UNIVERSITY OF SOUTHAMPTON

AROMATIC IMINIUM IONS AS 2-AZADIENES IN AZA DIELS-ALDER REACTIONS.

A thesis submitted for the degree of
Master of Philosophy

by

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Department of Chemistry

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A mon pere, ma mere
et a mes enfants.

The consequences of every act are included in the act itself.

George Orwell, "1984".

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ABSTRACT

FACULTY OF SCIENCE
CHEMISTRY
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AROMATIC IMINIUM IONS AS 2-AZADIENES IN AZA DIELS-ALDER REACTIONS

by Patrice Jacques Gregoire.

This thesis generalizes the earlier reported [4+2] cycloaddition reactions of aromatic iminium ions generated from substituted anilines and formaldehyde as 2-azadienes with cyclopentadiene acting as an electron-rich dienophile to bicyclic and tricyclic aromatic iminium ions. Such cyclisations may be considered to be examples of hetero Diels-Alder reactions with inverse electron demand. The following introduction is consequently devoted to an overview of the Diels-Alder reaction. Nevertheless, the alternative of a non concerted process is dicussed. Starting tetralin-, indane-, naphthalene- and anthraquinone-based amines were investigated in the different cyclisation modes. The dicyclisations were the most successful type and led diastereoselectively to a pair of separable isomers in high yields. The monocyclisations and double monocyclisations provided more interesting species, a number of which possess the 11-azasteroidal skeleton and may exhibit some appreciable bioactivity. The difference of results obtained from 7- and 5-amino-α-tetralones and 6-amino-α-indanone on the one hand, and 1-amino-5,6,7,8-tetrahydro-naphthalene and 5-amino-indane on the other hand illustrate the controlling role of both reactivity (higher yields with the amino-ketones) and regioselectivity (a single isomer from the "meta" amino-ketones) shown by a carbonyl in the aliphatic side ring.The necessity of a nearby electron withdrawing group was confirmed by the poor results obtained from simple 1-amino- and 1,8-diamino-naphthalenes. The beneficial influence of a carbonyl group was further studied throughout the anthraquinone series which led to the mono- and dicyclisation adducts in high yields but to the double monocyclisation products in lower yields. Besides their potential application as dyestuffs, the anthraquinonoid species may be of particular interest for their electrochemical properties along with their ability to transport cations.

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Abbreviations

Bn : benzyl

MOMO : CH_3-O-CH_2-O-

TBDMS : t$BuMe_2Si$-

THP : tetrahydro-pyranyl

α-tetralone : 3,4-dihydro-1(2*H*)-naphthalenone

TFA : trifluoroacetic acid

CHAPTER 1 : INTRODUCTION

[A] THE DIELS-ALDER REACTION : GENERALITIES.

I] History.

In 1928, Otto Diels and Karl Alder reported[1] that an all-carbon cisoid electron-rich 1,3-diene adds to a dienophile having an electron-poor double or triple bond to give an unsaturated six-membered ring (scheme 1).

Scheme 1

These reactions proceed in good yields often at room temperature in a regio- and stereoselective fashion. A process with such electronic features is now known as a Diels-Alder reaction with a normal electron demand. Subsequently an alternative type of reaction involving an electron-poor diene and an electron-rich dienophile has been described.

II] Features and extension.

In the three decades following this discovery, Diels, Alder and other groups of workers generalized this reaction as a [4π+2π] thermal cycloaddition. A number of features of the reaction emerged such as the necessity of the cisoid conformation of dienes, the role of substituents of both dienes and dienophiles on the reactivity and the course of the reaction, the regiospecificity, the cis-stereospecificity, the Alder's "endo" rule, and the influence of catalysts, solvents and pressure on the rate and course of the cycloaddition.

Extensions of the reaction have involved the introduction of one or several heteroatoms in the diene and dienophile, its application in intramolecular processes, and, more recently, its usefulness in asymmetric synthesis.

The importance of this reaction has justified a thorough mechanistic analysis. Therefore different models have been proposed over thirty years among which the Frontier Molecular Orbital model has constituted the most general and convincing interpretation. A further subject of investigation has

been the degree to which the reaction should be considered to be a concerted process.

All these points are now described.

[B] THE ALL-CARBON DIELS-ALDER REACTION.

A) MAIN ASPECTS [2-12].

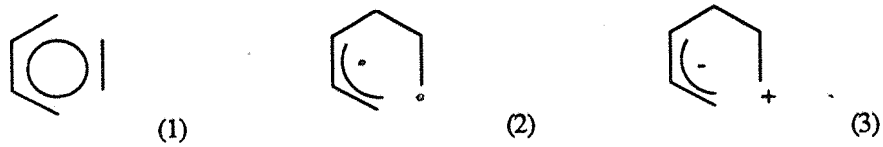
I] Mechanistic aspects.

Since the Diels-Alder reaction has been recognized as a powerful synthetic tool, several theoretical interpretations of the reactivity have been presented. On mathematical grounds, a theoretical analysis should provide complete information as regards the "energy hypersurface" through which reagents and reaction products are connected. Hence, for a reaction implying N atoms, 3N-6 degrees of freedom of vibration should be considered on the corresponding energy hypersurface of the same dimension.

The complexity of the problem cannot be solved nowadays with the present computerised means. Therefore, all these methods of interpretation have been limited by the restriction to very simple model reactions and the approximations necessary in each theory.

Moreover, since these models have usually been established for isolated molecules in the gas phase, solvent effects have not been taken into account. As a result, some experimental conclusions have been misinterpreted.

Although chemists tend to choose a uniform, mechanistic theory as the exclusive interpretation of all reactions of the same type, the Diels-Alder reaction might be considered to proceed either in a concerted fashion via a transition state (1) (scheme 2) or in a non-concerted fashion involving biradical (2) or ionic ("zwitterionic") (3) intermediates.



(1) (2) (3)

Scheme 2

II] Molecular orbital methods.

Different methods are based on the molecular orbitals of the diene and the dienophile.

1] Ab initio and semi-empirical calculations.

The increasing power of computers has been permitting more and more investigations by theoretical methods. There has been an emphasis on simple systems such as the cycloaddition of ethylene and butadiene leading to cyclohexene.

In short, while ab initio calculations propose a reaction pathway via a symmetrical transition state without any intermediate, the SINDO approaches show a profile still without any intermediate but via an unsymmetrical transition state. On the other hand, MINDO calculations propose an unsymmetrical, diradicaloid transition state and a biradical intermediate.

On the whole, ab initio and semi-empirical calculations have failed to clarify fully the course of Diels-Alder reactions.

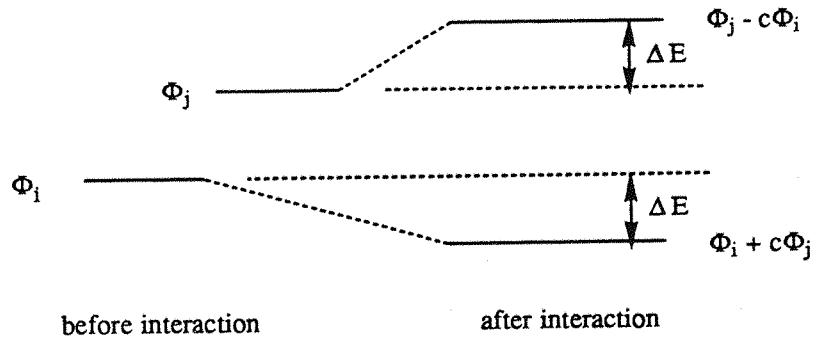
2] Approximative theoretical methods.

They are based on the analysis of symmetrical relations between the diene and the dienophile. Orbital-, configuration-, and state-correlation diagrams would imply that the suprafacial approach ($\pi_{2s} + \pi_{4s}$) of diene and dinophile is symmetry allowed and, consequently, the reaction can be synchronous. Hence the Woodward-Hoffmann rules[10] constituted the first non-numerical approach to describe the energy hypersurface.

3] Frontier Molecular Orbital (FMO) method.

It is an extension to the perturbation theory (PMO) which has already been applied to different chemical phenomena.

A new system of orbitals arises from two orbitals interacting, as shown in scheme 3.



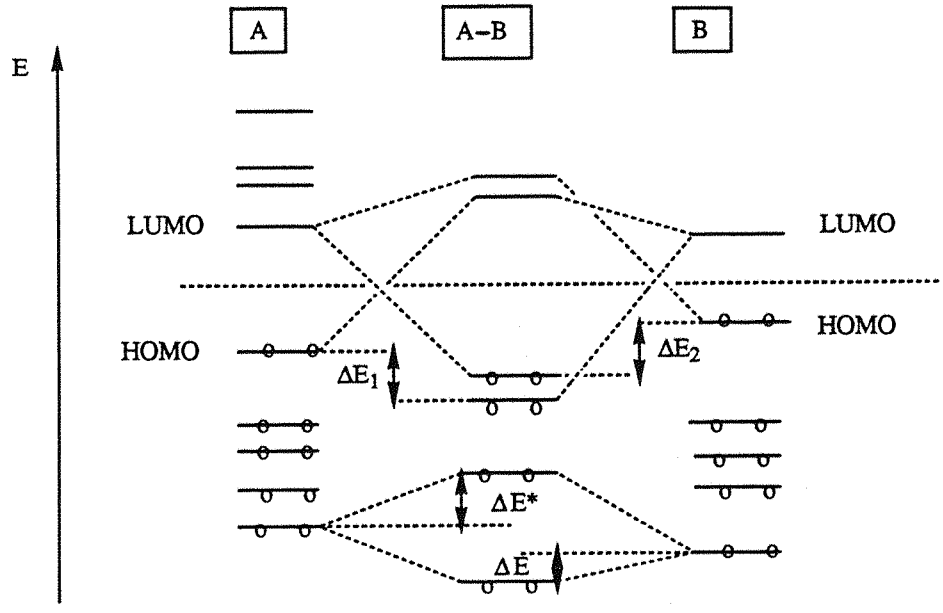
Scheme 3

The neglect of the overlap leads to a second order perturbation expression which gives the difference in energy before and after the interaction:

$$\Delta E=(H_{ij})^2 / (E_i-E_j)$$

Hence, the closer the starting levels in energy are, the greater ΔE will be; in other words the more the two orbitals will interact (conclusion 1).

The general interactions between the orbitals of two reagents in a cycloaddition are summed up in scheme 4.



Scheme 4: MO interaction diagram for two molecules A and B.

Two main conclusions can be drawn from this diagram:

-> two interacting occupied orbitals of the two molecules can lead only to a destabilization of the system ($\Delta E^* > \Delta E$). (conclusion 2).

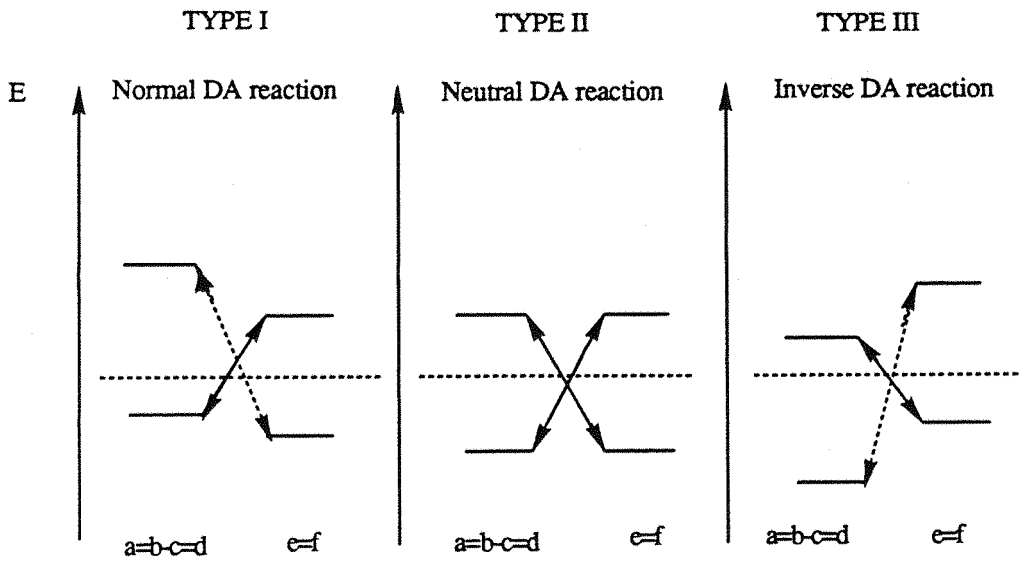
-> the system is stabilized only when some occupied orbitals of the first molecule interact with some vacant orbitals of the second. (conclusion 3).

From these three basic ideas of the qualitative perturbation theory, one can conclude that the interaction between the HOMO (Highest Occupied Molecular Orbital) of one molecule with the LUMO (Lowest Unoccupied Molecular Orbital) of the second will constitute the greatest energetic change[17].

In line with this statement, Fukui has successfully applied this "frontier orbital" approximation and hence the HOMO-LUMO interaction as the leading phenomenon in reactivity to various cycloaddition reactions. But it would be dangerous to assign no role either to the interaction of other orbitals or to other electronic effects.

III] Normal, neutral and inverse electron demand Diels-Alder reactions.

Diels-Alder reactions can be classified into three categories, as described in scheme 5.



Scheme 5: types of Diels-Alder reactions according to the frontier orbital model

-> In type I, the $HOMO_{diene}$ - $LUMO_{dienophile}$ separation is smaller than the $HOMO_{dienophile}$ - $LUMO_{diene}$ separation. In line with conclusion 1, the $HOMO_{diene}$ - $LUMO_{dienophile}$ interaction is the most important and will direct the cycloaddition. This case corresponds to the normal electron demand Diels-Alder reaction.

-> In type II, the two HOMO-LUMO separations are similar, therefore both of them will have to be considered. It is the neutral Diels-Alder reaction.

-> Type III is the converse of type I. The reactivity will be dominated by the $HOMO_{dienophile}$ - $LUMO_{diene}$ separation. This case is named the inverse electron demand Diels-Alder reaction[14].

In order to complete the above qualitative description, the effects of any substituent either on the diene or dienophile and thereby on their HOMO and LUMO must be pointed out here.

IV] Effects of substituents.

The classification of substituents and their control of the reactivity of Diels-Alder reactions have been described mainly by Houk et al.

-> As far as the normal Diels-Alder process is concerned, an electron-withdrawing group Z in the dienophile decreases its HOMO and LUMO by the same amount of energy. Hence, while one of the two frontier orbital energy separations ($HOMO_{dienophile}$ - $LUMO_{diene}$) is increased (scheme 5), the second ($HOMO_{diene}$ - $LUMO_{dienophile}$) is reduced. Thus, since the overall stabilization of the system is inversely proportional to the orbital separation, the reaction must be accelerated.

Likewise, an electron-releasing substituent X in the diene will allow a better reactivity.

-> It is logical that the Diels-Alder with inverse electron demand shows the opposite conclusion to that of the normal mode: an electron-withdrawing group Z in the dienophile lowers the leading orbital interaction $HOMO_{dienophile}$ - $LUMO_{diene}$ and hence favors the reaction.

-> In a neutral Diels-Alder process, since the two HOMO-LUMO energy separations are similar, any X or Z substituent in either the diene or the dienophile, by lowering one HOMO-LUMO separation at the expense of the second, increases the overall reactivity.

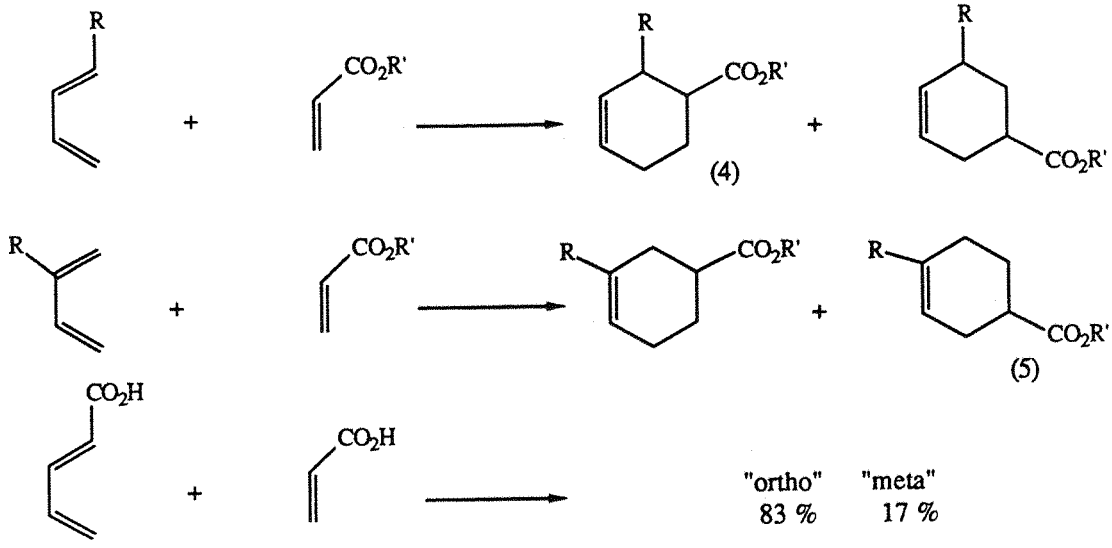
V] Orbital coefficients and regioselectivity.

Retrospectively, some numerical methods and frontier orbital based statements have constituted the main approaches to explain the regioselectivity of the Diels-Alder reactions. In 1973, Houk[13] proposed a generalization as regards the orbital energies mentioned earlier and orbital coefficients ("eigenvector coefficients") of the main varieties of dienes and dienophiles used. His experimentally based conclusions gave a clear understanding of both reactivity and regioselectivity in Diels-Alder cycloadditions as well as in other concerted cycloadditions.

Once the orbital coefficients of the dominant HOMO-LUMO interaction are known, the regiochemical issue of the reaction is well defined[16,18]. Indeed, the atoms of diene and dienophile which have the greatest and smallest coefficients respectively in the HOMO and LUMO, unite with each other.

The following conclusions are in line with this statement :

As far as a $HOMO_{diene}$ - $LUMO_{dienophile}$ controlled reaction is concerned, a 1-substituted diene, whatever the substituent, will yield after cycloaddition with an electron-poor dienophile mainly the "ortho" regioisomer (4) while a 2-substituted one will afford the "para" isomer (5), as shown in scheme 6.



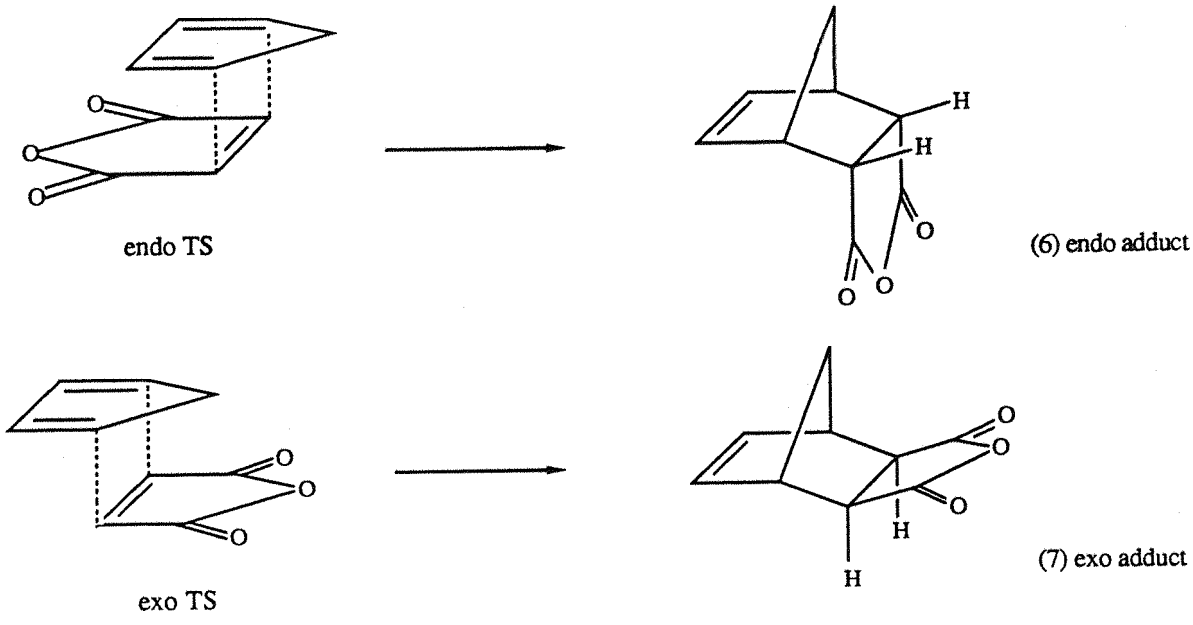
Scheme 6

The interpretation of the regiochemistry by means of the FMO model does confirm a multicentre mechanism, but also suggests that the reaction can occur via an unsymmetric transition state, even while the bonds are created simultaneously.

Besides the orientating role of the orbital coefficients of the dominant HOMO-LUMO interaction, the secondary orbital interactions may interfere with the expected regiochemistry. But the way of acting and the real effect of such forces have not been completely understood and described yet.

VI] Endo/exo selectivity.

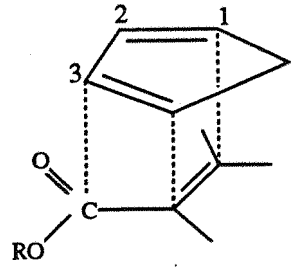
The dienophile can cycloadd to the diene through two different transition states in terms of the spatial position of the former with respect to the plane described by the latter while forming the two new bonds. The "endo" (6) and "exo" (7) cycloadducts can thus be afforded, as shown in scheme 7.



Scheme 7

It was indicated earlier that the "ortho" and "para" products can be obtained selectively from unsymmetrical reagents; it has also been observed that the endo addition was favoured at the expense of the exo. This "Alder's rule" has been reanalysed by Woodward and Hoffmann[10] on the basis of secondary orbital interactions.

