(13)	1.394(3)	C(13)	C(14)	1.387(3)
C(14)	C(15)	1.522(3)	C(16)	C(17)	1.546(3)

Table 4. Bond Lengths(Å)

atom	atom	distance	atom	atom	distance
N(2)	H(5)	1.02	C(2)	H(1)	1.10
C(3)	H(2)	1.10	C(4)	H(3)	1.05
C(5)	H(4)	1.03	C(6)	H(6)	1.01
C(6)	H(7)	1.01	C(7)	H(8)	1.03
C(8)	H(9)	1.06	C(8)	H(10)	1.01
C(10)	H(11)	1.04	C(11)	H(12)	1.07
C(12)	H(13)	1.02	C(13)	H(14)	1.06
C(15)	H(15)	1.08			

Table 5. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(1)	N(1)	C(5)	120.6(2)	C(1)	N(1)	C(15)	122.1(2)
C(5)	N(1)	C(15)	117.1(2)	C(1)	N(2)	C(6)	122.8(2)
N(1)	C(1)	N(2)	120.2(2)	N(1)	C(1)	C(2)	118.7(2)
N(2)	C(1)	C(2)	121.1(2)	C(1)	C(2)	C(3)	120.0(2)
C(2)	C(3)	C(4)	120.3(2)	C(3)	C(4)	C(5)	118.7(2)
N(1)	C(5)	C(4)	121.6(2)	N(2)	C(6)	C(7)	110.7(2)
C(6)	C(7)	C(8)	109.2(2)	C(6)	C(7)	C(15)	109.1(2)
C(8)	C(7)	C(15)	103.0(2)	C(7)	C(8)	C(9)	102.9(2)
C(8)	C(9)	C(10)	128.9(2)	C(8)	C(9)	C(14)	110.5(2)
C(10)	C(9)	C(14)	120.5(2)	C(9)	C(10)	C(11)	118.4(2)
C(10)	C(11)	C(12)	121.0(2)	C(11)	C(12)	C(13)	120.5(2)
C(12)	C(13)	C(14)	118.4(2)	C(9)	C(14)	C(13)	121.2(2)
C(9)	C(14)	C(15)	108.8(2)	C(13)	C(14)	C(15)	129.8(2)
N(1)	C(15)	C(7)	113.4(2)	N(1)	C(15)	C(14)	114.4(2)
C(7)	C(15)	C(14)	103.4(2)	O(1)	C(16)	O(2)	130.6(2)
O(1)	C(16)	C(17)	114.0(2)	O(2)	C(16)	C(17)	115.4(2)
F(1)	C(17)	F(2)	106.2(2)	F(1)	C(17)	F(3)	106.0(2)
F(1)	C(17)	C(16)	111.3(2)	F(2)	C(17)	F(3)	106.3(2)
F(2)	C(17)	C(16)	112.5(2)	F(3)	C(17)	C(16)	113.9(2)

Table 6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(1)	N(2)	H(5)	118.8	C(6)	N(2)	H(5)	118.3
C(1)	C(2)	H(1)	117.2	C(3)	C(2)	H(1)	122.2
C(2)	C(3)	H(2)	122.0	C(4)	C(3)	H(2)	117.7
C(3)	C(4)	H(3)	120.2	C(5)	C(4)	H(3)	121.0
N(1)	C(5)	H(4)	115.1	C(4)	C(5)	H(4)	123.3
N(2)	C(6)	H(6)	107.2	N(2)	C(6)	H(7)	113.1
C(7)	C(6)	H(6)	111.6	C(7)	C(6)	H(7)	107.3
H(6)	C(6)	H(7)	106.9	C(6)	C(7)	H(8)	117.1
C(8)	C(7)	H(8)	106.1	C(15)	C(7)	H(8)	111.3
C(7)	C(8)	H(9)	112.8	C(7)	C(8)	H(10)	112.6
C(9)	C(8)	H(9)	113.9	C(9)	C(8)	H(10)	110.5
H(9)	C(8)	H(10)	104.4	C(9)	C(10)	H(11)	116.7
C(11)	C(10)	H(11)	124.5	C(10)	C(11)	H(12)	118.9
C(12)	C(11)	H(12)	120.0	C(11)	C(12)	H(13)	118.9
C(13)	C(12)	H(13)	120.5	C(12)	C(13)	H(14)	120.6
C(14)	C(13)	H(14)	121.0	N(1)	C(15)	H(15)	107.3
C(7)	C(15)	H(15)	103.0	C(14)	C(15)	H(15)	114.8