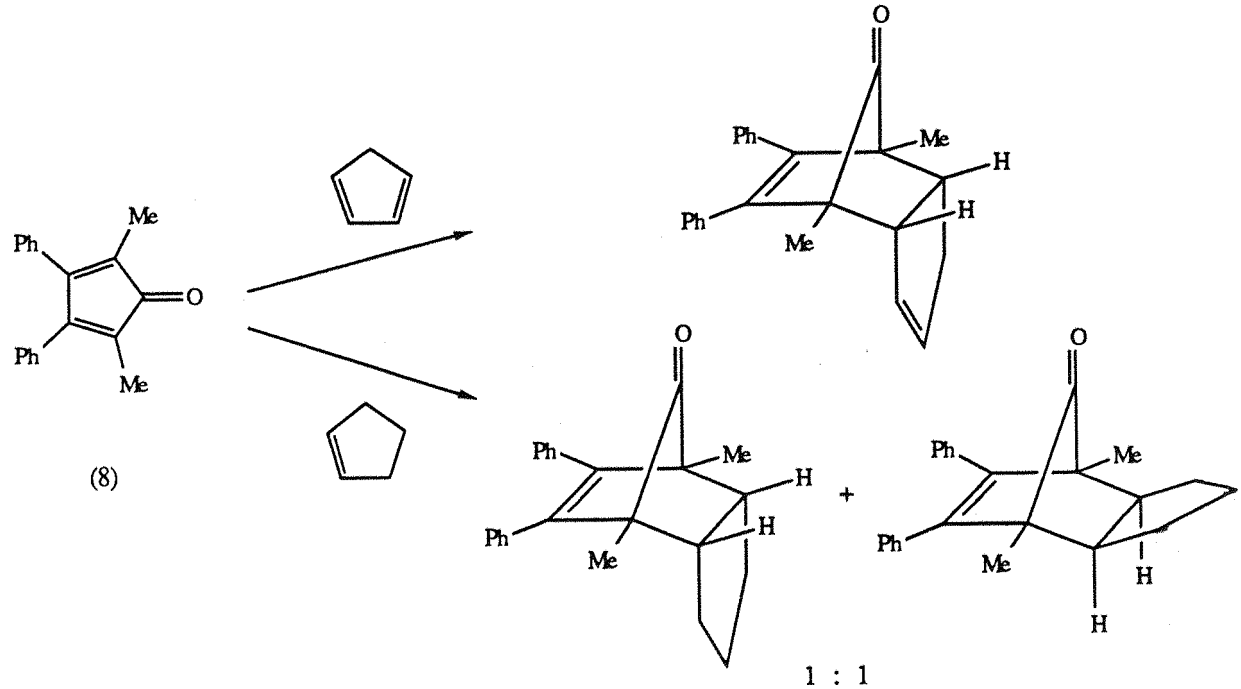
Indeed, as clearly illustrated by the example in scheme 8, the endo/exo selectivity is likely to depend on non-reacting atoms, like C_3 and the carbonyl carbon which interact with each other.



Scheme 8

Hence, Houk has shown[2] that 2,5-dimethyl-3,4-diphenyl-cyclopentadiene (8) leads to one or two

isomers according to the dienophile used, scheme 9.

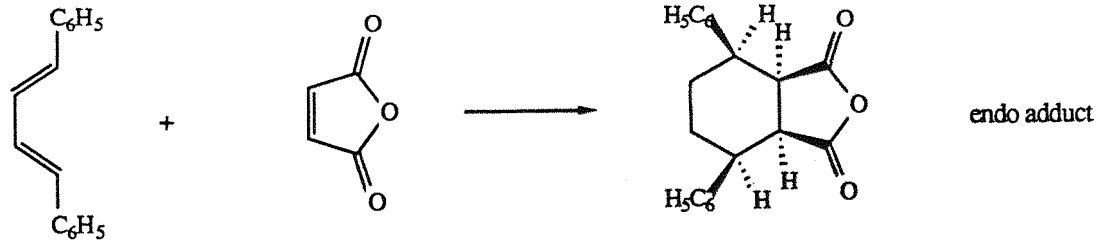


Scheme 9

It is now recognized that a balance of electronic and steric factors control endo/exo ratios which can rank from a 1:1 mixture to a 100:1 preference for one isomer, since the difference of energy required to get either the former result or the latter is of the order of 3 kcal/mol.

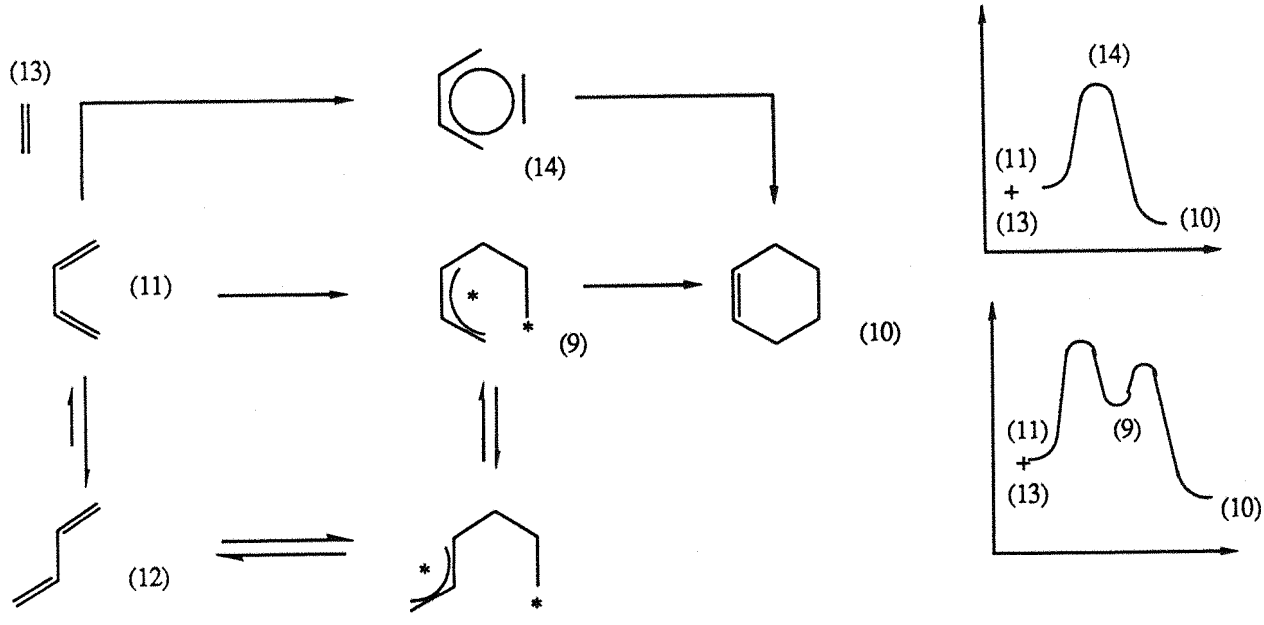
VII] Stereoselectivity: one-step versus two-step mechanism.

When a simultaneous closure of two new bonds between a diene and a dienophile takes place, this involves a transition state (14) and a highly stereospecific reaction[15] (scheme 11). A cis-addition occurs and the relative orientation of substituents in the dienophile on one side, and at the positions 1 and 4 in the diene on the other side are preserved in the final adduct (scheme 10).



Scheme 10

But if the cycloaddition occurs via a radical or zwitterionic intermediate in a two step mechanism, this stereospecificity might not be observed any longer if rotations about single bonds in the intermediate (9) take place faster than ring closure giving the cycloadduct (10) (figure 11).



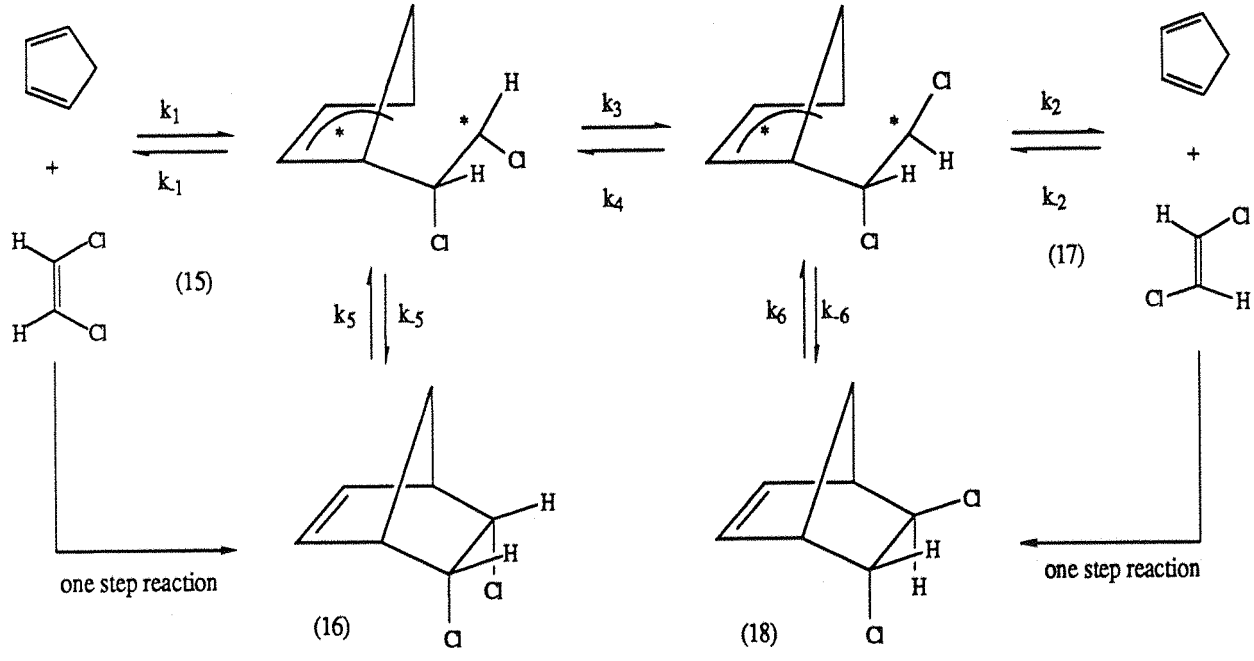
* = · , $^{+}$ or $^{-}$ (biradical or zwitterionic intermediate).

Scheme 11

However, when these rotations are slower, the two-step reaction can afford a single diastereoisomer (10).

Moreover, the reaction in a multi-step process from a trans-diene (12) cannot be excluded. But, after attack of the olefin, a biradical or zwitterionic intermediate must be observed in order that the rotations about single bonds and allylic bond necessary for attaining the conformation (9) suitable to the ring closure occur.

As an illustration, the cycloaddition adducts (16) and (18) stereospecifically obtained[2] from pure (15) and (17) respectively confirm the simultaneous bond formation and the low values of k_3 and k_4 with respect to k_5 and k_6 (scheme 12).



Scheme 12

This also reveals that some substituents able to stabilize an intermediate could make possible a slower two-step process along with a loss of stereospecificity and an isomerization of the initial olefin.

VIII] Reactivity.

As the prototype of these [4+2] Diels-Alder reactions, the cycloaddition of an electron-rich diene

with an electron-poor dienophile has been theoretically interpreted with the FMO model by relating the high reactivity to the dominant influence of the $HOMO_{diene}$ - $LUMO_{dienophile}$ separation.

It has also been noticed that 1-substituted dienes show a higher reactivity than the corresponding 2-substituted dienes, which is in close relation with the difference of eigenvector coefficients between the 1- and 2-positions.

It is well known that Lewis acid catalysts often enhance the reactivity of the dienophiles and thus their selectivity. By complexing dienophiles, Lewis acids behave like a strong electron-withdrawing substituent, decreasing the LUMO level and thereby strengthening the $HOMO_{diene}$ - $LUMO_{dienophile}$ interaction, as far as the normal Diels-Alder reactions are concerned. They can also complex dienes and consequently favour the reverse mode. Their importance will be illustrated by a number of examples in this thesis.

IX] Solvent effects and pressure dependence.

Solvents play a role on the reactivity as well as the mechanistic outcome of the cycloaddition. Independently of the systems investigated, the influence of solvent on the reaction rate is however generally small, about a factor of ten. The nature of dienophiles and dienes have very little effect on the solvent dependence.One can say that the transition state of a Diels-Alder reaction is more polar than the ground state when the reactivity increases with increasing solvent polarity. A rise of pressure may accelerate a reaction. The pressure dependence is measured by the activation parameter ΔV^* (difference of volume between the transition state and ground state) and ΔV (decrease of volume for the overall reaction). These values vary from -30 to -50 cm^3/mol. They often permit important mechanistic conclusions. Some recent experiments at high pressure (10-20 kbars) have often afforded noticable improvements of yields.

B) LEADING ADVANCES.

I] Asymmetric Diels-Alder reactions.[19-22]

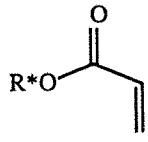
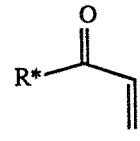
Simple Diels-Alder reactions between a diene and a dienophile provide cycloadducts regioselectively and stereoselectively (cis-addition). The use of a catalyst (Lewis acid) usually promotes diastereoselectivity. On the other hand, the presence of a chiral unit, whatever its nature, involves a facial stereodifferentiation with respect to the plane of the diene, thus permitting the

obtention of an optically active compound. These enantioselective cyclisations constitute the area of asymmetric Diels-Alder reactions which have been reviewed several times[19-21]. One must distinguish the single from the double asymmetric Diels-Alder reactions: the former ones utilize an achiral substrate with a chiral reagent while the latter cyclisations concern the interaction of two chiral reactants.

The chirality may be shown by either the dienophile, the diene or a catalyst (Lewis acid). Consequently, the double asymmetric mode reviewed by Masamune[21] appear as an extension of the single asymmetric process.

In most of the reported cases, a chiral control group is covalently bound to the dienophile; chiral dienes or catalysts are less employed so far but chiral catalysts might appears to be the most efficient method for achieving asymmetric Diels-Alder reactions.

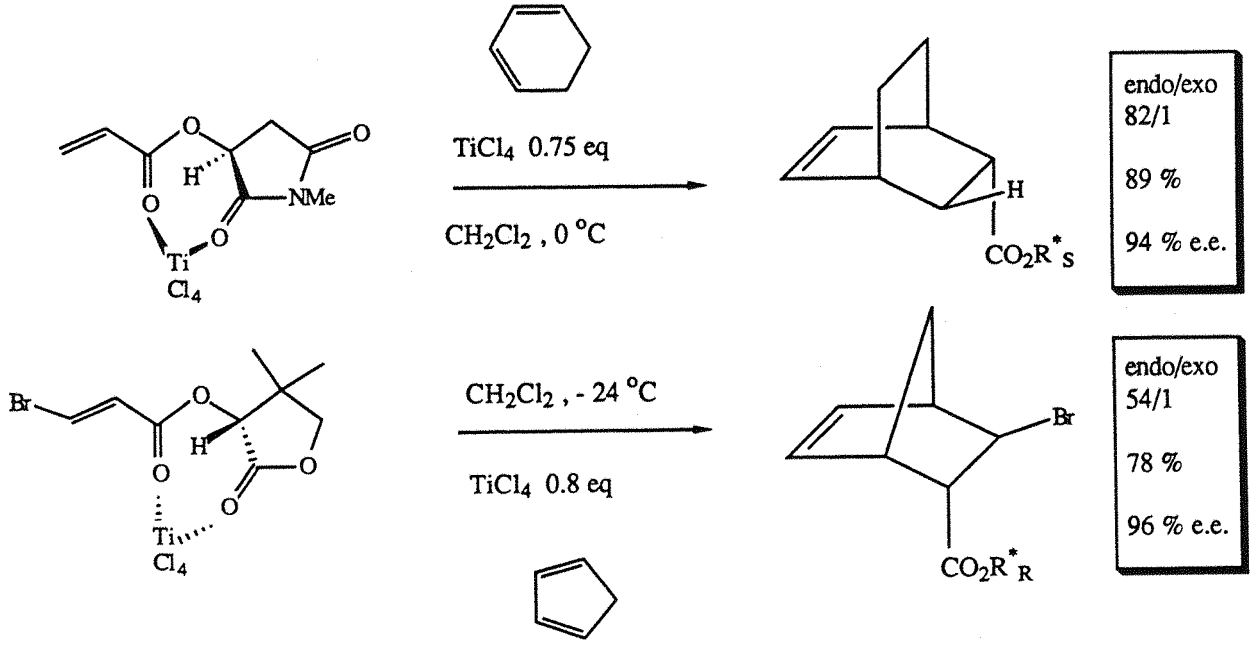
Once the chiral information has been transferred to the cycloadduct, it must be recovered from the adduct in a non-reductive manner, and with total retention of the configuration which has been induced. The most commonly used chiral dienophiles are of type 1, conjugated carboxylic esters, or 2, α,β-unsaturated ketones (scheme 13). The chiral group R* is often derived from menthol, borneol or camphor.

Type 1   Type 2

Scheme 13

Asymmetric induction can be applied to hetero Diels-Alder reactions (section [C]) where usually three asymmetric carbons are formed. Finally, this powerful tool can be employed in the (all-carbon or hetero) intramolecular mode (next section) in which the chiral group is mostly either attached to the dienophile unit or a part of the bridge chain. Two typical examples of intermolecular all-carbon asymmetric Diels-Alder are given below; further applications are mentioned in this thesis.

(R)-Pentolactone (R_R^*-OH) and (S)-N-methyl-2-hydroxysuccinimide (R_S^*-OH) have been reported[22] to permit highly enantioselective Lewis acid catalysed Diels-Alder reactions with cyclopentadiene and cyclohexadiene as dienes and some α,β-unsaturated ketone systems. According to the chiral auxiliary used, the complex chiral dienophile/diene/Lewis acid have led to one very major endo enantiomer, as described in scheme 14.



Scheme 14

II] The intramolecular Diels-Alder (IMDA) reaction.[26-33]

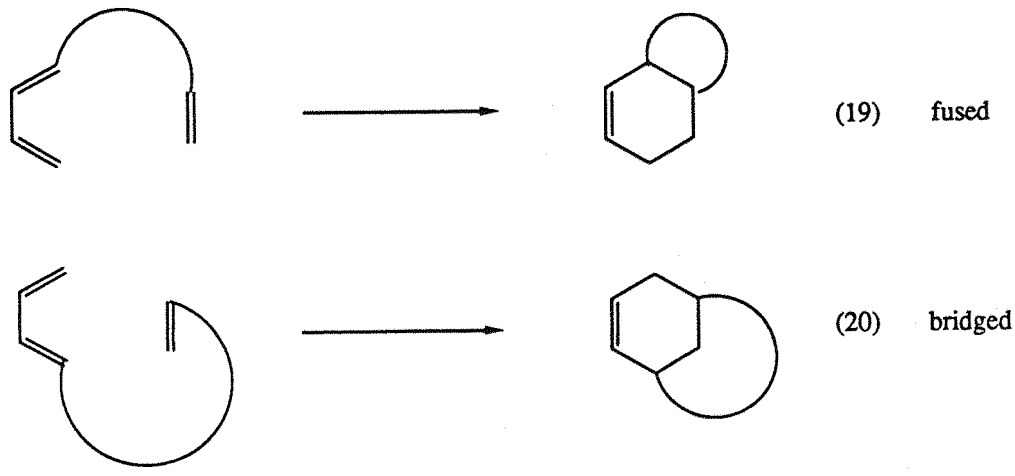
It is Alder who reported[23] in 1953 the first application of the Diels-Alder reactions in an intramolecular process. A few rare groups of workers then investigated this new area, but it is only from the early seventies that the usefulness and the efficiency of IMDA reactions have been thoroughly recognized thanks to some successful total syntheses such as the synthesis of chelidonine developed by Oppolzer[24] in 1971 via the then new ortho-quinodimethane[25,26].

After some general information regarding the chemical characteristics of the IMDA cycloadditions, this powerful synthetic tool will be briefly analysed according to the structural types of dienes. A variety of complementary examples as far as both all-carbon and hetero Diels-Alder reactions are concerned will be mentioned in this introduction.

1] Additional chemical features.[27,28]

IMDA reactions permit the formation of two rings in one step. Two regiochemical alternatives are

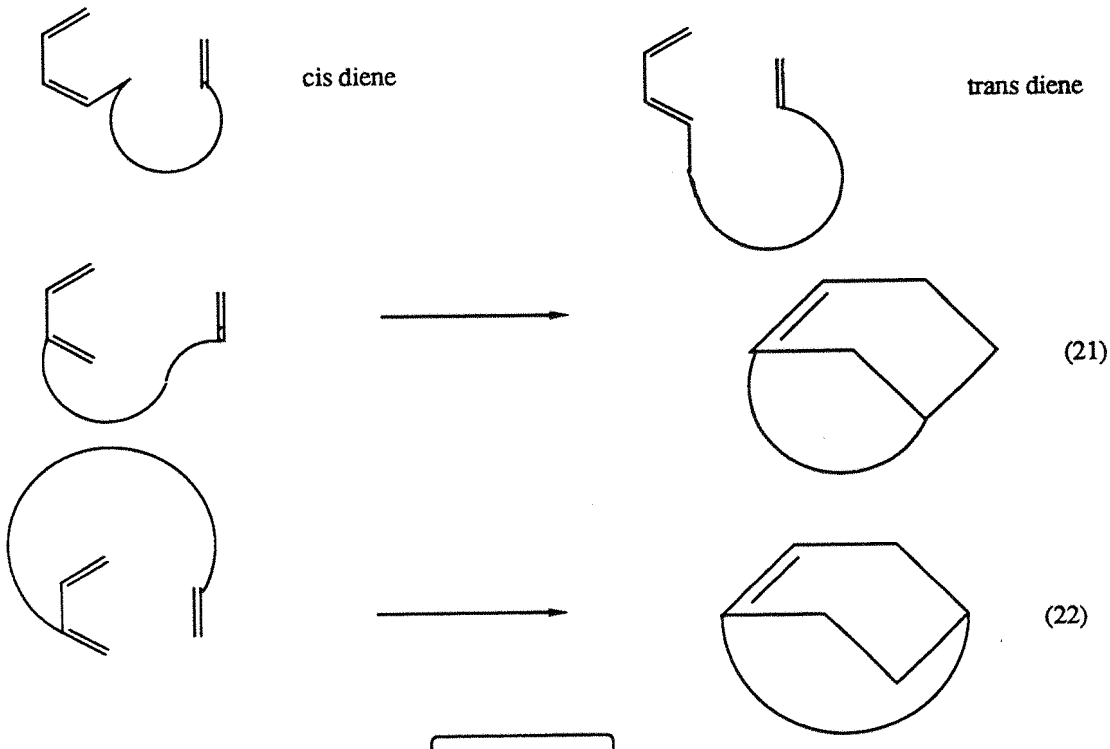
possible but in the majority of cases, the fused product (19) (scheme 15) is obtained at the expense of the bridged product (20).



Scheme 15

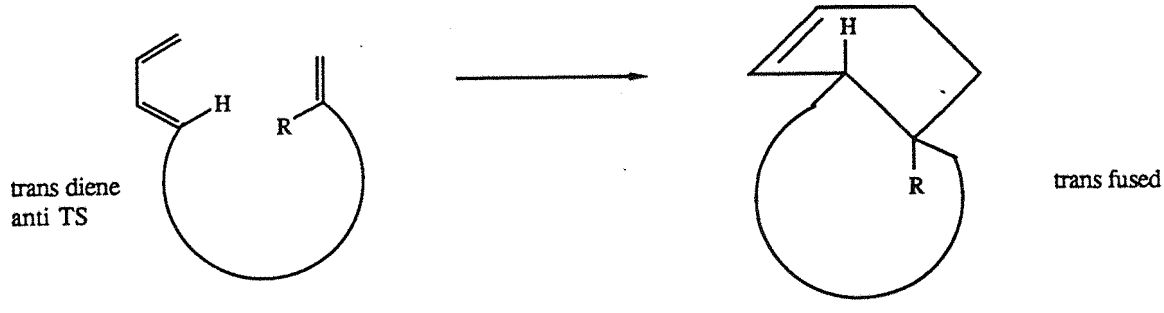
The terms cis and trans are used to describe the stereochemistry of the double bond of the diene to which the chain is linked (scheme 16).

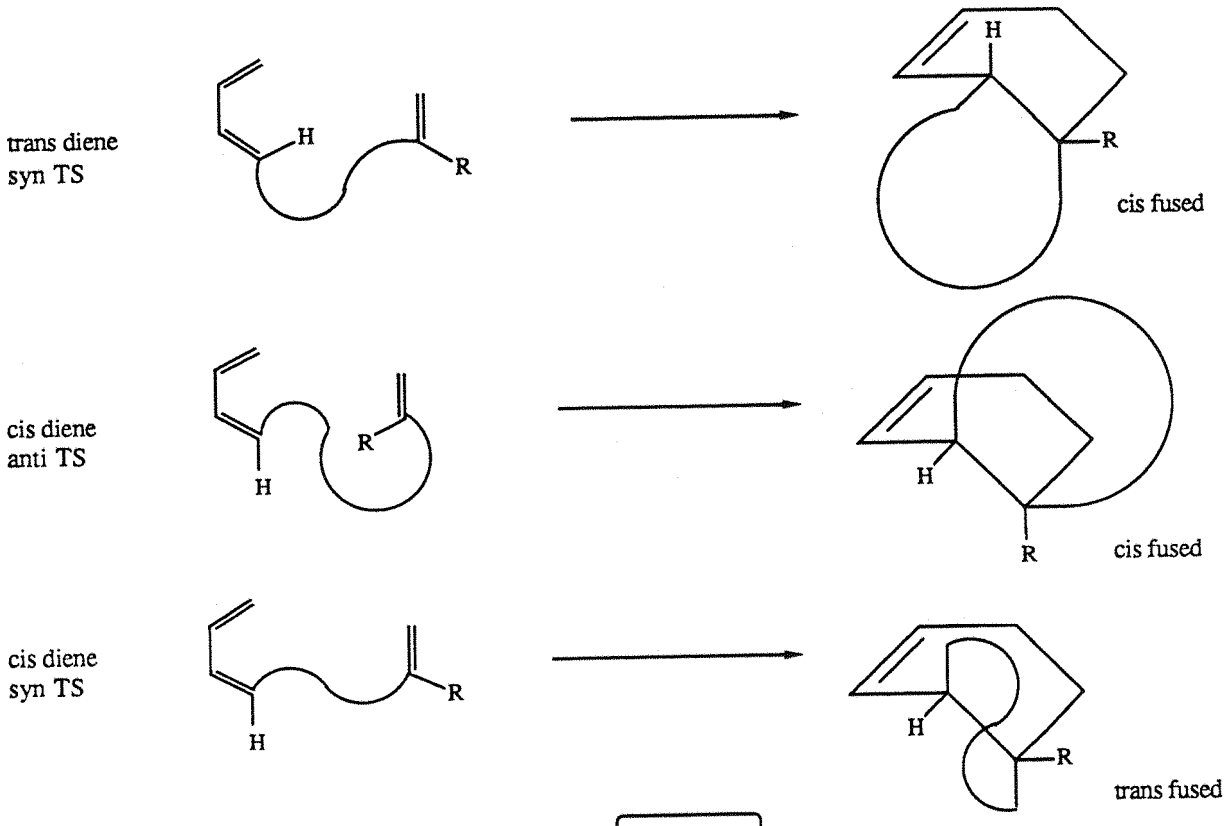
The bridged products are favoured when the chain is attached to the 2 position of the diene. It may then lead to both meta- (21) and para- (22) bridged adducts (scheme 16).



Scheme 16

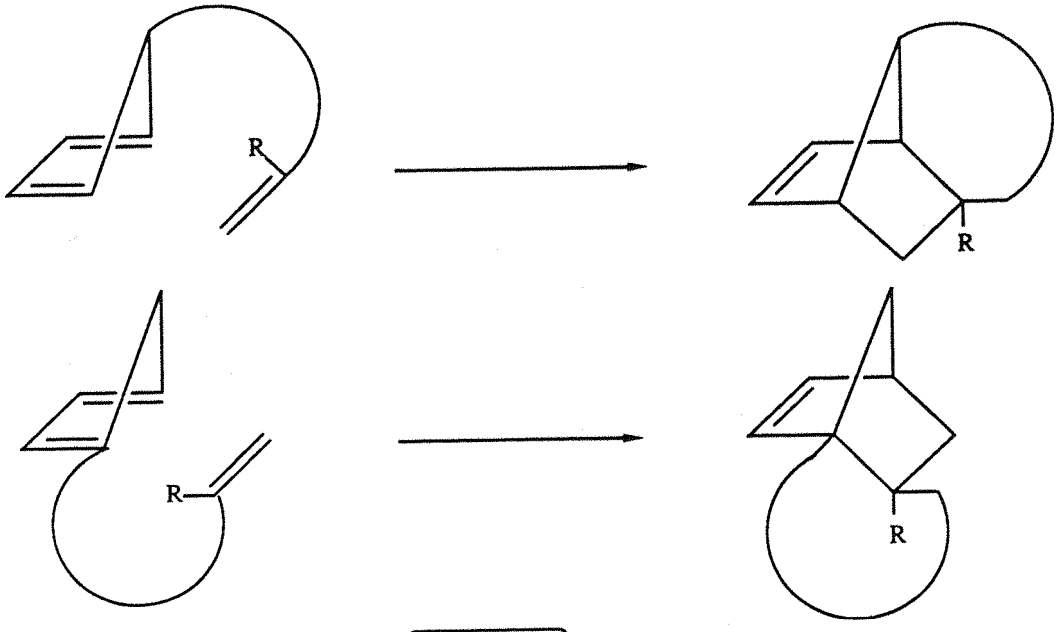
The cycloaddition may occur through either a syn- or anti-transition state. These terms describe the orientation of the dienophile to the diene. It shows the advantage with respect to the endo/exo terminology that it is not dependent upon the nature of the substituent R of the dienophile. Both cis and trans dienes may cycloadd to dienophiles through a syn or anti transition state and both syn and anti transition states may lead to cis-fused and trans-fused products; the four possible systems tend to observe the following rules (scheme 17):





Scheme 17

Finally, the two cases of cyclic dienes below (scheme 18) cyclise via an anti-transition state.



Scheme 18

2] Illustrations.[26-32]

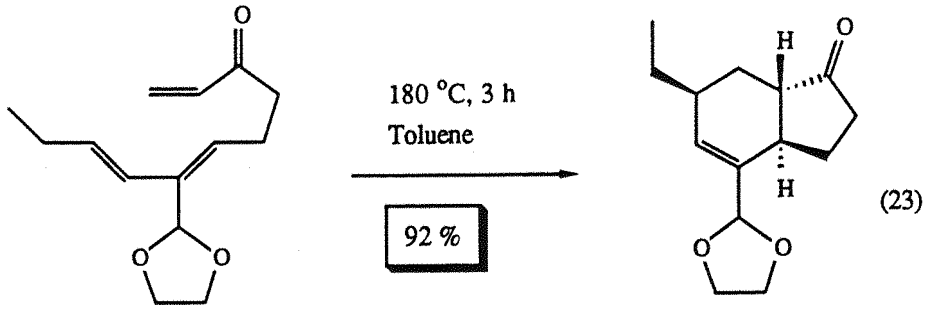
a/ Acyclic dienes.

They provide mainly bicyclo [4.3.0] nonene and bicyclo [4.4.0] decene derivatives. Adducts are usually fused rather than bridged and predominantly trans-fused.

The spatial orientation of the dienophile while approaching the diene establishes the stereochemistry of the cyclisation. The ring fusion is dependent upon complex conformational, electronic and especially steric factors. Hence, the previous "Alder's rule" fails in the intramolecular mode, showing the minor role of secondary orbital interactions.

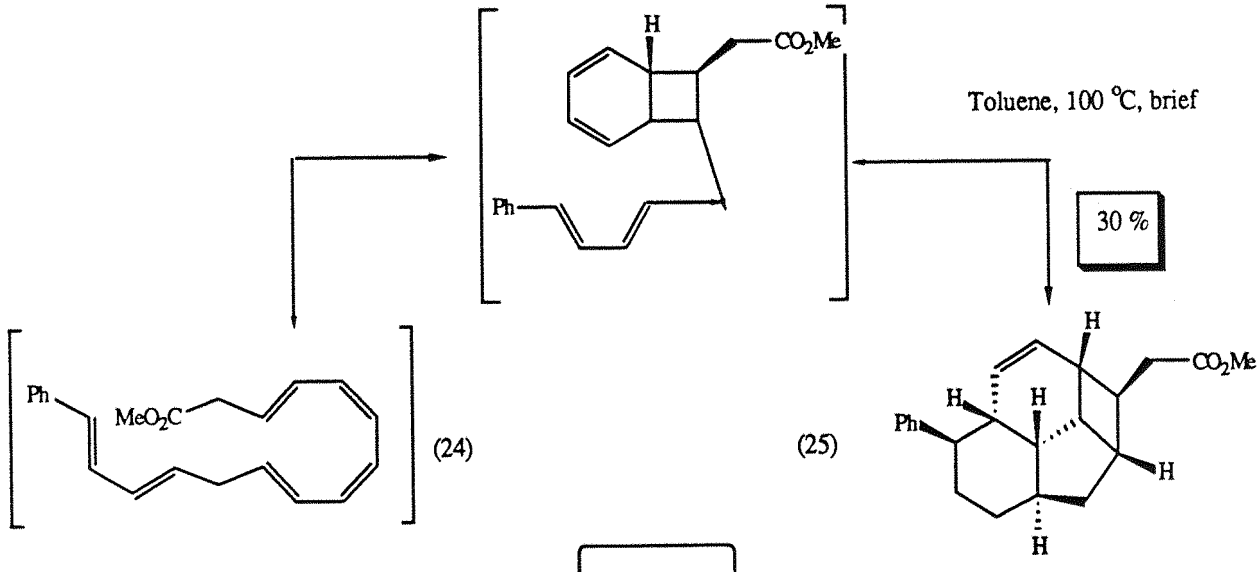
A few simple examples of IMDA cycloadditions illustrating the different alternatives possible in this mode of Diels-Alder reactions are now given.

The intermediate (23) has been used[34] to synthesize coronafaric acid, scheme 19.



Scheme 19

The obtention of endiandric acids via an IMDA reaction deserves mention[35,36]. Indeed, the in situ generation of the polyunsaturated acyclic ester (24) affords after ring closure, rearrangement and IMDA cyclisation the 4-ringed skeleton (25) showing eight asymmetric centres, scheme 20.



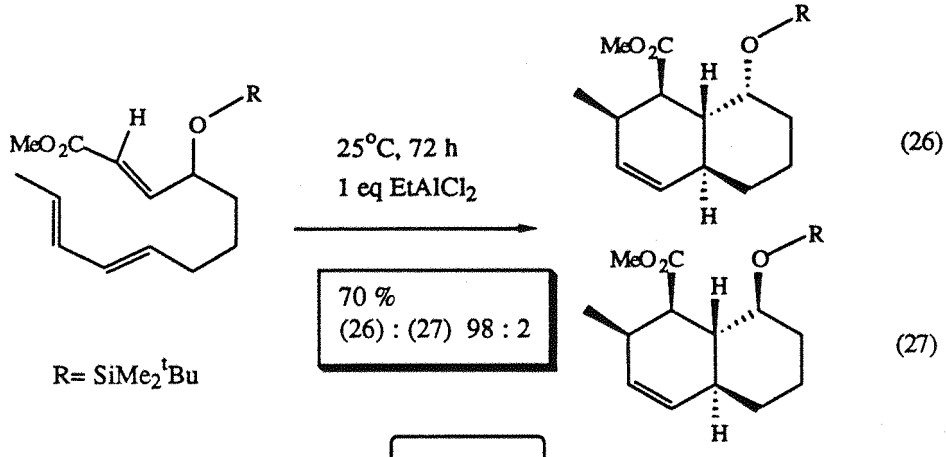
Scheme 20

The same type of species provide bicyclo [4.4.0] decene derivatives. Here, the transition state will often tend to be more ordered than previously mainly because six-membered rings prefer to take a chair conformation and substituents adopt more easily an equatorial than axial orientation.

A number of natural products have thereby been synthesized[30], such as α-eudesmol, epizonarene,

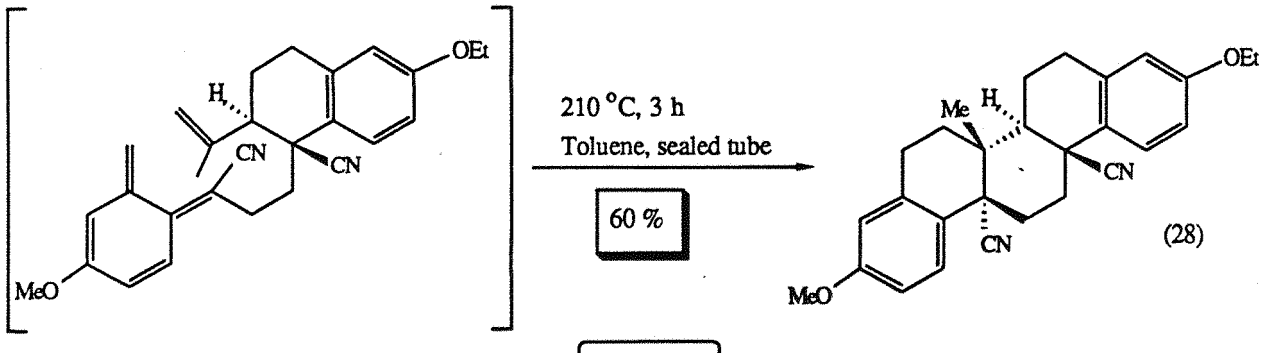
eremoligenol and valeriol.

A Lewis acid catalysed IMDA cycloaddition[37] has permitted the fixation of the stereochemistry of five asymmetric carbons of the bicyclic decene (26) used in a synthesis of compactin, scheme 21.



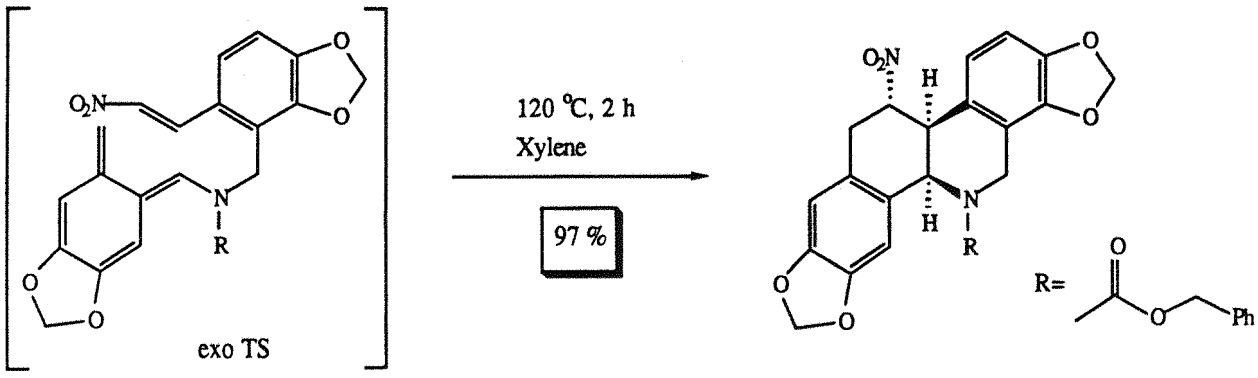
Scheme 21

The thermal in situ generation of ortho-quinodimethanes from intermediate benzocyclobutenes and their trapping intramolecularly by a dienophile to give fused ring systems was investigated by Oppolzer in the early seventies[24,25]. This area has been since studied extensively as regards its applications in the total syntheses of natural products[31], diterpenes, triterpenes and steroids[26] (cortisone, estradiol, estrone, ...). Now, orthoquinodimethanes are widely used in IMDA reactions. Thus, the key intermediate (28) has been similarly prepared[38] for the total synthesis of friedelin, scheme 22.



Scheme 22

Only rare examples with a heterodiene or a heterodienophile have been reported. In contrast, a number of IMDA cycloadditions having heteroatoms in the side chain have been applied to the preparation of interesting molecules. For instance, chelidonine synthesis was improved[24] by Oppolzer in 1981 via the stereoselective step described in scheme 23.

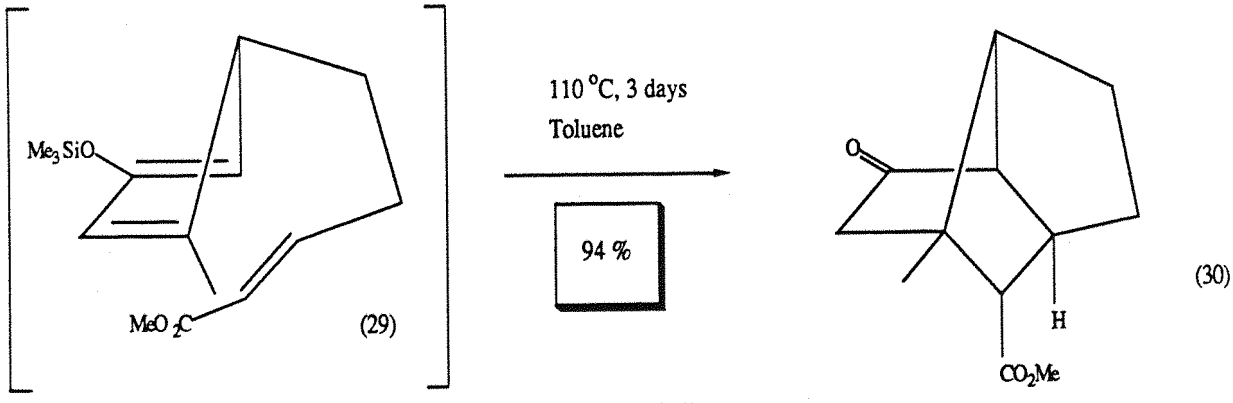


Scheme 23

b) Cyclic dienes.

These dienes are mostly endocyclic in a 5- or 6-membered ring.

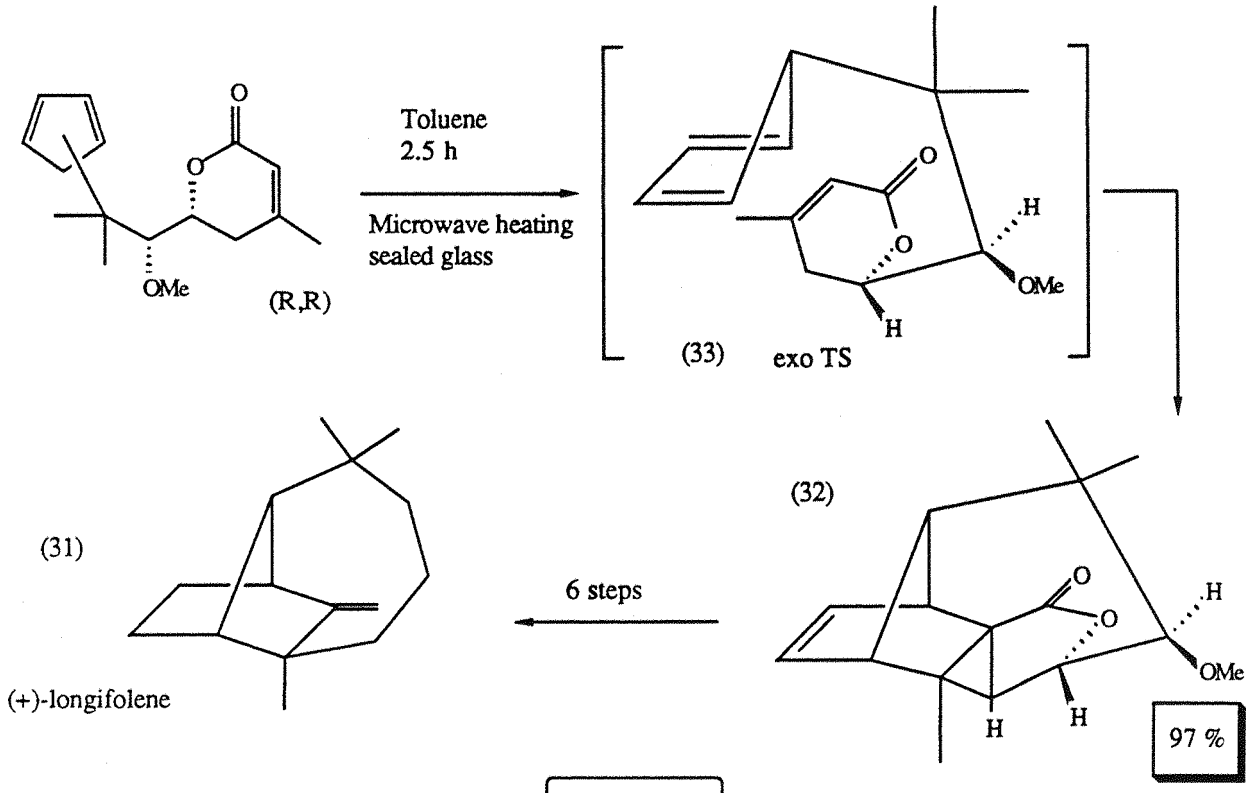
In a majority of cases, 5-alkylcyclopentadienes undergo quick 1,5-sigmatropic rearrangement to the corresponding C_1 isomer. It is usually from this new form that IMDA reactions occur to give only the fused regioisomer. But certain systems tend to react from the original C_5 substituted isomer because of the strain which would be inherent to the second isomer. Then, one or two regioisomers may be afforded according to cyclopentadiene and dienophile substituents. The bridged compound (30) has thus been regioselectively generated[39] by IMDA cycloaddition from (29) and has been utilized in a total synthesis of sativene[40] (scheme 24).