Table 7. Torsion Angles(°)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
F(1)	C(17)	C(16)	O(1)	76.2(2)	F(1)	C(17)	C(16)	O(2)	-103.4(2)
F(2)	C(17)	C(16)	O(1)	-42.9(3)	F(2)	C(17)	C(16)	O(2)	137.6(2)
F(3)	C(17)	C(16)	O(1)	-164.0(2)	F(3)	C(17)	C(16)	O(2)	16.5(3)
N(1)	C(1)	N(2)	C(6)	-8.2(3)	N(1)	C(1)	C(2)	C(3)	2.8(3)
N(1)	C(5)	C(4)	C(3)	2.8(3)	N(1)	C(15)	C(7)	C(6)	40.7(2)
N(1)	C(15)	C(7)	C(8)	156.6(2)	N(1)	C(15)	C(14)	C(9)	-144.9(2)
N(1)	C(15)	C(14)	C(13)	39.0(3)	N(2)	C(1)	N(1)	C(5)	178.3(2)
N(2)	C(1)	N(1)	C(15)	-5.9(3)	N(2)	C(1)	C(2)	C(3)	-176.2(2)
N(2)	C(6)	C(7)	C(8)	-164.5(2)	N(2)	C(6)	C(7)	C(15)	-52.6(2)
C(1)	N(1)	C(5)	C(4)	-2.1(3)	C(1)	N(1)	C(15)	C(7)	-12.4(3)
C(1)	N(1)	C(15)	C(14)	106.0(2)	C(1)	N(2)	C(6)	C(7)	38.8(3)
C(1)	C(2)	C(3)	C(4)	-2.2(3)	C(2)	C(1)	N(1)	C(5)	-0.7(3)
C(2)	C(1)	N(1)	C(15)	175.1(2)	C(2)	C(1)	N(2)	C(6)	170.8(2)
C(2)	C(3)	C(4)	C(5)	-0.6(3)	C(4)	C(5)	N(1)	C(15)	-178.1(2)
C(5)	N(1)	C(15)	C(7)	163.5(2)	C(5)	N(1)	C(15)	C(14)	-78.1(2)
C(6)	C(7)	C(8)	C(9)	84.4(2)	C(6)	C(7)	C(15)	C(14)	-83.8(2)
C(7)	C(8)	C(9)	C(10)	-162.3(2)	C(7)	C(8)	C(9)	C(14)	19.7(2)
C(7)	C(15)	C(14)	C(9)	-21.0(2)	C(7)	C(15)	C(14)	C(13)	162.9(2)
C(8)	C(7)	C(15)	C(14)	32.1(2)	C(8)	C(9)	C(10)	C(11)	-176.7(2)
C(8)	C(9)	C(14)	C(13)	177.2(2)	C(8)	C(9)	C(14)	C(15)	0.7(2)
C(9)	C(8)	C(7)	C(15)	-31.5(2)	C(9)	C(10)	C(11)	C(12)	-0.6(3)
C(9)	C(14)	C(13)	C(12)	0.2(3)	C(10)	C(9)	C(14)	C(13)	-0.9(3)
C(10)	C(9)	C(14)	C(15)	-177.4(2)	C(10)	C(11)	C(12)	C(13)	-0.2(3)
C(11)	C(10)	C(9)	C(14)	1.1(3)	C(11)	C(12)	C(13)	C(14)	0.3(3)

Table 7. Torsion Angles(°) (continued)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
C(12)	C(13)	C(14)	C(15)	175.9(2)					

Table 8. Non-bonded Contacts out to 3.60 Å

atom	atom	distance	ADC	atom	atom	distance	ADC
F(1)	C(8)	3.420(3)	54502	F(1)	C(11)	3.531(3)	66603
F(1)	C(3)	3.537(3)	54602	F(1)	C(4)	3.538(3)	54602
F(1)	C(7)	3.559(3)	54502	F(2)	C(5)	3.249(3)	1
F(2)	C(6)	3.252(3)	54502	F(2)	C(10)	3.318(3)	46504
F(2)	C(4)	3.463(3)	1	F(3)	C(8)	3.216(3)	55601
F(3)	C(3)	3.375(3)	54602	F(3)	C(11)	3.475(3)	46504
O(1)	C(13)	3.239(3)	1	O(1)	C(15)	3.407(3)	56504
O(1)	C(2)	3.541(3)	67603	O(2)	N(2)	2.746(2)	67603
O(2)	C(5)	3.423(3)	56504	O(2)	C(6)	3.558(3)	67603
O(2)	C(15)	3.564(3)	56504	O(2)	C(10)	3.572(3)	55601
N(2)	C(16)	3.480(3)	67603	C(1)	C(3)	3.310(3)	67603
C(1)	C(13)	3.585(3)	2	C(2)	C(9)	3.376(3)	2
C(2)	C(3)	3.459(3)	67603	C(2)	C(14)	3.520(3)	2
C(2)	C(4)	3.536(3)	67603	C(2)	C(2)	3.553(4)	67603
C(3)	C(10)	3.368(3)	2	C(3)	C(9)	3.525(3)	2
C(4)	C(10)	3.583(3)	2	C(5)	C(11)	3.577(3)	2

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ±4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

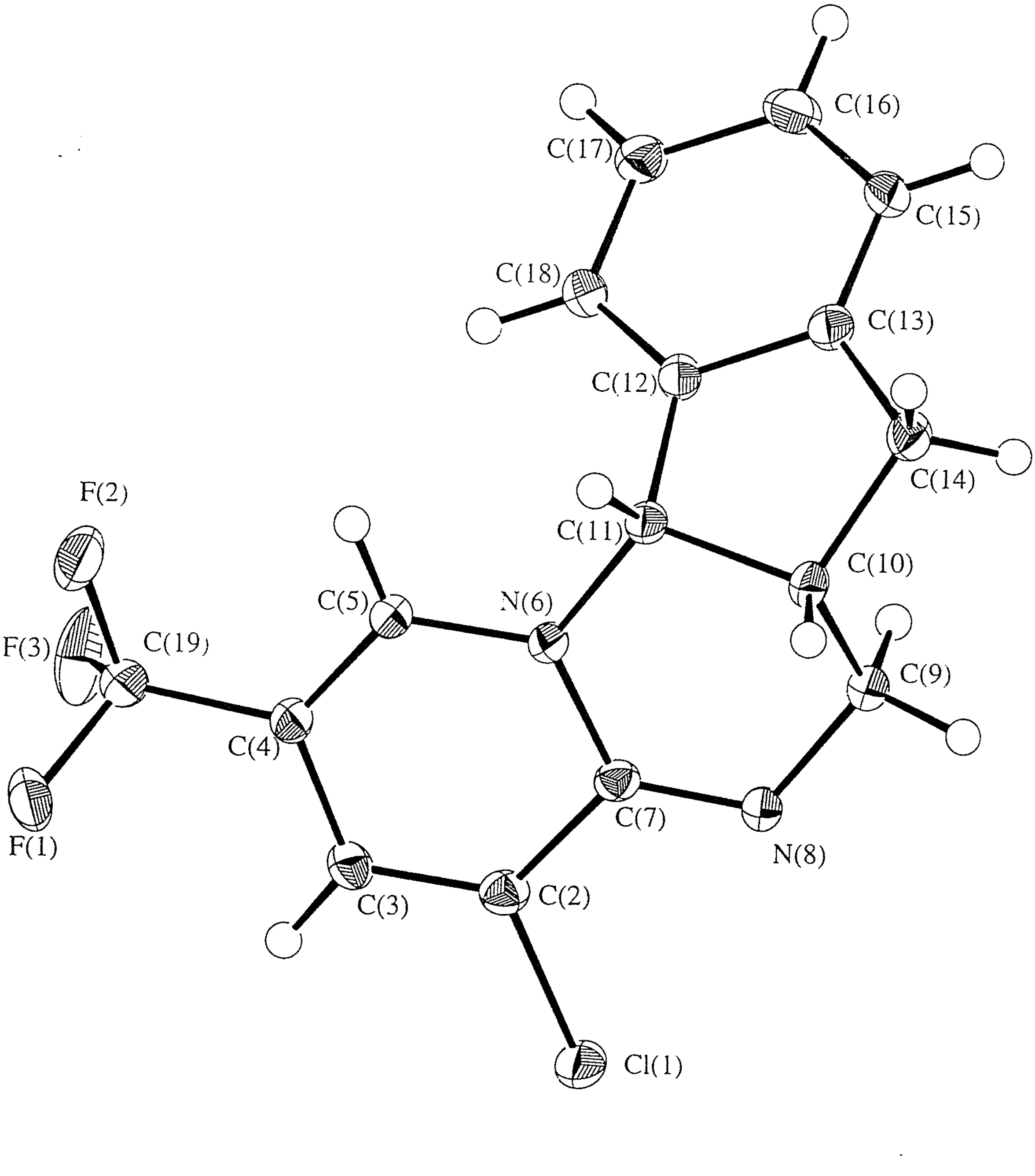
The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1)	X,	Y,	Z	(2)	1/2-X,	1/2+Y,	1/2-Z
(3)	-X,	-Y,	-Z	(4)	1/2+X,	1/2-Y,	1/2+Z