Scheme 24

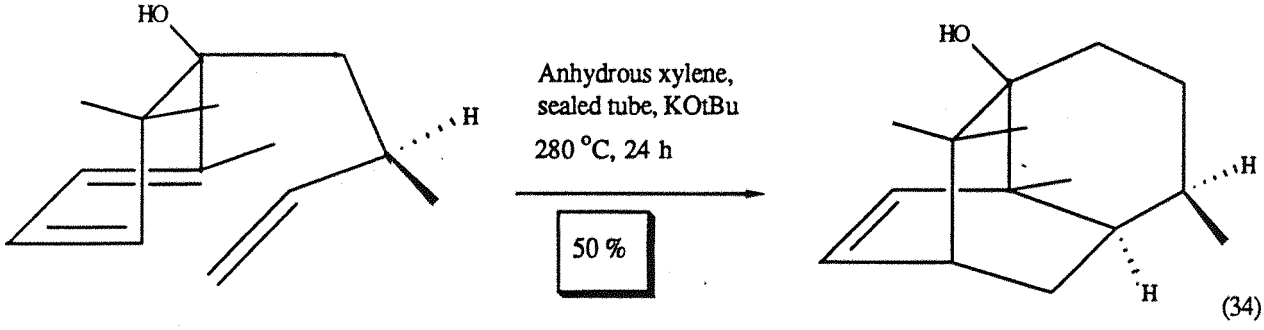
The usually undesired rearrangement may also be avoided by blocking the C_5 position with a suitable group like a cyclopropane unit.

Fallis has recently solved[41] the problem of the isomerisation of cyclopentdiene in a total synthesis of (+)-longifolene (31) (scheme 25) via a clever IMDA reaction. Hence, the presence of a six-membered dienophile unit having a high constraint along with chirality inducing the desired configuration has led to the bridged tricyclic structure (32) almost quantitatively via the exo transition state (33) with the substitution at the position 5.



Scheme 25

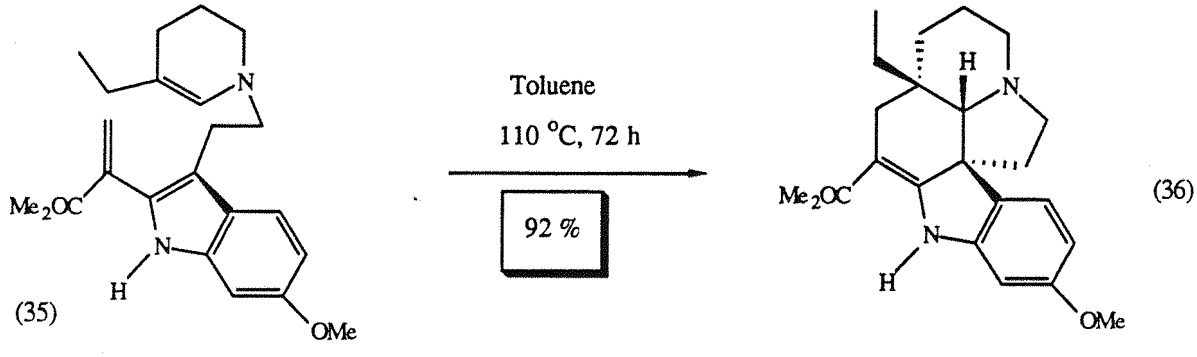
Such rearrangements do not occur from endo 6-ring dienes. Some total syntheses of khusimone and seychellene have been developed. The intermediate (34) has been successfully employed in a chiral synthesis of patchouli alcohol by Naf et al[42], scheme 26.



Scheme 26

A wide series of IMDA reactions from anthracene derivatives has been investigated[43] and the cyclisations have always been regioselective.

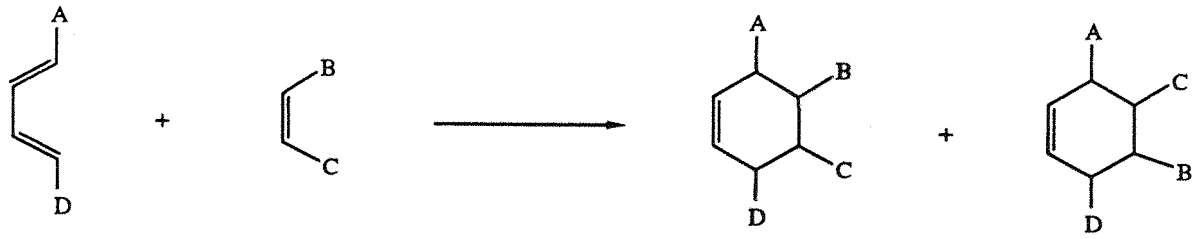
Finally, IMDA reactions of endocyclic dienes in superior rings are scarce as well as their application to the synthesis of strategic molecules. In contrast, certain endo-exo dienes have been utilized in natural product synthesis. Hence, some dehydrosecodines generated in situ like (35) have undergone IMDA cyclisations to give species employed for a number of alkaloid syntheses including taberso nine[44], minovine and ervinceine (36)[45,46], scheme 27.



Scheme 27

C) THE ALL-CARBON DIELS-ALDER REACTION: SYNTHETIC TOOL.[36,47]

The all-carbon Diels-Alder reaction is one of the most powerful synthetic tools which can be exploited in both inter- and intramolecular processes. Indeed, it combines two carbon-carbon bond formations with regioselectivity and potential control of stereochemistry at the new tetrahedral centres. Thereby, only one pair of enantiomers is obtained, as illustrated in scheme 28.



2^4 stereoisomers 2^4 stereoisomers

Non specific cycloadditions	---------->	$2^1 \times 2^4 = 32$ isomers
+ supra-suprafacial specificity	---------->	$2^1 \times 2^2 = 8$ isomers
+ regiospecificity	---------->	$2^0 \times 2^2 = 4$ isomers
+ end/exo specificity	---------->	$2^0 \times 2^1 = 2$ isomers
+ enantiospecificity	---------->	$2^0 \times 2^0 = 1$ isomer

Scheme 28

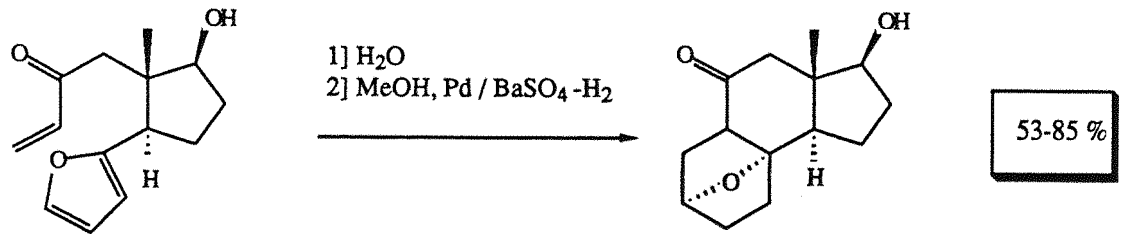
Therefore, all-carbon Diels-Alder reactions are very useful in the syntheses of many complex and various molecules[36,47] such as steroids[48], alkaloids, natural products, CnHn polyhedra , bioactive species, terpenes, etc.....

A small number of recent examples are given below, most of which take place in the intramolecular mode.

I] Route to steroids.

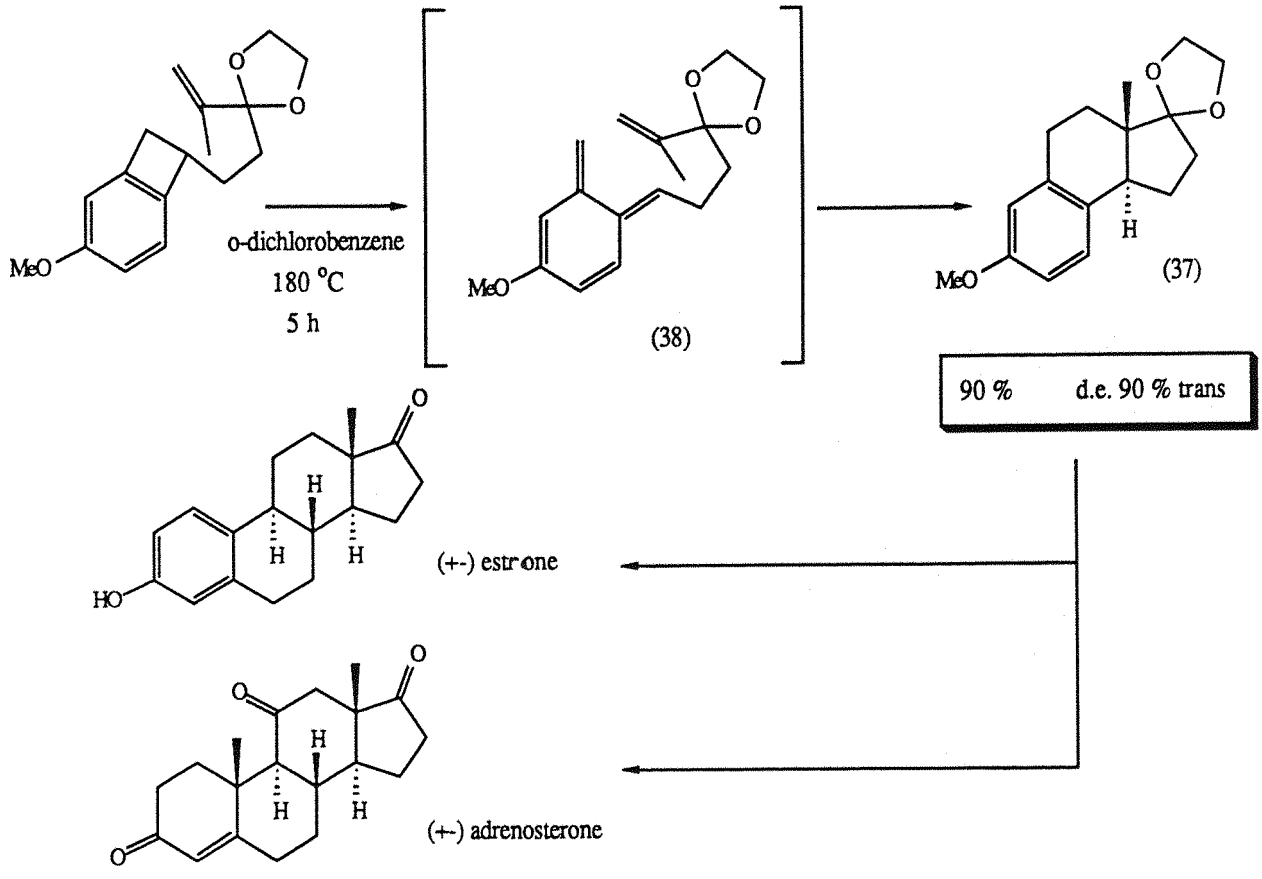
Classical steroids were first synthesized in the fifties: cholesterol, cortisone, estrone, adrenosterone, ...

Van Royen et al obtained[49] adrenosterone in 1985 via a new synthetic pathway featuring an IMDA reaction between a furan and an α,β-unsaturated ketone, scheme 29.



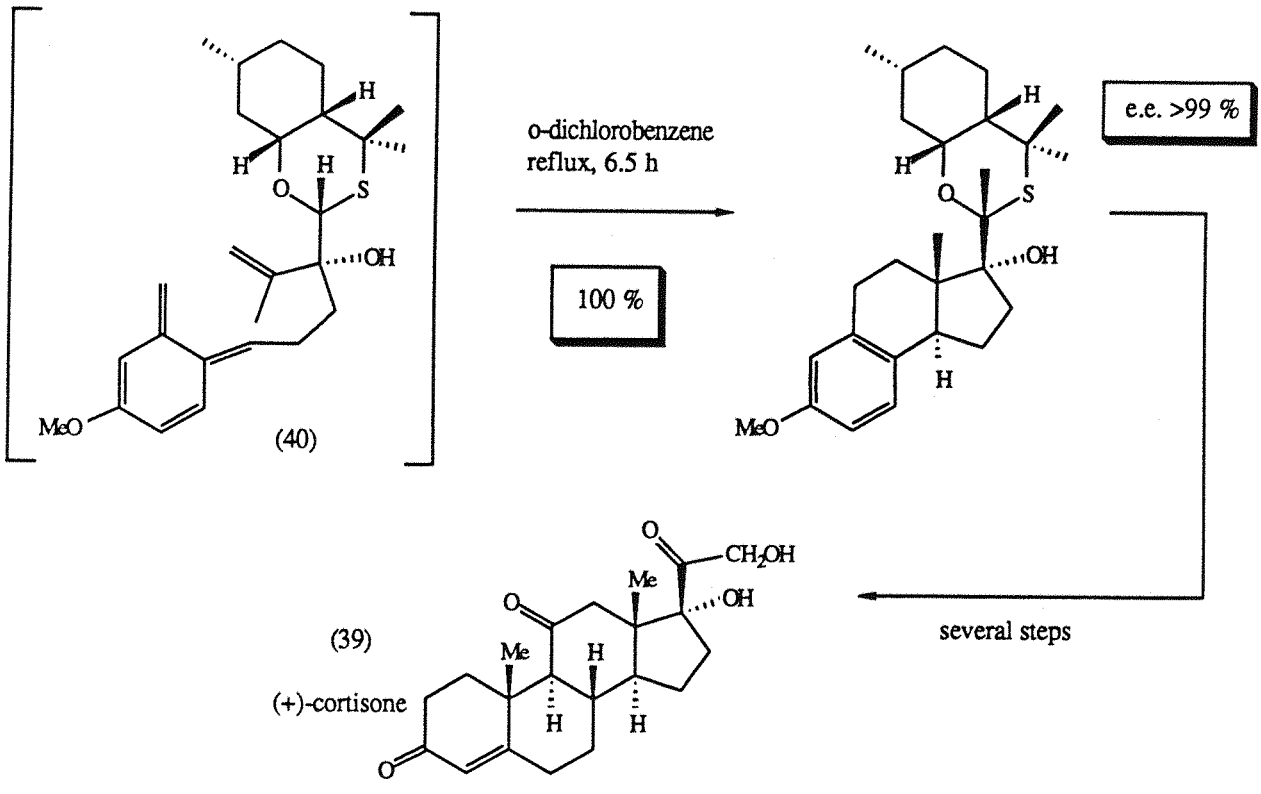
Scheme 29

Kametami and Fukumoto have reported[50] an expedient obtention of the trans-benzoperhydrindan skeleton (37) thanks to a highly diastereoselective IMDA cycloaddition via the ortho quinodimethane (38) (scheme 30). The intermediate (37) has subsequently been used in total syntheses of (+-) estrone and (+-) adrenosterone.



Scheme 30

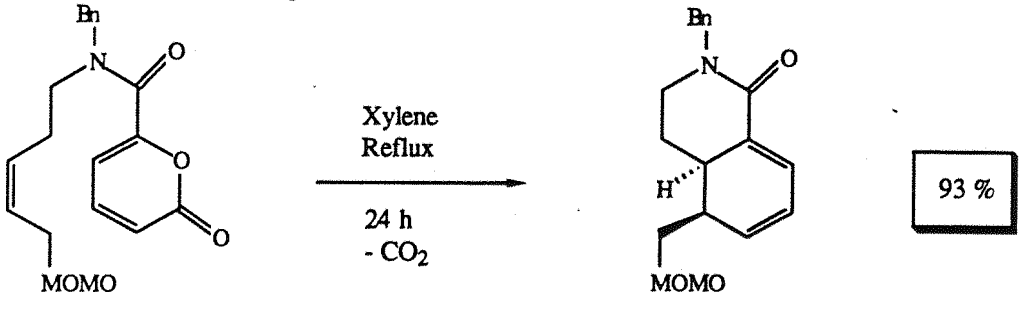
This chemistry has just been successfully applied[51] by Fukumoto to the first enantioselective synthesis of (+)-cortisone (39) (scheme 31). The ortho-quinodimethane intermediate (40) bears an optically active oxathiane unit as a stereo-controlling group in this totally enantioselective key step.



Scheme 31

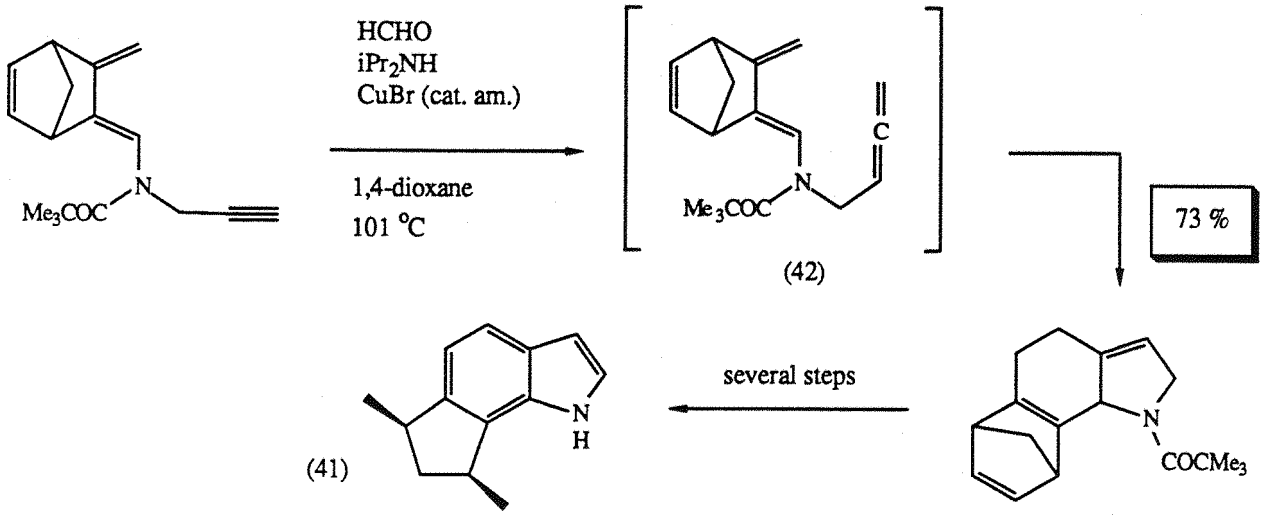
II] Route to alkaloids.

The alkaloid reserpine has been obtained via different synthetic pathways. The Martin's pathway[52] contains an interesting IMDA reaction, scheme 32.



Scheme 32

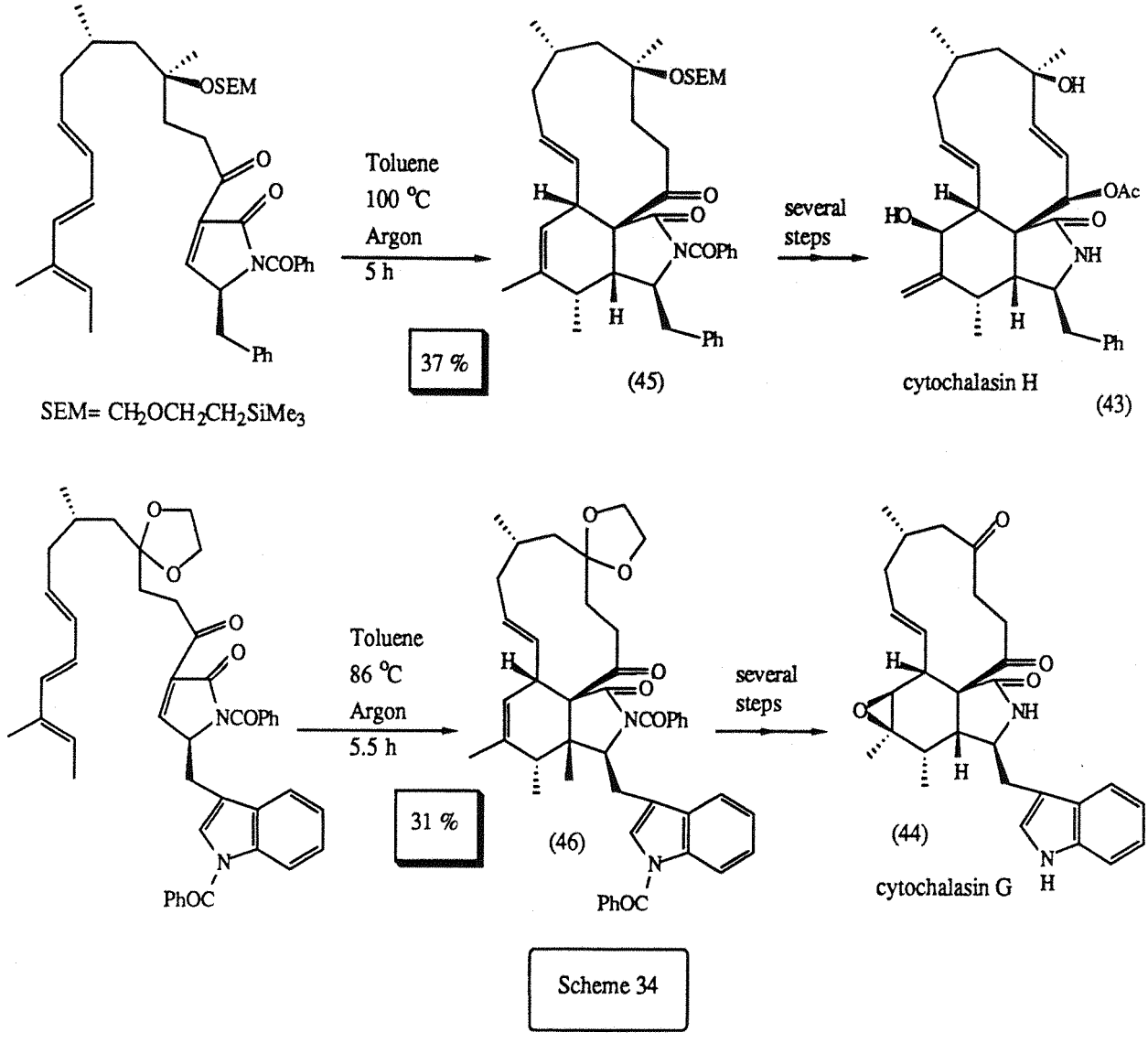
Kanematsu's group reported[53] in 1989 an efficient approach to the basic skeleton of the cis-trikentrin indole alkaloid (41) via an IMDA cycloaddition of the 2,3-disubstituted allenic dienamide (42) (scheme 33).