C(16)
C(17)
C(15)
C(18)
C(13)
C(12)
C(14)
F(2)
C(11)
C(10)
C(5)
N(6)
F(3)
C(19)
C(9)
C(4)
F(1)
C(7)
N(8)
C(3)
C(2)
Cl(1)

```
Table 1.  Crystal data and structure refinement for jmdata
Empirical formula C16H12ClF3N2
Formula weight 324.73
Temperature 120K
Wavelength 0.71073Å
Crystal system MONOCLINIC
Space group P21/C
&HUnit cell dimensions&6&6
a = 9.384(4)Å  α = 90.00°
b = 15.995(4)Å β = 92.59°
c =& 9.561(7)Å γ = 90°
Volume 1433.6(13)Å3
Z 4
Density (calculated) 1.505 Mg/m3
Absorption coefficient 0.297 mm-1
F(000) 664
Crystal size 0.32 x 0.25 x 0.14 mm
range for data collection 2.17 to 24.92°
&HIndex ranges -10 < H < 10, -18 < K < 17, -10 < L < 8
Reflections collected 6094
Independent reflections 2257 (Rint = 0.0552)
Refinement method Full-matrix least-squares on F&^2&0
Data / restraints / parameters 2256 / 0 / 199
Goodness-of-fit on F^2 0.967
Final R indices [I>2σ(I)] R1 = 0.0446, wR2 = 0.1088
R indices (all data) R1 = 0.0550, wR2 = 0.1130
Largest diff. peak and hole 0.591 and -0.265 eA-3
```

Table 1. Crystal data and structure refinement for jmdata
Empirical formula C16H12ClF3N2
Formula weight 324.73
Temperature 120K
Wavelength 0.71073Å
Crystal system MONOCLINIC
Space group P21/C
&HUnit cell dimensions&6&6
a = 9.384(4)Å α = 90.00°
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c =& 9.561(7)Å γ = 90°
Volume 1433.6(13)Å3
Z 4
Density (calculated) 1.505 Mg/m3
Absorption coefficient 0.297 mm-1
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Data / restraints / parameters 2256 / 0 / 199
Goodness-of-fit on F^2 0.967
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Largest diff. peak and hole 0.591 and -0.265 eA-3

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Wavelength 0.71073Å
Crystal system MONOCLINIC
Space group P21/C
&HUnit cell dimensions&6&6
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Density (calculated) 1.505 Mg/m3
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Goodness-of-fit on F^2 0.967
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R indices (all data) R1 = 0.0550, wR2 = 0.1130
Largest diff. peak and hole 0.591 and -0.265 eA-3

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [&GA&^2&0 x 10^3] for JMDATA. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Cl(1)	2798(1)	5316(1)	1280(1)	32(1)
C(2)	3067(2)	6244(1)	398(2)	23(1)
C(3)	4173(2)	6320(1)	-435(2)	24(1)
C(4)	4387(2)	7102(1)	-1128(2)	21(1)
C(5)	3459(2)	7732(1)	-949(2)	20(1)
N(6)	2338(2)	7660(1)	-84(2)	19(1)
C(7)	2072(2)	6919(1)	671(2)	20(1)
N(8)	1081(2)	6822(1)	1535(2)	22(1)
C(9)	184(3)	7537(1)	1829(2)	23(1)
C(10)	-94(2)	8144(1)	615(2)	21(1)
C(11)	1343(2)	8380(1)	-15(2)	20(1)
C(12)	1866(2)	9110(1)	890(2)	21(1)
C(13)	715(2)	9452(1)	1573(2)	23(1)
C(14)	-642(2)	8977(1)	1191(2)	24(1)
C(15)	924(3)	10142(1)	2436(2)	27(1)
C(16)	2269(3)	10484(1)	2602(2)	30(1)
C(17)	3412(3)	10153(2)	1901(2)	28(1)
C(18)	3205(2)	9460(2)	1041(2)	24(1)
C(19)	5671(3)	7218(1)	-1954(2)	26(1)
F(1)	5892(2)	6588(1)	-2840(2)	49(1)
F(2)	5628(2)	7908(1)	-2730(2)	49(1)
F(3)	6874(2)	7256(1)	-1153(2)	55(1)

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [&GA&^2&0 x 10^3] for JMDATA. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

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N(6)	2338(2)	7660(1)	-84(2)	19(1)
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N(8)	1081(2)	6822(1)	1535(2)	22(1)
C(9)	184(3)	7537(1)	1829(2)	23(1)
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C(15)	924(3)	10142(1)	2436(2)	27(1)
C(16)	2269(3)	10484(1)	2602(2)	30(1)
C(17)	3412(3)	10153(2)	1901(2)	28(1)
C(18)	3205(2)	9460(2)	1041(2)	24(1)
C(19)	5671(3)	7218(1)	-1954(2)	26(1)
F(1)	5892(2)	6588(1)	-2840(2)	49(1)
F(2)	5628(2)	7908(1)	-2730(2)	49(1)
F(3)	6874(2)	7256(1)	-1153(2)	55(1)