Scheme 33

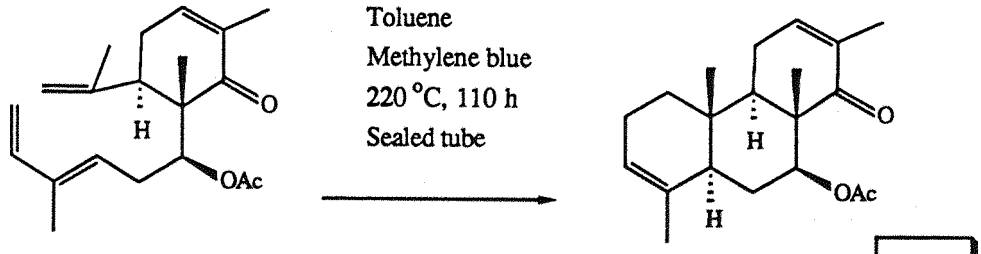
III] Route to strongly bioactive molecules.

The cytochalasans constitute a group of bioactive fungal metabolites of high interest. Thomas et al have just developed total syntheses of proxiphomin[54], cytochalasin H (43)[55] and cytochalasin G (44)[56], in each case through an IMDA reaction (scheme 34). The closure of the large ring takes place via an endo transition state to form the isoindolones (45) and (46) respectively with the desired stereochemistry.



Scheme 34

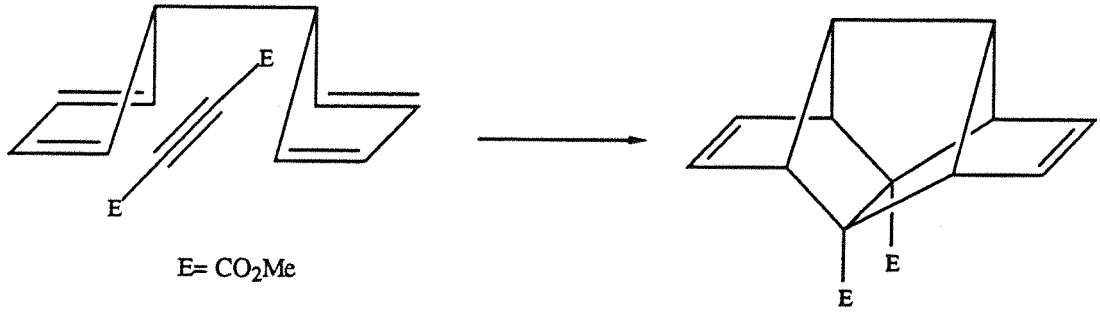
Quassin was approached in 1984 by Grieco[57]. This group has reported total syntheses of some related alkaloids since[58,59]. An enantioselective route to the ABC rings of the quassinoid skeleton was reported[60] in 1989 by Shing and Malone via the endo selective IMDA cyclisation, scheme 35.



Scheme 35

IV] Route to polyhedra

The Diels-Alder reaction has constituted maybe the main synthetic tool to build these polycyclic saturated hydrocarbons containing a free cavity. Alkynes have been often used as dienophiles in order to undergo two similar cyclisations. As a single and simple illustration, dodecahedrane was obtained[36] by Paquette's group in 1986 via the two consecutive inter- and intramolecular Diels-Alder reactions below (scheme 36).



Scheme 36

[C] THE HETERO DIELS-ALDER REACTION[61-69]

It has been known for a long time that a wide range of heterocyclic compounds can be obtained via a [4+2] Diels-Alder cycloaddition in which at least one of the six carbons involved in the cyclisation is replaced by a heteroatom.

This area of the hetero Diels-Alder reaction has not been thoroughly investigated yet, though it has

been applied in many syntheses of complex molecules such as natural products[62,69], alkaloids[68], (aza)steroids, bioactive unnatural products, etc.....

The absence of a general application to this mode of the FMO theory so useful in all-carbon Diels-Alder reactions and, consequently, a lack of mechanistic information do not allow a forecast of the outcome of reactions as far as regio- and stereospecificities are concerned.

Therefore, no general additional information as regards the machanism and the features of these hetero Diels-Alder can be stated here. Each type of hetero Diels-Alder reaction may occur in a particular way because of the very nature of the heteroatom, as well as its position and its substituents. New effects which may contribute with respect to the all-carbon Diels-Alder reactions are the valence index, the presence of lone electron pairs and the increase of polarity able to more stabilize the transition states. As before, Lewis acid catalysis, asymmetric induction, intramolecular mode[26-32] have been widely used.

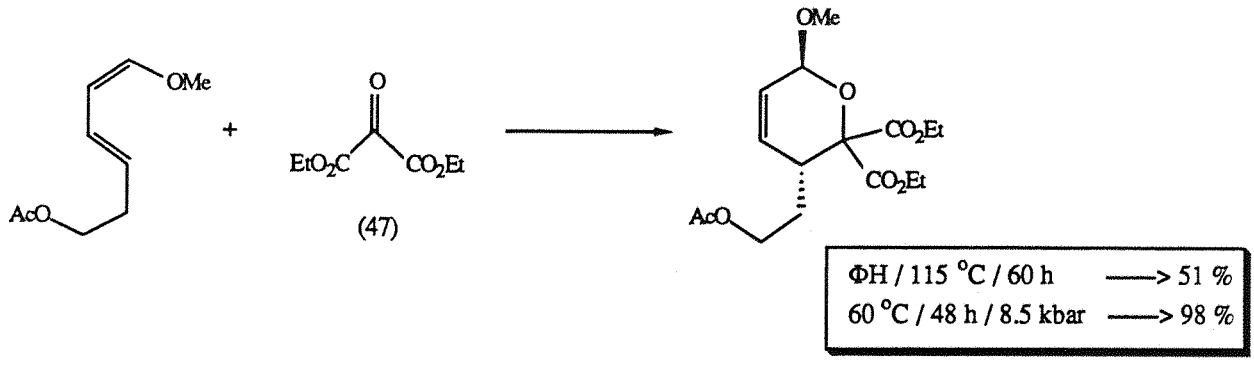
The area of hetero Diels-Alder reactions is reviewed below. A number of very recent applications, occurring mostly in an intramolecular process, are indicated. Nitrogen is the most utilized heteroatom in hetero Diels-Alder reactions, with next oxygen and sulphur. Therefore aza Diels-Alder cycloadditions will be dicussed in the second and main part of this present development.

I] Hetero Diels-Alder with heteroatoms X different from N.

1] Heterodienophiles.[61,63]

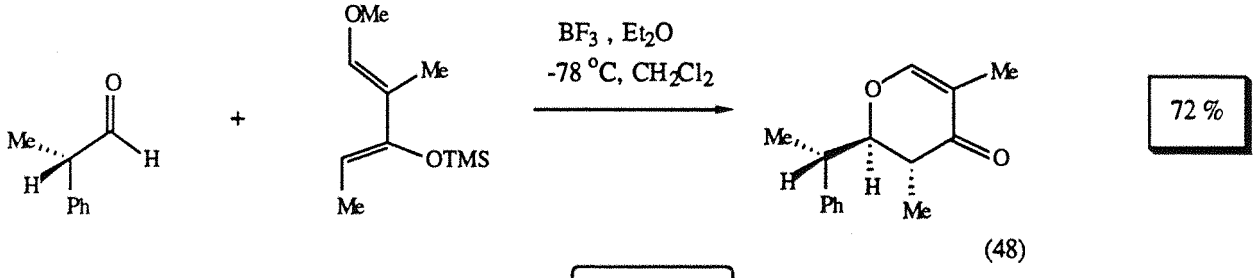
a/ C=O dienophiles.

Only a few types of very electrophilic carbonyl compound are able to behave as dienophiles, for instance formaldehyde, chloral, ketenes, ketomalonates, glyoxylates and miscellaneous fluorinated ketones. Mainly a number of glyoxylates have provided the Diels-Alder adducts with 1-alkoxybutadienes and cyclohexadienes, while diethylketomalonate (47) cycloadds smoothly to acyclic 1,3-dienes[70,71] (scheme 37); as shown by Jurczak[61a]: high pressures might favor these cyclisations and hence broaden the scope of useful carbonyl dienophiles.



Scheme 37

Danishefsky's group[61b] has developed applications of such dienophiles with highly oxygenated dienes under Lewis acid catalysis to afford γ-pyrones. This group has synthesized fucose, daunosamine, lincosamine, monensin and the Ireland alcohol via hetero Diels-Alder cyclo-additions with various aldehydes. By using chiral aldehydes, they have also approached some talose derivatives, the C_1-C_9 fragment of masamune via (48) (scheme 38), mouse androgen and exo-brevicomin.

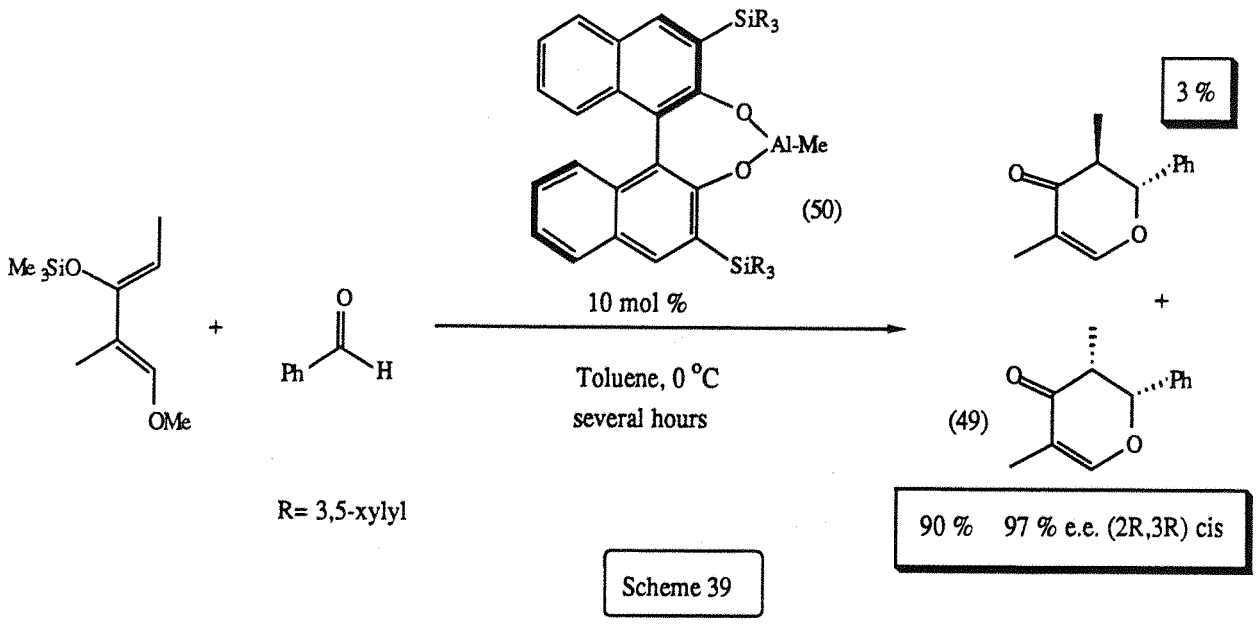


(48)

Scheme 38

As a recent related work[72], the pyrone (49) has been afforded with high diastereoselectivity by using the chiral aluminium catalyst (50) obtained from (R)-(+)-3,3'-bis(triarylsilyl)-binaphthol and triethylaluminium, scheme 39.

Rare examples of IMDA reactions with carbonyl dienophiles have been reported.

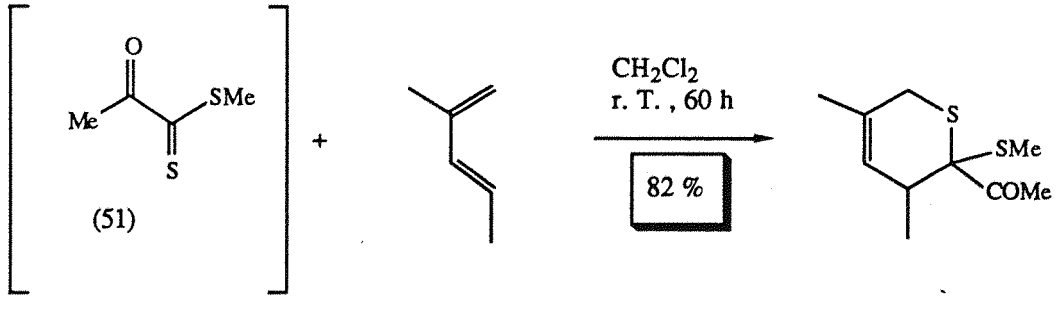


Scheme 39

b/ C=S dienophiles.

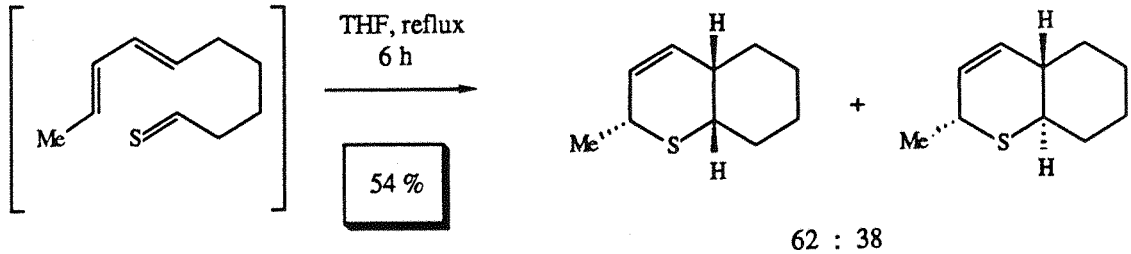
Thiocarbonyl dienophiles are at least as reactive as the corresponding carbonyl compounds. In particular, thiooxalates, thiophosgenes, trithiocarbonates, cyanodithioformates, cyanothioformamide, thioketenes, sulfines and dithienium salts cycloadd mostly at low temperature and regioselectively to various dienes to afford usually stable adducts.

Hence the thiooxalate (51) reacts[73] regioselectively with 1,3-dimethyl butadiene, scheme 40.



Scheme 40

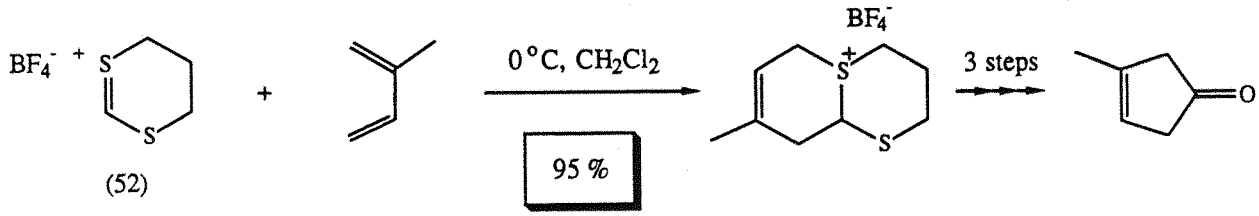
The intramolecular variation has also been studied; thus, despite a weak stereoselectivity, the IMDA cyclisation in scheme 41 is of interest for its completely controlled regiochemistry[74].



62 : 38

Scheme 41

Corey and Walinsky have developed[75] a new route to cyclopentenones which uses dithienium salts such as (52) as dienophiles, scheme 42.

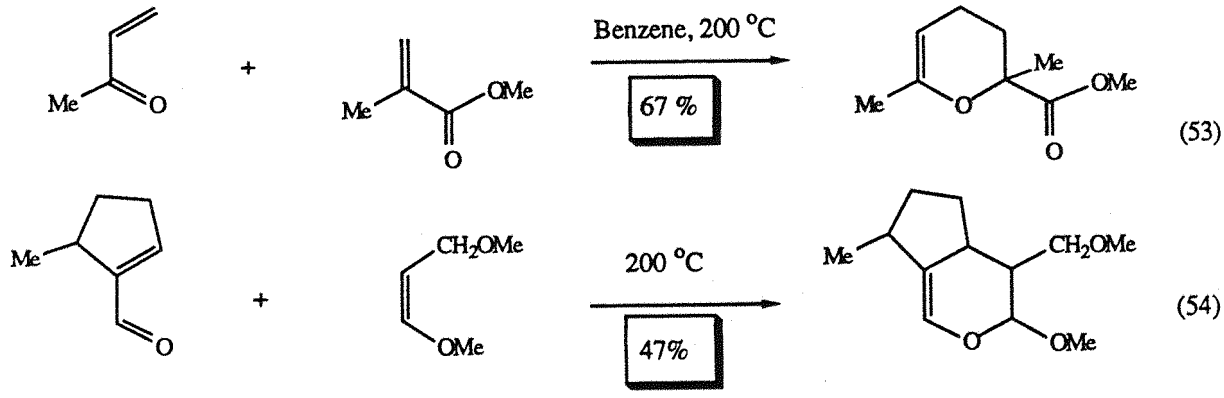


Scheme 42

2] Heterodienes.

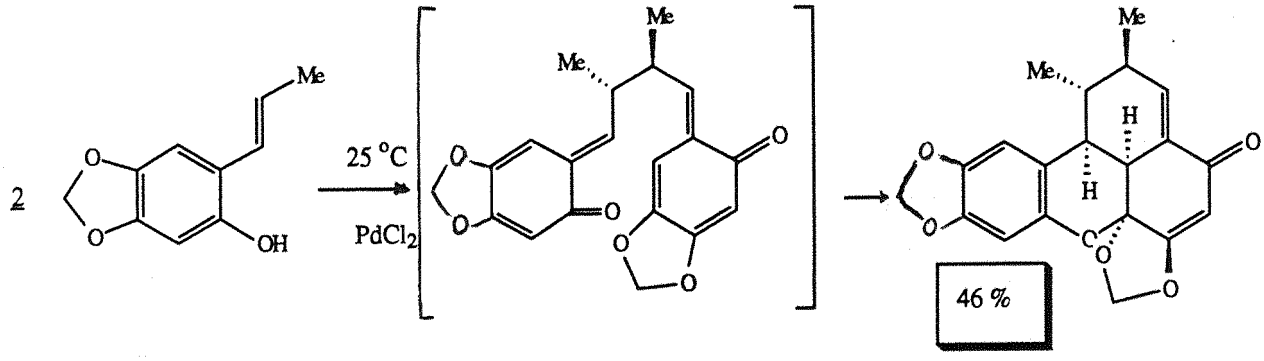
They are mainly 1-oxadiene systems: O=C–C=C.

The well known hetero Diels-Alder reactions of α,β-unsaturated carbonyl compounds have shown interesting applications which have been reviewed several times[67]. Hence, natural products such as adaline, frontaline via (53), brevicomine[76], and valerianine[77] via (54) have been synthesized (scheme 43).



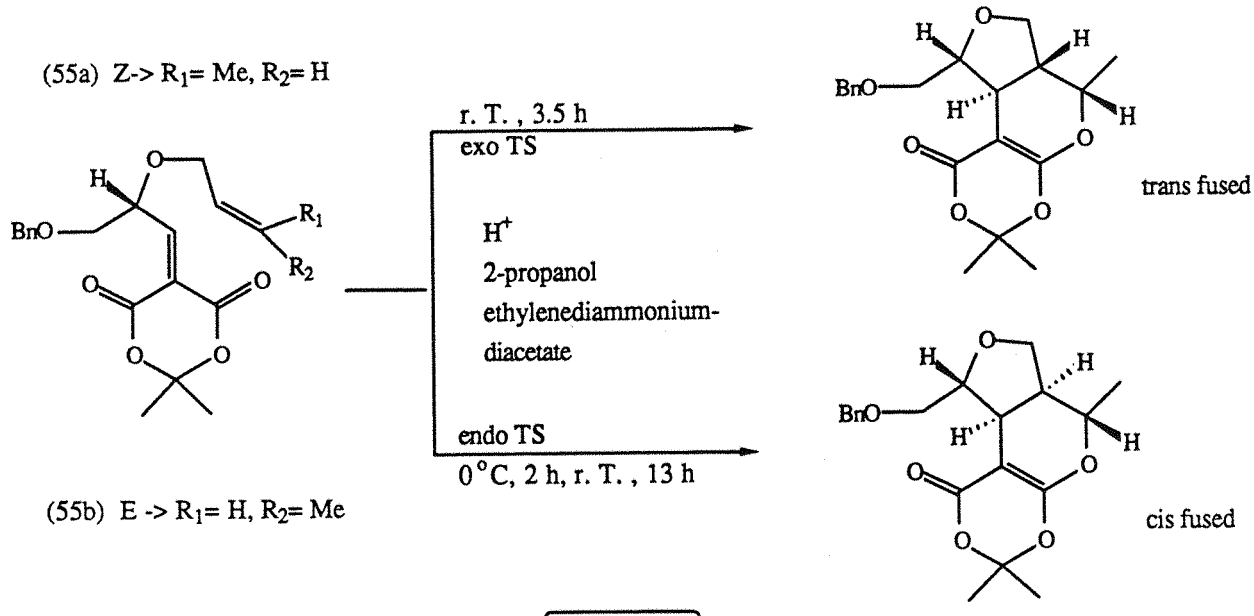
Scheme 43

Chapman et al have synthesized[78] carpanone through a clever use of an intramolecular hetero Diels-Alder reaction showing a 1-oxadiene system, scheme 44.



Scheme 44

Recently, the group of Takano[79] has demonstrated the highly diastereoselective role of the dienophile configuration in IMDA reactions of the olefinic heterodienes (55) yielding key intermediates for the syntheses of secoiridoid monoterpenes and heteroyohimbine indole alkaloids (scheme 45).