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [&GA&^2&0 x 10^3] for JMDATA. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Cl(1)	2798(1)	5316(1)	1280(1)	32(1)
C(2)	3067(2)	6244(1)	398(2)	23(1)
C(3)	4173(2)	6320(1)	-435(2)	24(1)
C(4)	4387(2)	7102(1)	-1128(2)	21(1)
C(5)	3459(2)	7732(1)	-949(2)	20(1)
N(6)	2338(2)	7660(1)	-84(2)	19(1)
C(7)	2072(2)	6919(1)	671(2)	20(1)
N(8)	1081(2)	6822(1)	1535(2)	22(1)
C(9)	184(3)	7537(1)	1829(2)	23(1)
C(10)	-94(2)	8144(1)	615(2)	21(1)
C(11)	1343(2)	8380(1)	-15(2)	20(1)
C(12)	1866(2)	9110(1)	890(2)	21(1)
C(13)	715(2)	9452(1)	1573(2)	23(1)
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C(15)	924(3)	10142(1)	2436(2)	27(1)
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F(3)	6874(2)	7256(1)	-1153(2)	55(1)

Table 3. Bond lengths [Å] and angles [°] for JMDATA

Cl(1)-C(2)	1.731(2)
C(2)-C(3)	1.342(3)
C(2)-C(7)	1.459(3)
C(3)-C(4)	1.434(3)
C(4)-C(5)	1.347(3)
C(4)-C(19)	1.481(3)
C(5)-N(6)	1.372(3)
N(6)-C(7)	1.416(3)
N(6)-C(11)	1.486(3)
C(7)-N(8)	1.281(3)
N(8)-C(9)	1.454(3)
C(9)-C(10)	1.526(3)
C(10)-C(14)	1.540(3)
C(10)-C(11)	1.548(3)
C(11)-C(12)	1.521(3)
C(12)-C(18)	1.377(3)
C(12)-C(13)	1.399(3)
C(13)-C(15)	1.387(3)
C(13)-C(14)	1.513(3)
C(15)-C(16)	1.378(4)
C(16)-C(17)	1.395(3)
C(17)-C(18)	1.389(3)
C(19)-F(2)	1.330(3)
C(19)-F(3)	1.337(3)
C(19)-F(1)	1.339(3)

C(3)-C(2)-C(7)	123.9(2)
C(3)-C(2)-Cl(1)	120.1(2)
C(7)-C(2)-Cl(1)	116.0(2)
C(2)-C(3)-C(4)	118.8(2)
C(5)-C(4)-C(3)	119.2(2)
C(5)-C(4)-C(19)	121.3(2)
C(3)-C(4)-C(19)	119.3(2)
C(4)-C(5)-N(6)	122.1(2)
C(5)-N(6)-C(7)	122.3(2)
C(5)-N(6)-C(11)	117.5(2)
C(7)-N(6)-C(11)	120.1(2)
N(8)-C(7)-N(6)	125.5(2)
N(8)-C(7)-C(2)	121.0(2)
N(6)-C(7)-C(2)	113.6(2)
C(7)-N(8)-C(9)	118.2(2)
N(8)-C(9)-C(10)	115.7(2)
C(9)-C(10)-C(14)	109.1(2)
C(9)-C(10)-C(11)	109.2(2)
C(14)-C(10)-C(11)	103.8(2)
N(6)-C(11)-C(12)	115.6(2)
N(6)-C(11)-C(10)	112.8(2)
C(12)-C(11)-C(10)	103.4(2)
C(18)-C(12)-C(13)	120.9(2)
C(18)-C(12)-C(11)	129.9(2)
C(13)-C(12)-C(11)	109.2(2)
C(15)-C(13)-C(12)	119.8(2)
C(15)-C(13)-C(14)	129.7(2)
C(12)-C(13)-C(14)	110.5(2)
C(13)-C(14)-C(10)	103.3(2)
C(16)-C(15)-C(13)	119.3(2)
C(15)-C(16)-C(17)	121.0(2)
C(18)-C(17)-C(16)	119.8(2)
C(12)-C(18)-C(17)	119.3(2)
F(2)-C(19)-F(3)	106.6(2)
F(2)-C(19)-F(1)	105.8(2)
F(3)-C(19)-F(1)	104.2(2)
F(2)-C(19)-C(4)	113.4(2)
F(3)-C(19)-C(4)	112.8(2)
F(1)-C(19)-C(4)	113.4(2)