Scheme 45

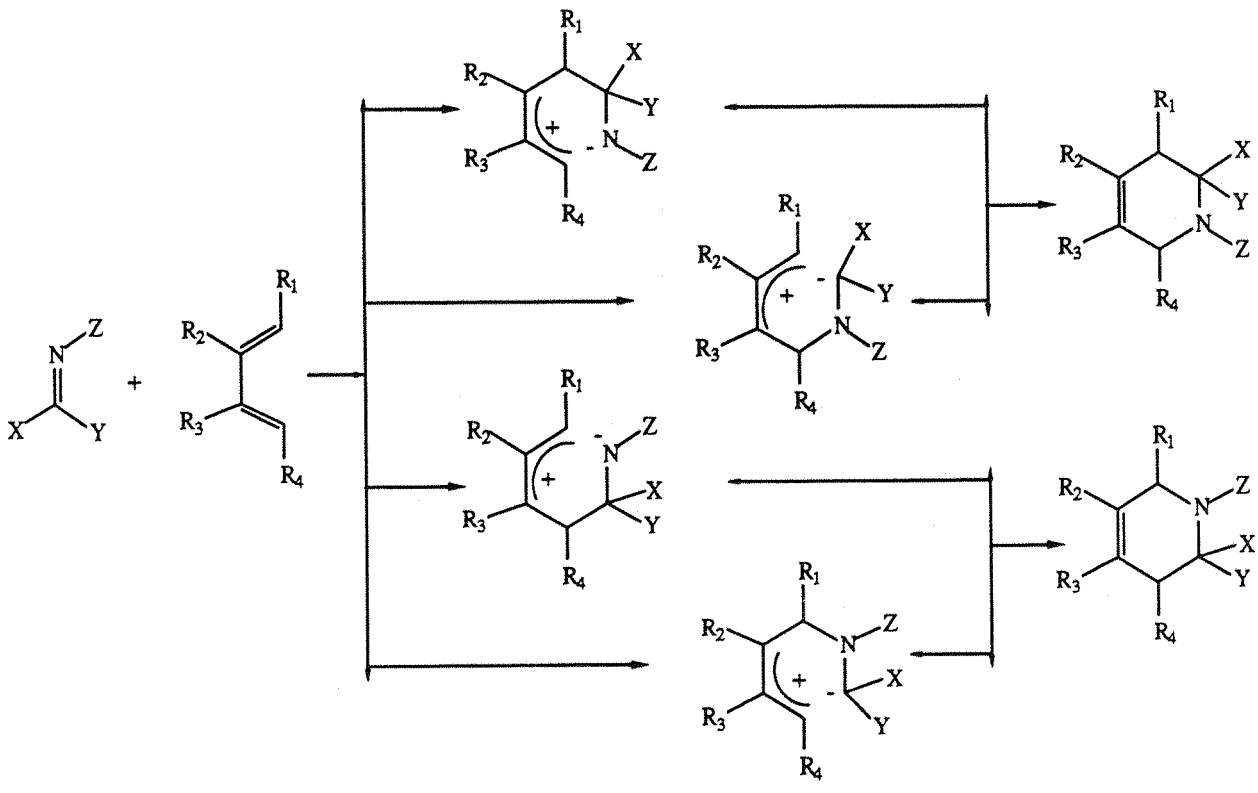
II] Aza Diels-Alder reactions.[61-66]

They constitute the bulk of hetero [4+2] cycloadditions. The systems having another heteroatom X, either in the diene or in the dienophile, other than nitrogen (X=O, S) will be discussed in sub-sections entitled hetero-azadienophiles and hetero-azadienes.

1] Azadienophiles.[61-64]

Imines and related substituted imines (N-acyl [64] and N-sulfonyl imines) represent the most employed azadienophiles. Unfortunately mechanistic studies in this area are quasi-non-existent. In general, electron-deficient amines are the most reactive dienophiles in a $HOMO_{diene}$ controlled process.

The regioselectivity may usually be predicted by considering the most stable transition state, as illustrated in scheme 46 in the case of imino-dienophiles, and a good stereoselectivity is mostly observed.

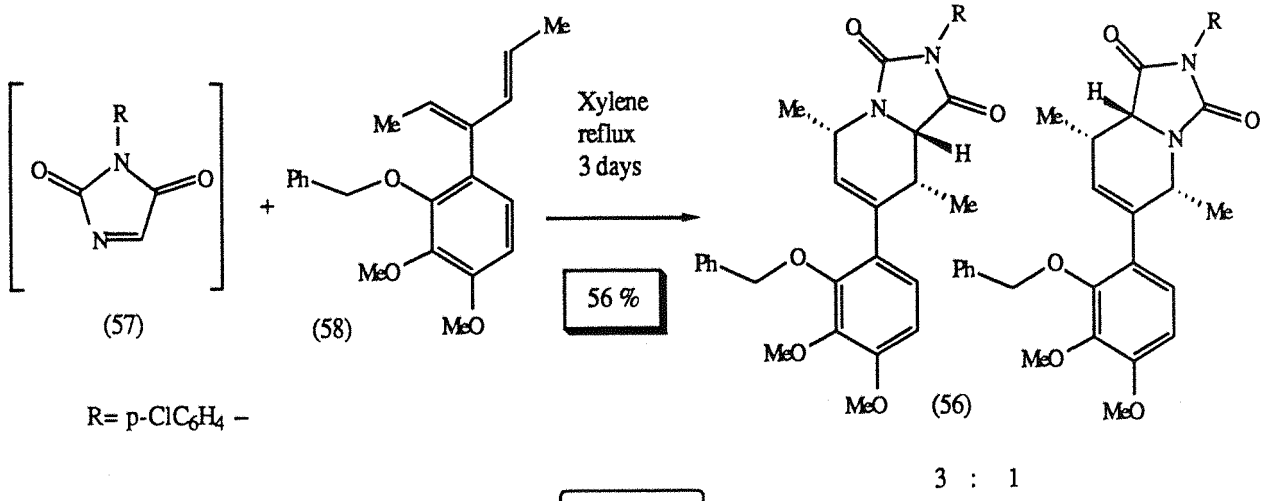


Scheme 46

a/ Non-hetero aza dienophiles.

1) C=N dienophiles.

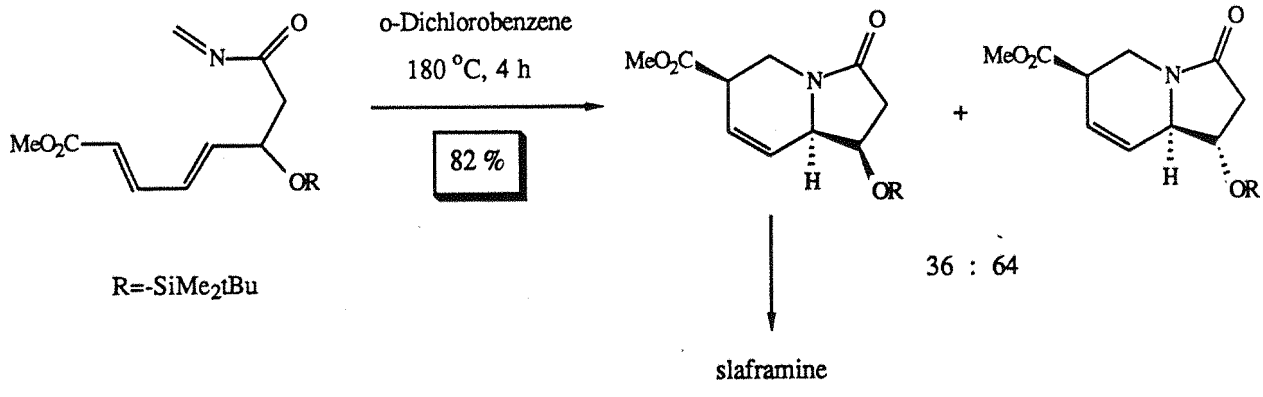
Electron-deficient N-acyl [64] and N-sulfonyl-imines are very reactive with electron-rich dienes. The nature of substituents on both nitrogen and carbonyl usually favors one isomer. This is illustrated by the synthesis of the antitumor antibiotic streptonigrin developed[80] by Weinreb et al in which (56) is the major isomer obtained from (57) and (58), scheme 47.



Scheme 47

Many quinolizidine, isoquinoline and indole alkaloids have thereby been approached. It is also been reported that iminium salts (see [**D**]) as well as amidines, hydrazones and azirines react with suitable dienes.

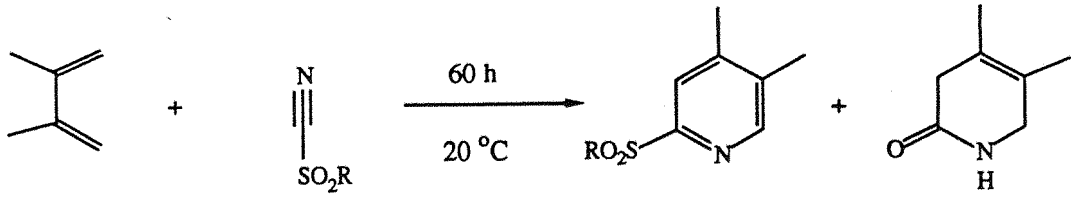
Since the first example of an intramolecular imino Diels-Alder reaction, this area has been widely investigated and exploited[68]. Hence, Weinreb et al have successfully prepared a series of indolizidine alkaloids like δ-coniceine, elaeokamine A and B, tylophorine or slaframine[81] via the following IMDA cyclisation (scheme 48).



Scheme 48

2) C≡N Dienophiles.

Usually high temperatures (200-500 °C) are required to obtain cycloadditions with nitriles. Only sulfonyl nitriles react under milder conditions, but a further oxidation or an in situ hydrolysis of the dihydropyridine formed always takes place and leads to pyridines or lactams[82] respectively, scheme 49.



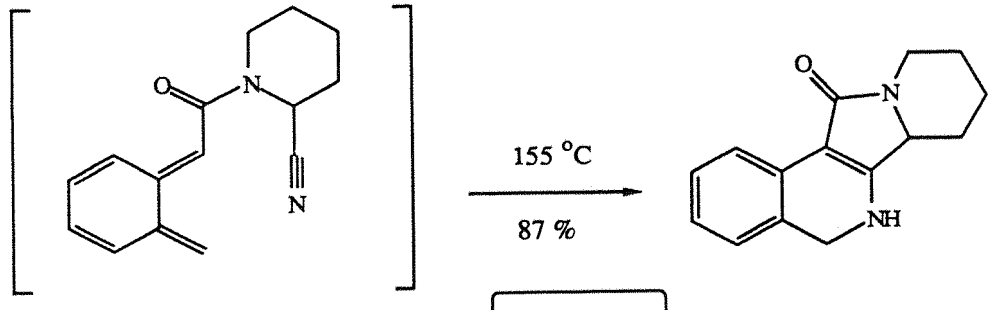
R= pMeC$_6$H$_4$

24 %

55 %

Scheme 49

Electron-rich nitriles also add to electrophilic tetrazines to yield substituted pyridines. Oppolzer has shown[25] that some benzocyclobutene-nitriles give isoquinoline derivatives in IMDA reactions via quinone methides like (59) as reactive dienic forms, scheme 50.



Scheme 50

3) N=N Dienophiles.

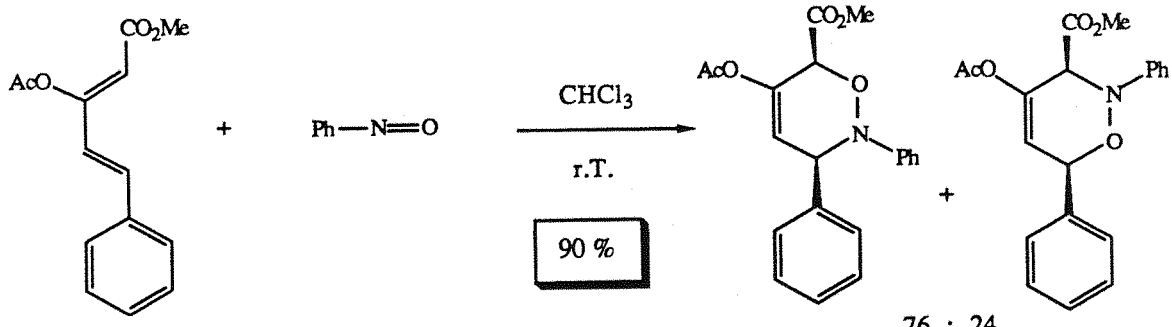
Cyclic and acyclic azadienophiles have been widely used in organic synthesis and more especially triazolines, electron-deficient diazonium salts and arenediazocyanides.

b/ Hetero-azadienophiles.

1) N=O Dienophiles.

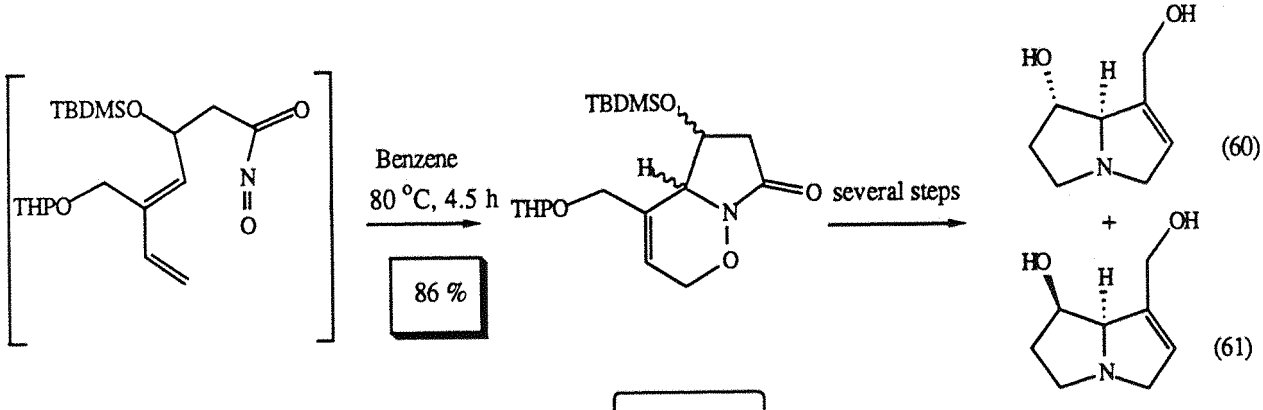
Kresze and Hartner have shown[83] that some aryl-nitroso species cycloadd to suitably substituted 1,3-dienes to yield a mixture of dihydro-1,2-oxazines according to the substituents of both

reagents, as illustrated in scheme 51.



Scheme 51

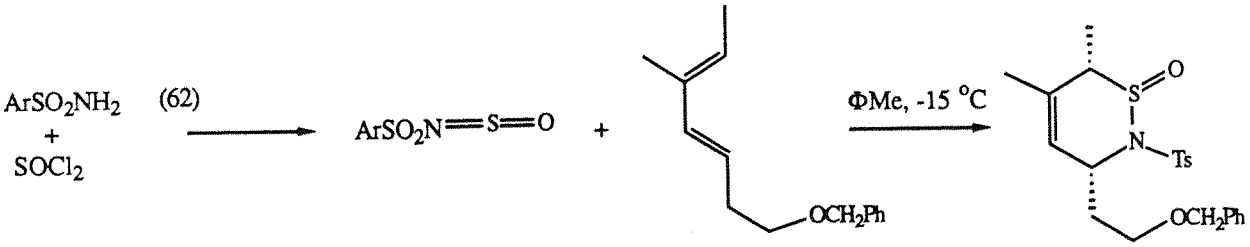
Kirby has discovered that electron-deficient acyl- and cyano-nitroso species can be readily generated and are excellent dienophiles. It has been applied by Keck et al [84] in alkaloid synthesis in inter- and intramolecular modes. Hence, heliotridine (60) and retronecine (61) have been obtained via the following IMDA reaction, scheme 52.



Scheme 52

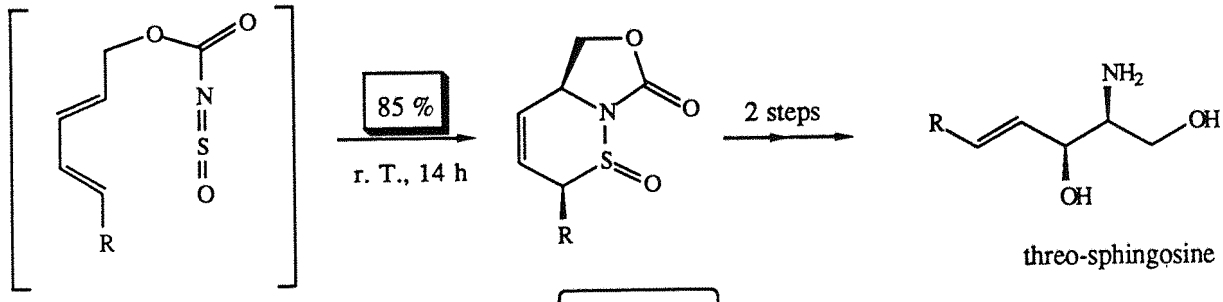
2) N=S Dienophiles.

N-Sulfinylsulfonamide must constitute the most studied class[63]. These sulfinyl compounds generated from arylsulfonamide (62) (scheme 53) and thionyl chloride add readily at low temperature to conjugated dienes to provide with a good regioselectivity Diels-Alder adducts.



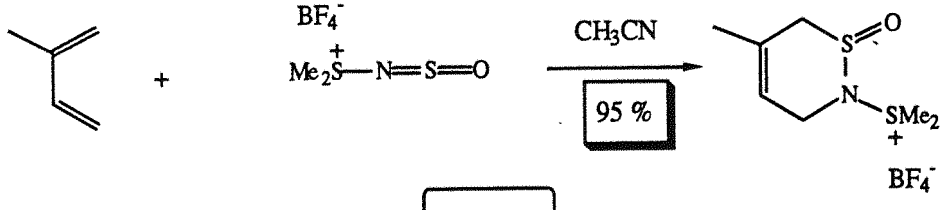
Scheme 53

Weinreb has developed[85] a simple procedure with N-sulfinyl dienophiles to afford particular unsaturated amino alcohols via an IMDA reaction. Thereby threo-sphingosine was obtained via the following cyclisation, scheme 54.



Scheme 54

Among other miscellaneous N=S dienophiles, the corresponding alkyl-N-sulfinylimmonium salts have been shown[86] to react with simple dienes, as illustrated in scheme 55.



Scheme55

2] Azadienes.[61,65,66]

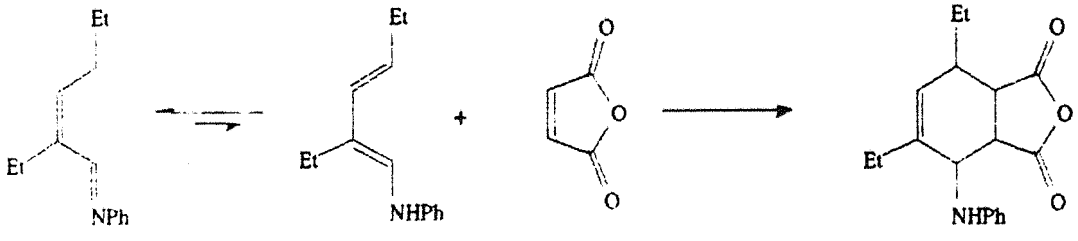
They can be cyclic or acyclic. Mostly, azadienes are electron-deficient and participate in inverse electron-demand ($LUMO_{diene}$ controlled) Diels-Alder reactions. But substitution of the azadiene with strongly electron-donating groups may lead with electron-deficient dienophiles to the normal process.

a/ Non-hetero azadienes.

1) Azabutadiene systems.

α] 1-Azabutadienes.

Such systems usually do not undergo [4+2] cycloadditions. On the other hand, unsaturated imines such as (63) via their enamine tautomer (64) may lead to such cyclisations, scheme 56.

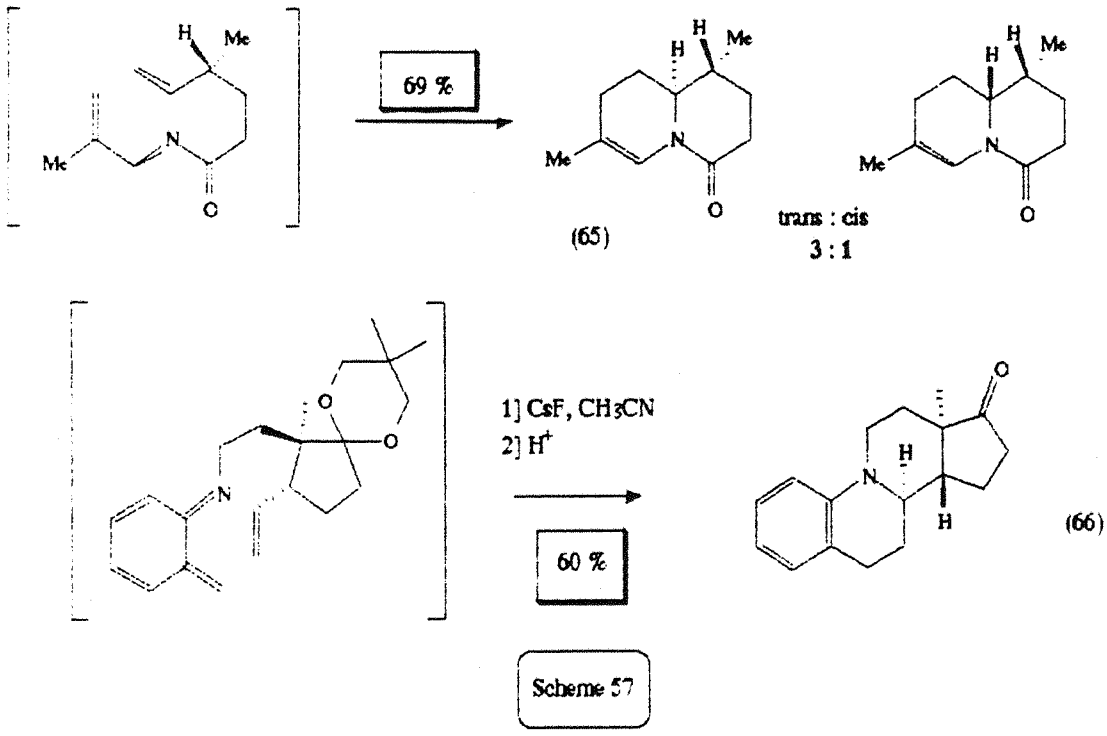


(63) (64)

Scheme 56

N-Acyl-1-azabutadienes have been described as good dienes in the intramolecular aza Diels-Alder reaction. It has been applied to provide a key diastereoisomer (65) for the synthesis of deoxynapharidin[87] and the intermediate (66) afforded from an ortho quinone methide imine in syntheses of 9-azaestrone derivatives (scheme 57).