Table 3. Bond lengths [A] and angles [°] for JMDATA

Cl(1)-C(2)	1.731(2)
C(2)-C(3)	1.342(3)
C(2)-C(7)	1.459(3)
C(3)-C(4)	1.434(3)
C(4)-C(5)	1.347(3)
C(4)-C(19)	1.481(3)
C(5)-N(6)	1.372(3)
N(6)-C(7)	1.416(3)
N(6)-C(11)	1.486(3)
C(7)-N(8)	1.281(3)
N(8)-C(9)	1.454(3)
C(9)-C(10)	1.526(3)
C(10)-C(14)	1.540(3)
C(10)-C(11)	1.548(3)
C(11)-C(12)	1.521(3)
C(12)-C(18)	1.377(3)
C(12)-C(13)	1.399(3)
C(13)-C(15)	1.387(3)
C(13)-C(14)	1.513(3)
C(15)-C(16)	1.378(4)
C(16)-C(17)	1.395(3)
C(17)-C(18)	1.389(3)
C(19)-F(2)	1.330(3)
C(19)-F(3)	1.337(3)
C(19)-F(1)	1.339(3)

C(3)-C(2)-C(7)	123.9(2)
C(3)-C(2)-Cl(1)	120.1(2)
C(7)-C(2)-Cl(1)	116.0(2)
C(2)-C(3)-C(4)	118.8(2)
C(5)-C(4)-C(3)	119.2(2)
C(5)-C(4)-C(19)	121.3(2)
C(3)-C(4)-C(19)	119.3(2)
C(4)-C(5)-N(6)	122.1(2)
C(5)-N(6)-C(7)	122.3(2)
C(5)-N(6)-C(11)	117.5(2)
C(7)-N(6)-C(11)	120.1(2)
N(8)-C(7)-N(6)	125.5(2)
N(8)-C(7)-C(2)	121.0(2)
N(6)-C(7)-C(2)	113.6(2)
C(7)-N(8)-C(9)	118.2(2)
N(8)-C(9)-C(10)	115.7(2)
C(9)-C(10)-C(14)	109.1(2)
C(9)-C(10)-C(11)	109.2(2)
C(14)-C(10)-C(11)	103.8(2)
N(6)-C(11)-C(12)	115.6(2)
N(6)-C(11)-C(10)	112.8(2)
C(12)-C(11)-C(10)	103.4(2)
C(18)-C(12)-C(13)	120.9(2)
C(18)-C(12)-C(11)	129.9(2)
C(13)-C(12)-C(11)	109.2(2)
C(15)-C(13)-C(12)	119.8(2)
C(15)-C(13)-C(14)	129.7(2)
C(12)-C(13)-C(14)	110.5(2)
C(13)-C(14)-C(10)	103.3(2)
C(16)-C(15)-C(13)	119.3(2)
C(15)-C(16)-C(17)	121.0(2)
C(18)-C(17)-C(16)	119.8(2)
C(12)-C(18)-C(17)	119.3(2)
F(2)-C(19)-F(3)	106.6(2)
F(2)-C(19)-F(1)	105.8(2)
F(3)-C(19)-F(1)	104.2(2)
F(2)-C(19)-C(4)	113.4(2)
F(3)-C(19)-C(4)	112.8(2)
F(1)-C(19)-C(4)	113.4(2)

Table 3. Bond lengths [Å] and angles [°] for JMDATA

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C(5)-N(6)	1.372(3)
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C(16)-C(17)	1.395(3)
C(17)-C(18)	1.389(3)
C(19)-F(2)	1.330(3)
C(19)-F(3)	1.337(3)
C(19)-F(1)	1.339(3)

C(3)-C(2)-C(7)	123.9(2)
C(3)-C(2)-Cl(1)	120.1(2)
C(7)-C(2)-Cl(1)	116.0(2)
C(2)-C(3)-C(4)	118.8(2)
C(5)-C(4)-C(3)	119.2(2)
C(5)-C(4)-C(19)	121.3(2)
C(3)-C(4)-C(19)	119.3(2)
C(4)-C(5)-N(6)	122.1(2)
C(5)-N(6)-C(7)	122.3(2)
C(5)-N(6)-C(11)	117.5(2)
C(7)-N(6)-C(11)	120.1(2)
N(8)-C(7)-N(6)	125.5(2)
N(8)-C(7)-C(2)	121.0(2)
N(6)-C(7)-C(2)	113.6(2)
C(7)-N(8)-C(9)	118.2(2)
N(8)-C(9)-C(10)	115.7(2)
C(9)-C(10)-C(14)	109.1(2)
C(9)-C(10)-C(11)	109.2(2)
C(14)-C(10)-C(11)	103.8(2)
N(6)-C(11)-C(12)	115.6(2)
N(6)-C(11)-C(10)	112.8(2)
C(12)-C(11)-C(10)	103.4(2)
C(18)-C(12)-C(13)	120.9(2)
C(18)-C(12)-C(11)	129.9(2)
C(13)-C(12)-C(11)	109.2(2)
C(15)-C(13)-C(12)	119.8(2)
C(15)-C(13)-C(14)	129.7(2)
C(12)-C(13)-C(14)	110.5(2)
C(13)-C(14)-C(10)	103.3(2)
C(16)-C(15)-C(13)	119.3(2)
C(15)-C(16)-C(17)	121.0(2)
C(18)-C(17)-C(16)	119.8(2)
C(12)-C(18)-C(17)	119.3(2)
F(2)-C(19)-F(3)	106.6(2)
F(2)-C(19)-F(1)	105.8(2)
F(3)-C(19)-F(1)	104.2(2)
F(2)-C(19)-C(4)	113.4(2)
F(3)-C(19)-C(4)	112.8(2)
F(1)-C(19)-C(4)	113.4(2)