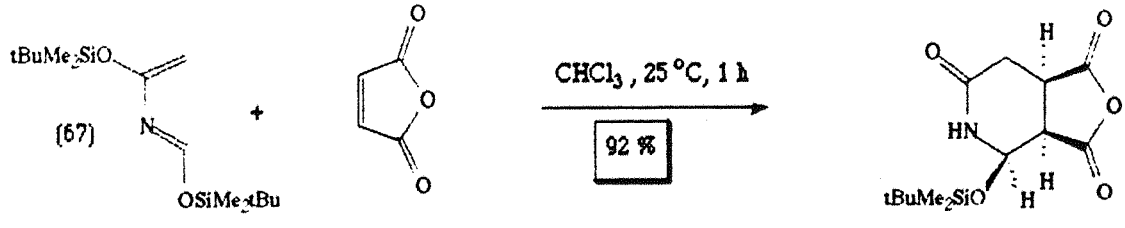
Boger has just reported the endo-selective $LUMO_{diene}$-controlled cycloadditions of N-sulfonyl-4-(ethoxycarbonyl)-1-aza-1,3-butadienes occurring with simple electron-rich alkenes at roomtemperature[89].



Scheme 57

β] 2-Azabutadienes.

In most of the studied cases, the diene bears some electron-donating groups in order to increase its reactivity towards classical electron-deficient dienophiles in a normal Diels-Alder reaction. For instance[90], 1,3-bis(tertiobutyldimethylsilyloxy)-2-azabutadiene (67) shows a high reactivity, scheme 58.

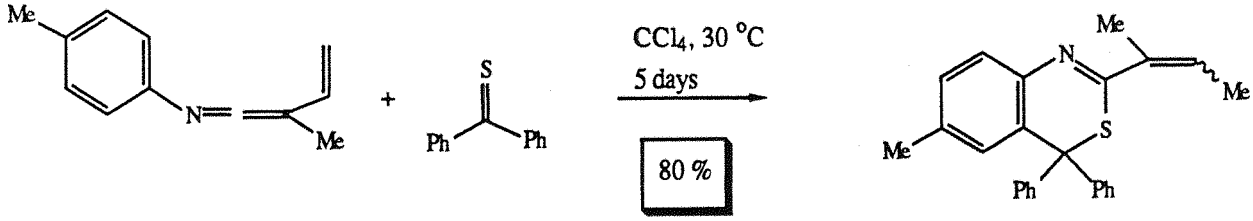


Scheme 58

Aromatic imines generated from aniline and arylaldehydes have been studied as azadienes. While they do not cycloadd to electron-deficient dienophiles, they react with electron-rich olefins under acid-catalysed conditions. This will be further developed in sections [D] and [E].

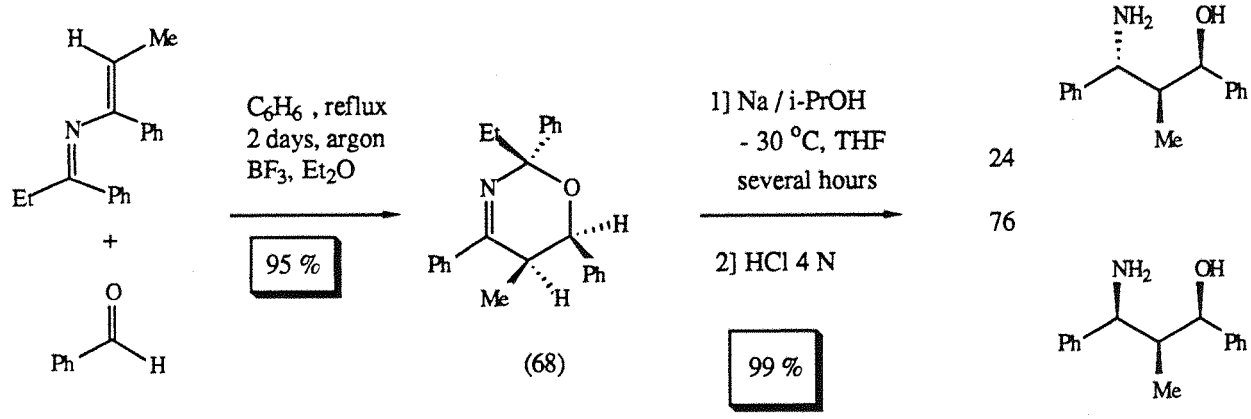
Vinyl isocyanates, vinyl thioisocyanates, vinyl diimides, N-aryl ketenimines and N-aryl vinyl

ketenimines have been described as 4π components in Diels-Alder cycloadditions with electron-rich dienophiles, ynamines, ethoxyacetylenes or heterodienophiles, as illustrated in scheme 59 with the cycloaddition of a N-aryl vinyl ketenimine with thiobenzophenone[91].



Scheme 59

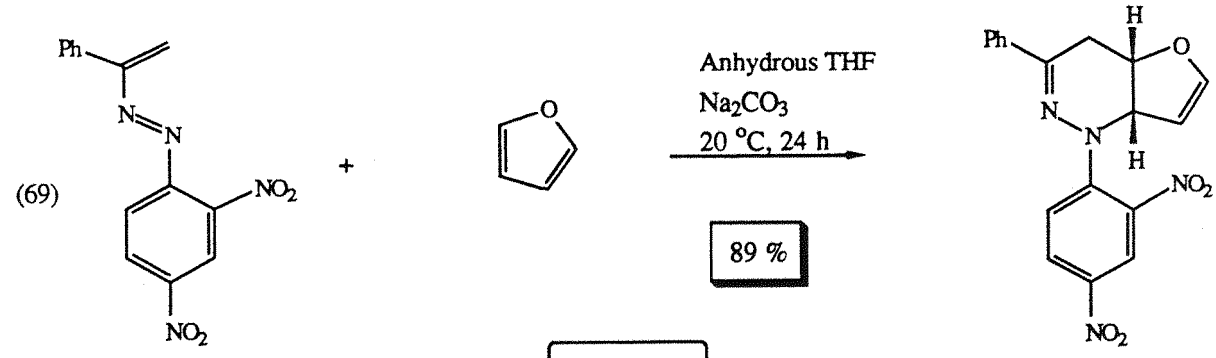
Finally, Barluenga has developed a simple pathway to 1,3-aminoalcohols[93] via 5,6-dihydro-2*H*-1,3-oxazine derivatives[92] such as (68) obtained by Diels-Alder cyclisation from 2-aza-1,3-dienes and aldehydes as dienophiles, as summed up in scheme 60.



Scheme 60

γ] 1,2-Diazabutadienes.

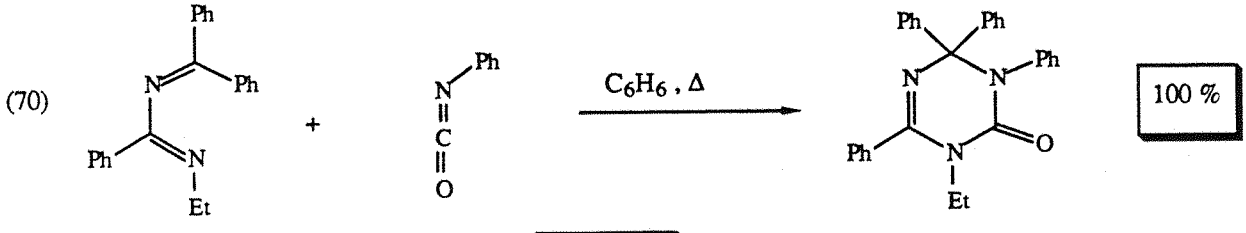
Electron-deficient azo-alkenes such as (69) may react[94] as dienes with reactive electron-rich olefins (scheme 61), typical electron-deficient dienophiles, ketenes, azodicarboxylates and thio-isocyanates.



Scheme 61

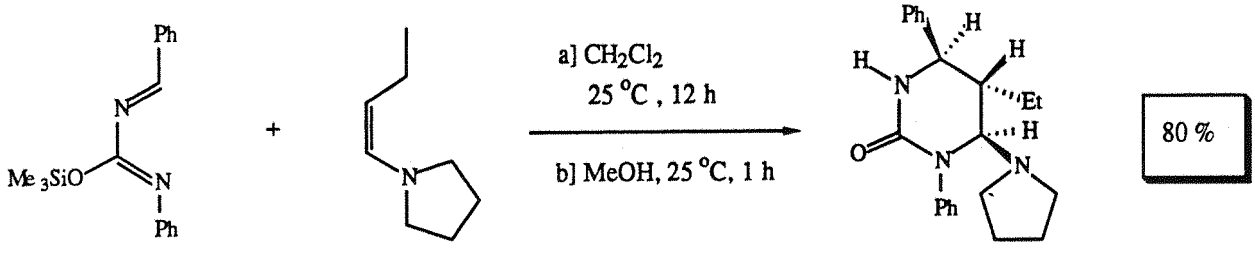
δ] 1,3-Diazabutadienes.

The main species acting as dienes are some simple diazabutadienes. Hence (70) adds to isocyanates to give 1,3,5-triazine derivatives in a regioselective fashion[95], scheme 62.



Scheme 62

Barluenga has recently used[96] such dienes with enamines such as (E)-1-pyrrolidino-1-butene to afford diastereoselectively tetrahydropyrimidinone derivatives (scheme 63) in an inverse electron demand process via an endo transition state.



Scheme 63

ε] 1,4 and 2,3-Diazabutadienes.

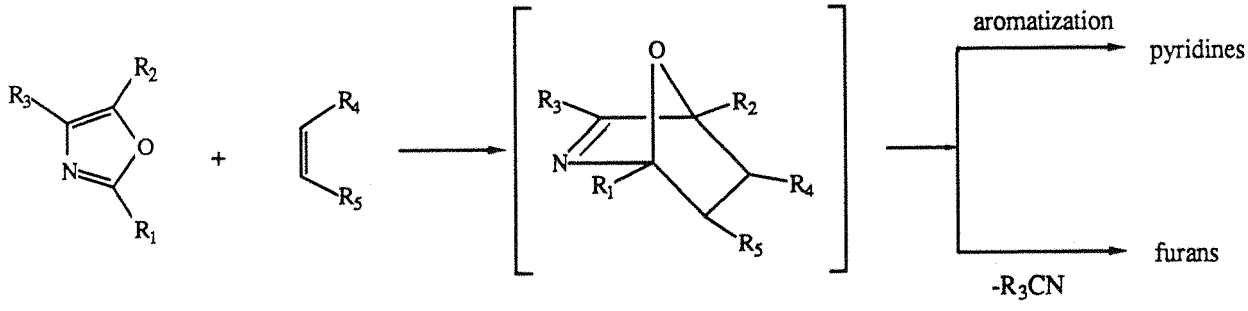
Only a few [4+2] Diels-Alder cycloadditions involving a 1,4-diazabutadiene skeleton have been reported. These dienes are very specific species like ortho-benzoquinone diimines.

Rare acyclic 2,3-diazabutadiene structures have undergone successful Diels-Alder reactions; cyclic systems such as 2,5-diphenyl-3,4-diazacyclopentadienones and 2,3-diazacyclopentadienes are such examples.

2) Heterocyclic azadienes.

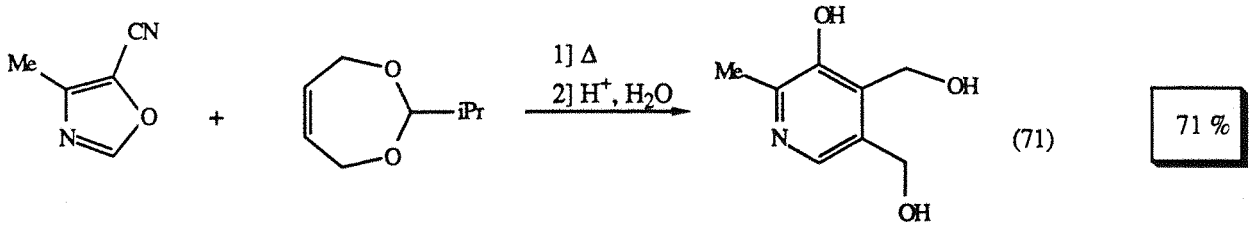
α] Oxazoles.

The first successful use of alkyloxazoles in Diels-Alder cycloadditions with maleic anhydride was observed by Kondrat'eva[97] in 1957. Since, these dienic systems have been applied to the synthesis of pyridines after further aromatization, or furan derivatives after loss of RCN via a retro Diels-Alder reaction. This outcome depends on the dienophile and the reaction conditions. As regards the route to a pyridine skeleton, the aromatization may occur by various ways and thus lead to different substituted adducts (scheme 64).



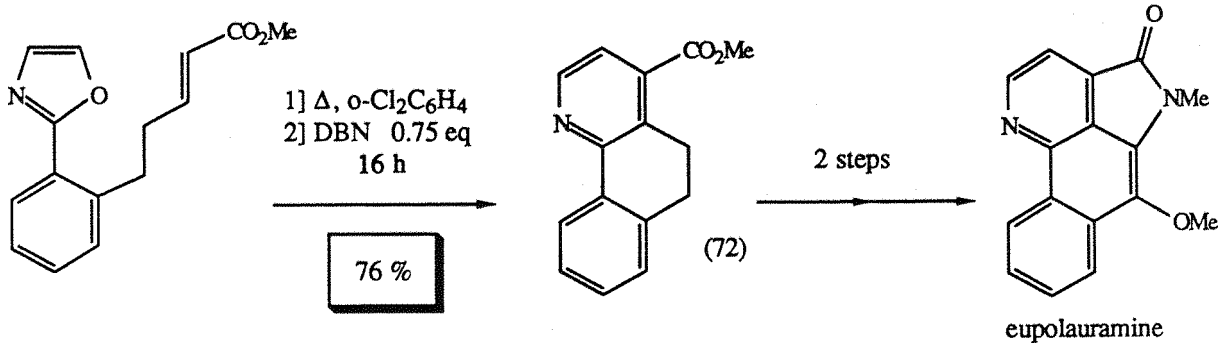
Scheme 64

This generally normal process is enhanced by the substitution of an electron-releasing group on the oxazole. This ability to provide the pyridine structure has constituted the key step in many alkaloid syntheses. Among others, interesting pathways leading to vitamine B_6, pyridoxol (71), via an inverse electron-demand mode have been reported[66], scheme 65.



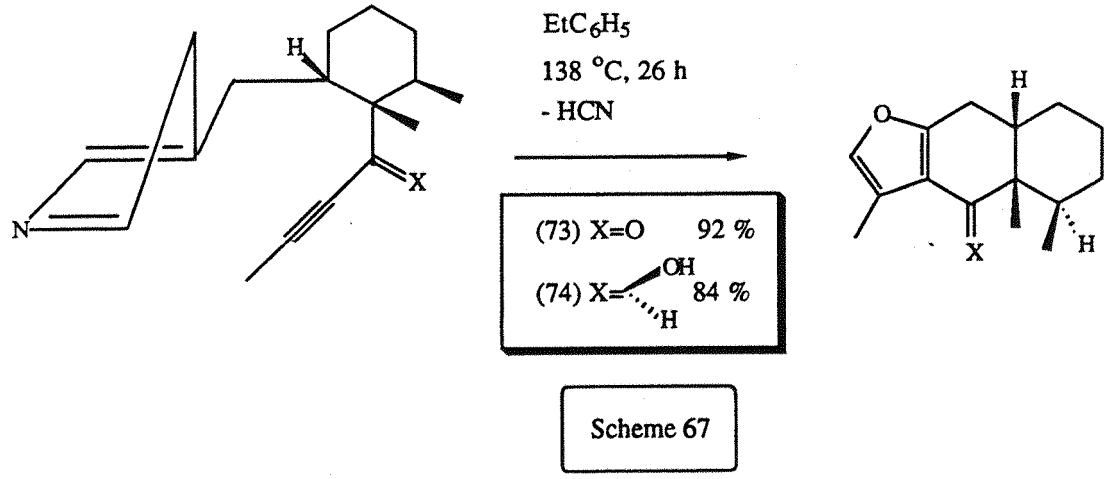
Scheme 65

Weinreb has developed a total synthesis of the azaphenanthrene alkaloid, eupolauramine[98], via the following IMDA cyclisation[99] leading to the pyridine intermediate (72) (scheme 66).



Scheme 66

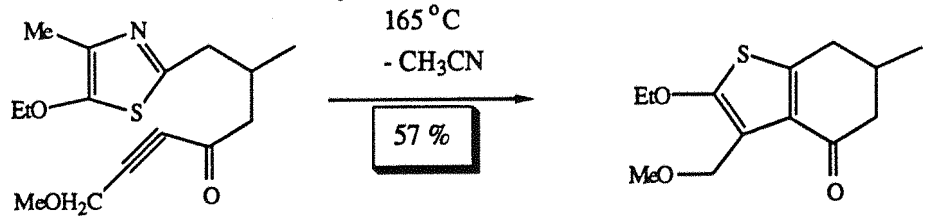
With regard to the obtention of the furan skeleton with an acetylenic dienophile, many interesting intramolecular applications of this process have been studied. Hence, ligularone (73) and petalsalbine (74) (scheme 67) have been afforded via the following high yield cyclisation and the consequent bridge loss[100].



Scheme 67

β] Thiazoles.

Very rare examples of aza Diels-Alder reactions with thiazoles have been described. In line with the latter case (scheme 67) where the oxazole leads to a furan derivative, the thiophene adduct (75) has been provided[101] intramolecularly from an acetylene thiazole (76), scheme 68.

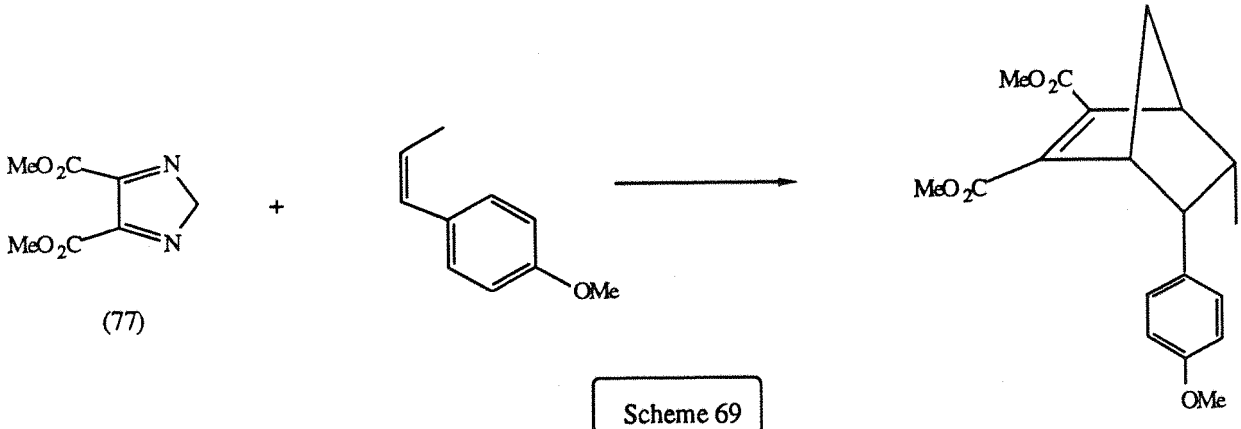


(76) (75)

Scheme 68

γ] Imidazoles.

Dimethylimidazole-4,5-dicarboxylate (77), as an electron-deficient 1,4-diaza-diene, is one of the scarce imidazoles to undergo Diels-Alder reactions, as shown in scheme 69.



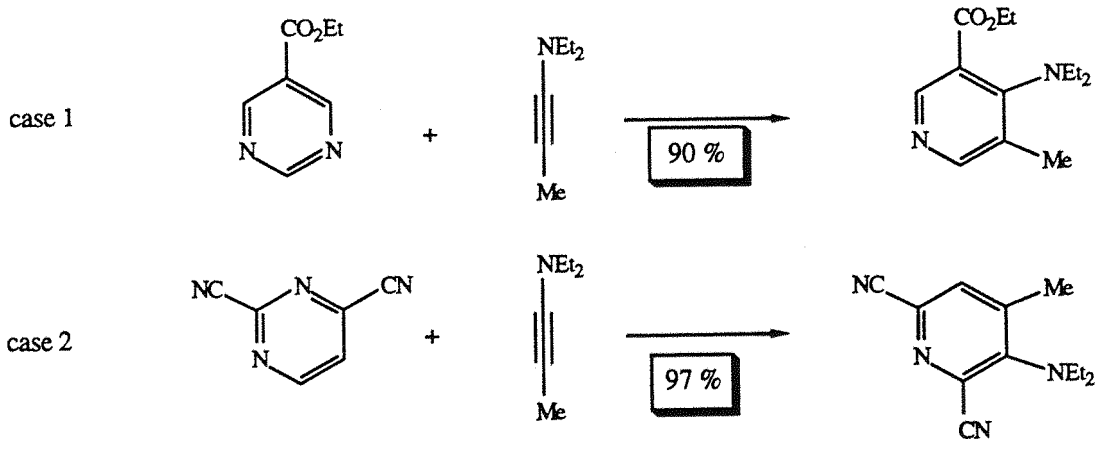
(77)

Scheme 69

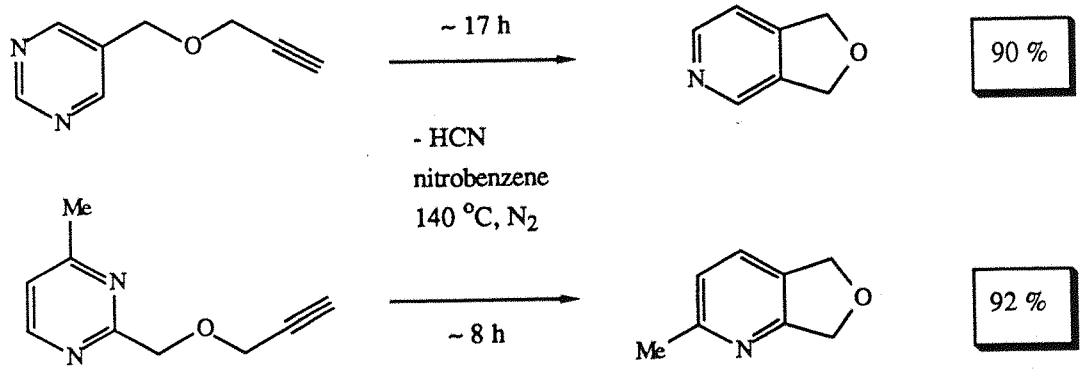
δ] Pyrimidines.