Table 4. Anisotropic displacement parameters [A^2 x 10^3] for JMDATA.

	U11	U22	U33	U23	U13	U12
Cl(1)	31(1)	20(1)	45(1)	10(1)	13(1)	6(1)
C(2)	23(1)	19(1)	26(1)	3(1)	0(1)	1(1)
C(3)	20(1)	22(1)	30(1)	-1(1)	3(1)	4(1)
C(4)	19(1)	21(1)	24(1)	-3(1)	4(1)	-3(1)
C(5)	20(1)	20(1)	20(1)	0(1)	3(1)	-2(1)
N(6)	18(1)	16(1)	22(1)	2(1)	4(1)	1(1)
C(7)	21(1)	18(1)	20(1)	-1(1)	0(1)	-3(1)
N(8)	22(1)	20(1)	24(1)	2(1)	7(1)	1(1)
C(9)	22(1)	20(1)	28(1)	2(1)	8(1)	0(1)
C(10)	16(1)	22(1)	25(1)	1(1)	5(1)	-1(1)
C(11)	20(1)	17(1)	22(1)	4(1)	3(1)	2(1)
C(12)	21(1)	20(1)	21(1)	4(1)	3(1)	4(1)
C(13)	24(1)	20(1)	24(1)	5(1)	5(1)	3(1)
C(14)	19(1)	24(1)	30(1)	5(1)	5(1)	5(1)
C(15)	30(1)	19(1)	32(1)	2(1)	10(1)	6(1)
C(16)	39(2)	20(1)	33(1)	-4(1)	3(1)	2(1)
C(17)	24(1)	24(1)	38(1)	-1(1)	3(1)	-3(1)
C(18)	21(1)	23(1)	29(1)	0(1)	5(1)	2(1)
C(19)	23(1)	23(1)	31(1)	-2(1)	4(1)	-2(1)
F(1)	40(1)	44(1)	64(1)	-25(1)	32(1)	-11(1)
F(2)	44(1)	38(1)	68(1)	21(1)	33(1)	8(1)
F(3)	20(1)	100(2)	45(1)	0(1)	1(1)	-11(1)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$] for JMDATA.

	U11	U22	U33	U23	U13	U12
Cl(1)	31(1)	20(1)	45(1)	10(1)	13(1)	6(1)
C(2)	23(1)	19(1)	26(1)	3(1)	0(1)	1(1)
C(3)	20(1)	22(1)	30(1)	-1(1)	3(1)	4(1)
C(4)	19(1)	21(1)	24(1)	-3(1)	4(1)	-3(1)
C(5)	20(1)	20(1)	20(1)	0(1)	3(1)	-2(1)
N(6)	18(1)	16(1)	22(1)	2(1)	4(1)	1(1)
C(7)	21(1)	18(1)	20(1)	-1(1)	0(1)	-3(1)
N(8)	22(1)	20(1)	24(1)	2(1)	7(1)	1(1)
C(9)	22(1)	20(1)	28(1)	2(1)	8(1)	0(1)
C(10)	16(1)	22(1)	25(1)	1(1)	5(1)	-1(1)
C(11)	20(1)	17(1)	22(1)	4(1)	3(1)	2(1)
C(12)	21(1)	20(1)	21(1)	4(1)	3(1)	4(1)
C(13)	24(1)	20(1)	24(1)	5(1)	5(1)	3(1)
C(14)	19(1)	24(1)	30(1)	5(1)	5(1)	5(1)
C(15)	30(1)	19(1)	32(1)	2(1)	10(1)	6(1)
C(16)	39(2)	20(1)	33(1)	-4(1)	3(1)	2(1)
C(17)	24(1)	24(1)	38(1)	-1(1)	3(1)	-3(1)
C(18)	21(1)	23(1)	29(1)	0(1)	5(1)	2(1)
C(19)	23(1)	23(1)	31(1)	-2(1)	4(1)	-2(1)
F(1)	40(1)	44(1)	64(1)	-25(1)	32(1)	-11(1)
F(2)	44(1)	38(1)	68(1)	21(1)	33(1)	8(1)
F(3)	20(1)	100(2)	45(1)	0(1)	1(1)	-11(1)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$] for JMDATA.

	U11	U22	U33	U23	U13	U12
Cl(1)	31(1)	20(1)	45(1)	10(1)	13(1)	6(1)
C(2)	23(1)	19(1)	26(1)	3(1)	0(1)	1(1)
C(3)	20(1)	22(1)	30(1)	-1(1)	3(1)	4(1)
C(4)	19(1)	21(1)	24(1)	-3(1)	4(1)	-3(1)
C(5)	20(1)	20(1)	20(1)	0(1)	3(1)	-2(1)
N(6)	18(1)	16(1)	22(1)	2(1)	4(1)	1(1)
C(7)	21(1)	18(1)	20(1)	-1(1)	0(1)	-3(1)
N(8)	22(1)	20(1)	24(1)	2(1)	7(1)	1(1)
C(9)	22(1)	20(1)	28(1)	2(1)	8(1)	0(1)
C(10)	16(1)	22(1)	25(1)	1(1)	5(1)	-1(1)
C(11)	20(1)	17(1)	22(1)	4(1)	3(1)	2(1)
C(12)	21(1)	20(1)	21(1)	4(1)	3(1)	4(1)
C(13)	24(1)	20(1)	24(1)	5(1)	5(1)	3(1)
C(14)	19(1)	24(1)	30(1)	5(1)	5(1)	5(1)
C(15)	30(1)	19(1)	32(1)	2(1)	10(1)	6(1)
C(16)	39(2)	20(1)	33(1)	-4(1)	3(1)	2(1)
C(17)	24(1)	24(1)	38(1)	-1(1)	3(1)	-3(1)
C(18)	21(1)	23(1)	29(1)	0(1)	5(1)	2(1)
C(19)	23(1)	23(1)	31(1)	-2(1)	4(1)	-2(1)
F(1)	40(1)	44(1)	64(1)	-25(1)	32(1)	-11(1)
F(2)	44(1)	38(1)	68(1)	21(1)	33(1)	8(1)
F(3)	20(1)	100(2)	45(1)	0(1)	1(1)	-11(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for JMDATA

	x	y	z	U(eq)
H(3)	4790(2)	5874(1)	-560(2)	50
H(5)	3583(2)	8231(1)	-1426(2)	50
H(9A)	627(3)	7844(1)	2608(2)	50
H(9B)	-726(3)	7332(1)	2125(2)	50
H(10)	-763(2)	7909(1)	-97(2)	50
H(11)	1145(2)	8587(1)	-969(2)	50
H(14A)	-1220(2)	9274(1)	486(2)	50
H(14B)	-1201(2)	8887(1)	2007(2)	50
H(15)	165(3)	10372(1)	2898(2)	50
H(16)	2416(3)	10942(1)	3189(2)	50
H(17)	4311(3)	10396(2)	2009(2)	50
H(18)	3962(2)	9234(2)	572(2)	50

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for JMDATA

	x	y	z	U(eq)
H(3)	4790(2)	5874(1)	-560(2)	50
H(5)	3583(2)	8231(1)	-1426(2)	50
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H(11)	1145(2)	8587(1)	-969(2)	50
H(14A)	-1220(2)	9274(1)	486(2)	50
H(14B)	-1201(2)	8887(1)	2007(2)	50
H(15)	165(3)	10372(1)	2898(2)	50
H(16)	2416(3)	10942(1)	3189(2)	50
H(17)	4311(3)	10396(2)	2009(2)	50
H(18)	3962(2)	9234(2)	572(2)	50

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for JMDATA

	x	y	z	U(eq)
H(3)	4790(2)	5874(1)	-560(2)	50
H(5)	3583(2)	8231(1)	-1426(2)	50
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H(10)	-763(2)	7909(1)	-97(2)	50
H(11)	1145(2)	8587(1)	-969(2)	50
H(14A)	-1220(2)	9274(1)	486(2)	50
H(14B)	-1201(2)	8887(1)	2007(2)	50
H(15)	165(3)	10372(1)	2898(2)	50
H(16)	2416(3)	10942(1)	3189(2)	50
H(17)	4311(3)	10396(2)	2009(2)	50
H(18)	3962(2)	9234(2)	572(2)	50

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