1,3-Diazines substituted by electron-attracting groups afford inverse electron-demand cycloadditions with electron-rich dienophiles like ynamines which add àcross C_2/C_5 of the pyrimidine nucleus. The nucleophilic carbon of the ynamine tends to attach preferably to this C_2 when it does not bear any strong electron-withdrawing functionality (case 1, scheme 70), which usually controls the regiospecificity. A subsequent loss of RCN leads to pyridine derivatives.

It has been recently applied[102] in the intramolecular mode to provide furo-pyridines in high yields, scheme 71.

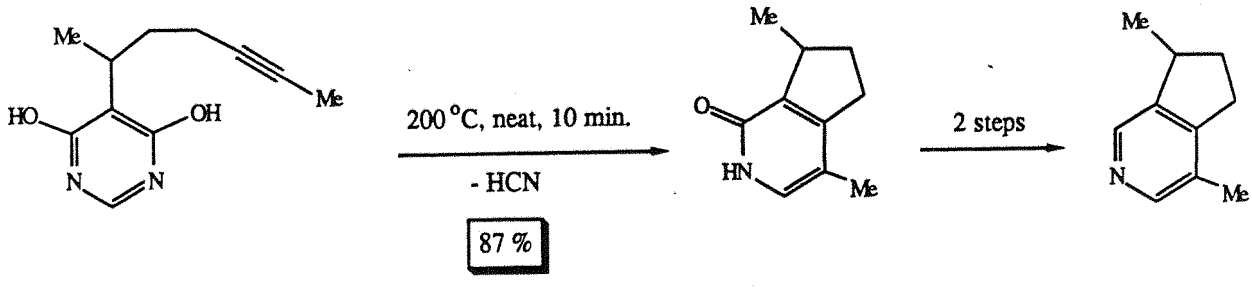


Scheme 70



Scheme 71

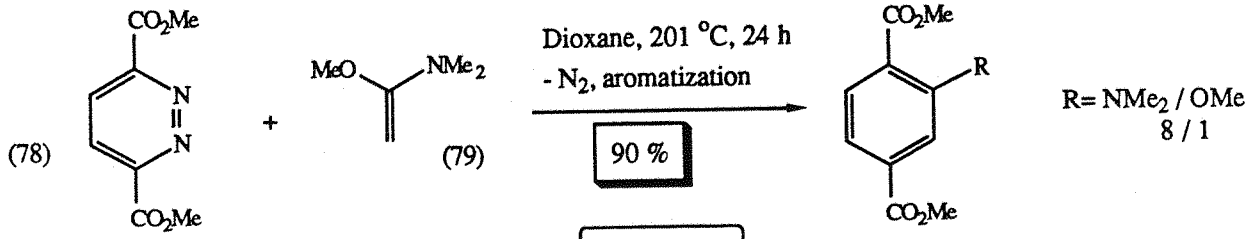
4,6-Dihydroxypyrimidines add to certain dienophiles and provide after loss of cyanic acid pyridone derivatives. It has been applied[103] by Sammes et al to a total synthesis of acetinidine via the following IMDA reaction, scheme 72.



Scheme 72

ε] Pyridazines.

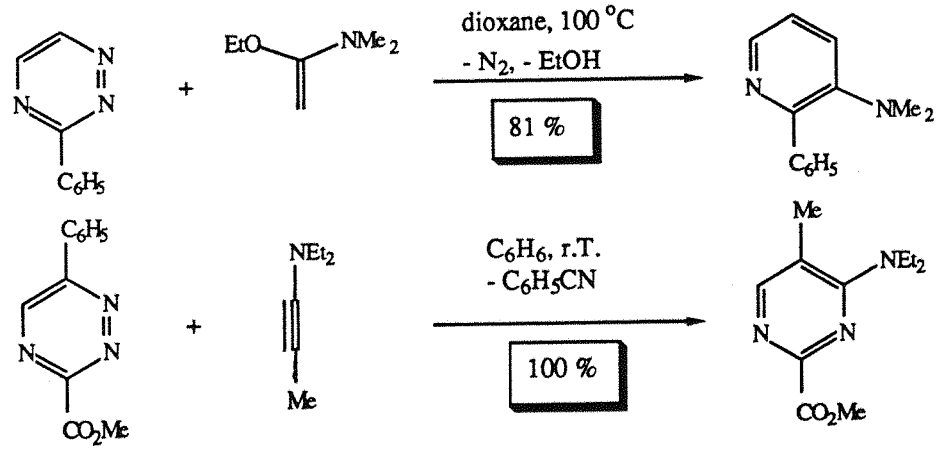
Electron-deficient 1,2-diazine carboxylates such as (78) react with electron-rich dienophiles like (79) (scheme 73) which add across C_3-C_6 of the pyridazine nucleus to provide substituted benzenes[104]. With ynamines, the addition may occur across N_1-C_4 and lead to pyridine products.



Scheme 73

ζ] 1,2,4-Triazines.

They constitute one of the most investigated azadiene systems, because of their ability to behave as 4π components. In contrast they can react either across C_3-C_6 or C_5-N_2. This regioselectivity is mainly dependent upon the nature and the position of substituents. Hence, C_3-C_6 additions yield substituted pyridines[105] while N_2-C_5 additions lead to substituted pyrimidines, scheme 74.

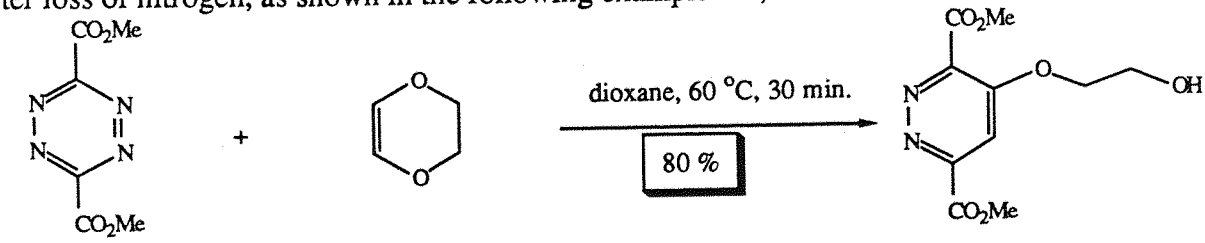


Scheme 74

η] 1,2,4,5-Tetrazines.

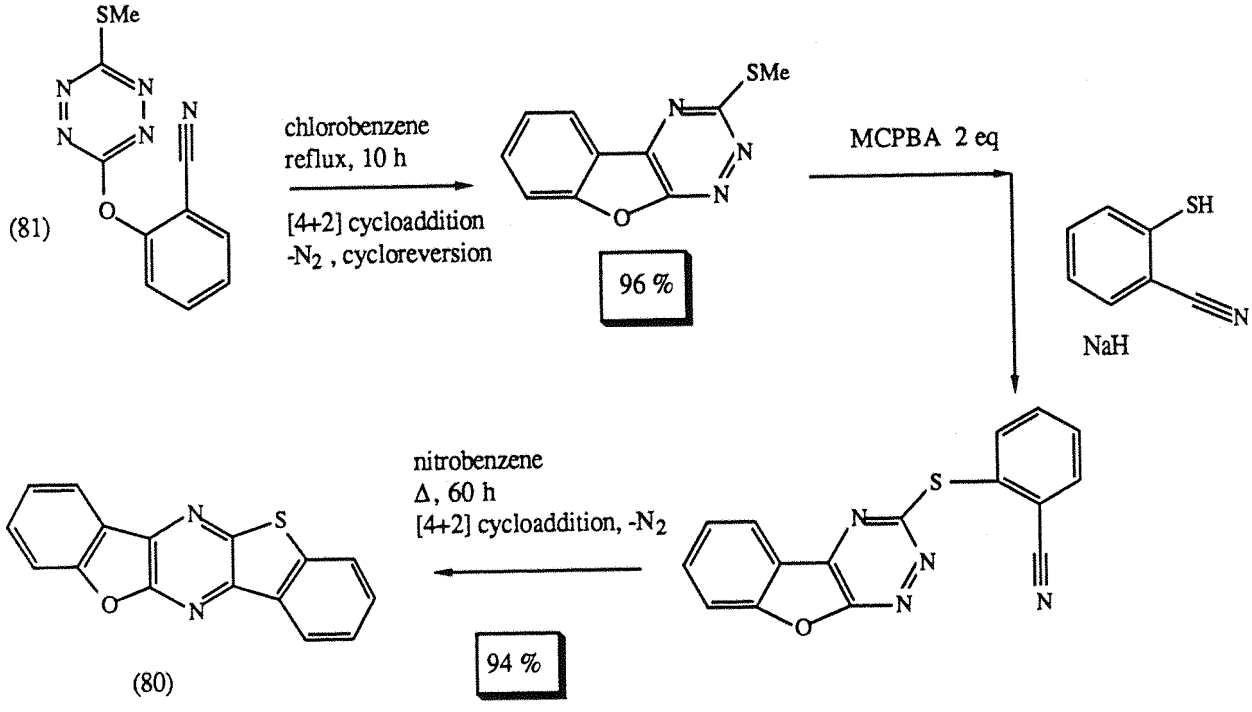
They represent the most extensively studied examples of inverse electron-demand Diels-Alder reactions. In most cases, symmetrical 3,4-disubstituted 1,2,4,5-tetrazines are used. A very wide variety of dienophiles cycloadd across C_3-C_6 and thereby yield one simple pyrimidine derivative

after loss of nitrogen, as shown in the following example[106], scheme 75.



Scheme 75

Seitz obtained[107] in 1989 the benzofuro[2,3-b]benzothieno[2,3-e]pyrazine (80) in high yield through two consecutive IMDA reactions from the starting tetrazine (81), scheme 76.



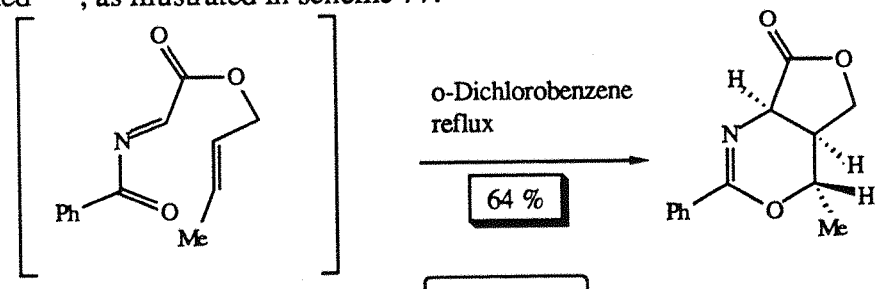
Scheme 76

b/ Hetero azadienes.

1) N-Acyl imines.

When the imino carbon bears a strong electron-withdrawing group, the diene system does react as the 4π component with vinyl ethers, enamines, sulphenes, acetylenes and ketenes, and not as an imino dienophile. This area of inverse electron-demand Diels-Alder reactions provides oxazine

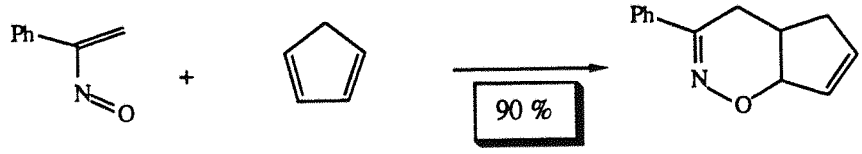
derivatives and it has been reviewed by Weinreb and Scola[64]. The intramolecular variation has also been investigated[108], as illustrated in scheme 77.



Scheme 77

2) Vinyl-nitroso compounds.

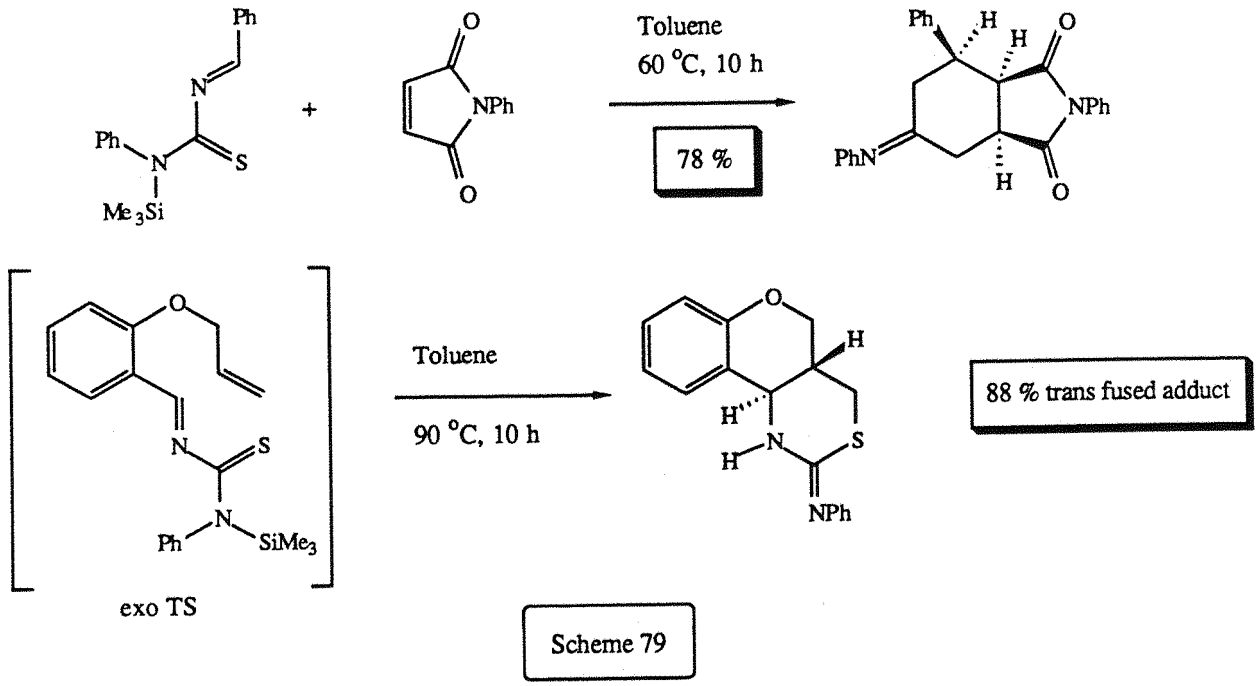
They constitute the second major class herein. Their reactivity toward typical olefins is enhanced by the substitution of electron-withdrawing groups[109] (scheme 78).



Scheme 78

3) 1-Thia-3-azabutadienes.

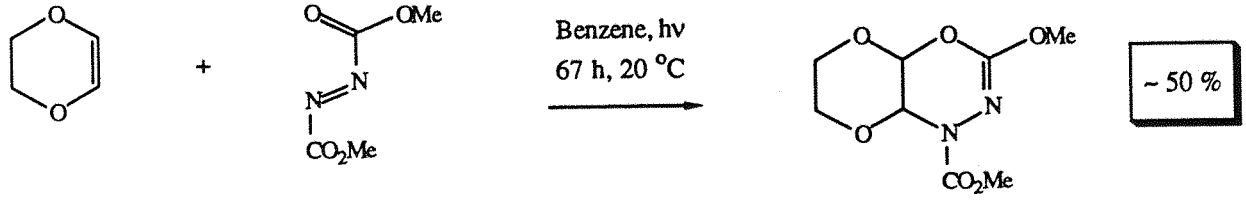
They have been investigated by Barluenga and co-workers in both inter-[110] and intramolecular[111] modes, scheme 79. The IMDA reaction below[111] was the first one reported with such a dienic system.



Scheme 79

4) Azodicarboxylate compounds.

Azodicarboxylates tend to behave as 2π components with other dienes in Diels-Alder reactions or with olefins in [2+2] cycloadditions; they have been shown[112] to undergo as 4π components the expected Diels-Alder rection with olefins showing no reactive allylic hydrogen, as shown in scheme 80.



Scheme 80

[D] RECENT ADVANCES IN THE USE OF IMINIUM SALTS IN HETERO DIELS-ALDER REACTIONS.

The usefulness of the imino system in hetero Diels-Alder reactions has been recognized earlier. It can constitute the dienophile or it may be included as part of the diene. Besides the neutral N-acyl imino skeleton, iminium salts represent another important variation of the imino Diels-Alder

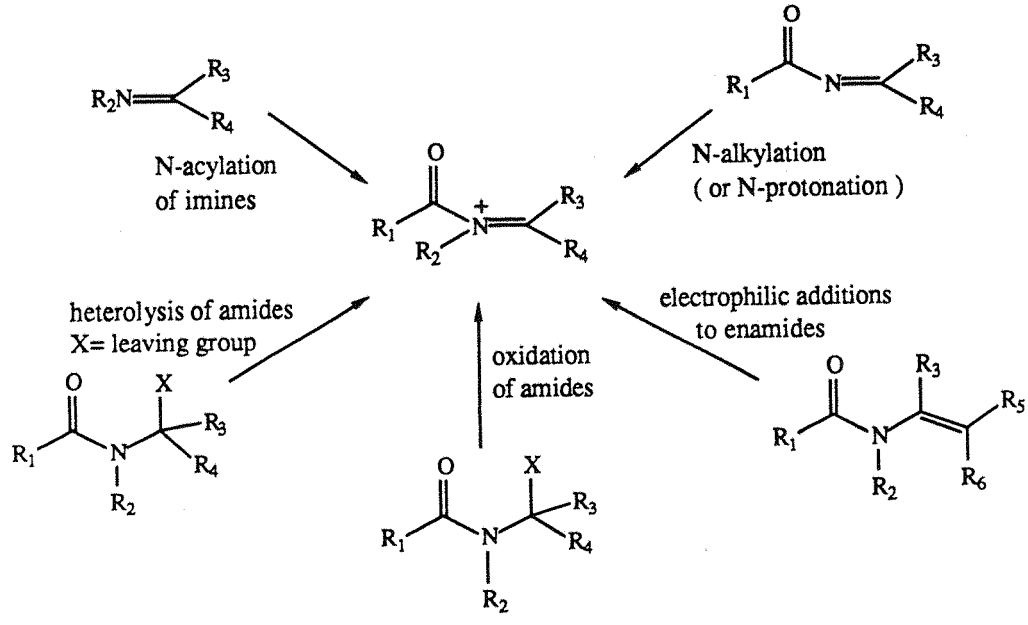
cycloadditions

In consequence of the electro-deficient feature of iminium salts, an iminium ion dienophile will mostly undergo normal Diels-Alder reactions while an iminium ion diene will usually cycloadd in an inverse electron-demand process.

Iminium ions can be utilized in both inter- and intramolecular modes.

I] Generation of iminium ions.

In most cases, they are generated in situ because of their limited stability and high reactivity. This formation depends on the solvent and the nature of the acidic catalyst. Scheme 81 sums up the different routes to N-acyl iminium salts which are the most used iminium salts.



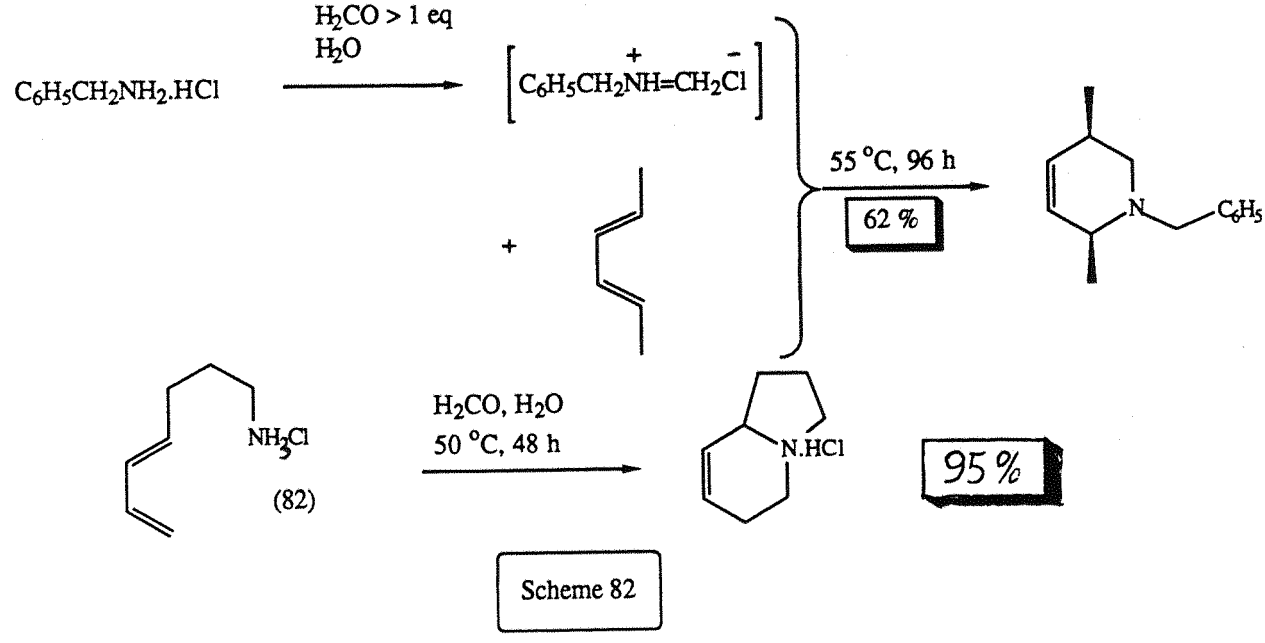
Scheme 81

A simple iminium ion is commonly generated from the corresponding amine and an aldehyde under acid catalysis conditions. The main results afforded with iminium salts in hetero Diels-Alder reactions can be found in previous reviews by Povarov[113], Boger[65,66] and Weinreb[63,64].

II] The recent studies of Grieco.

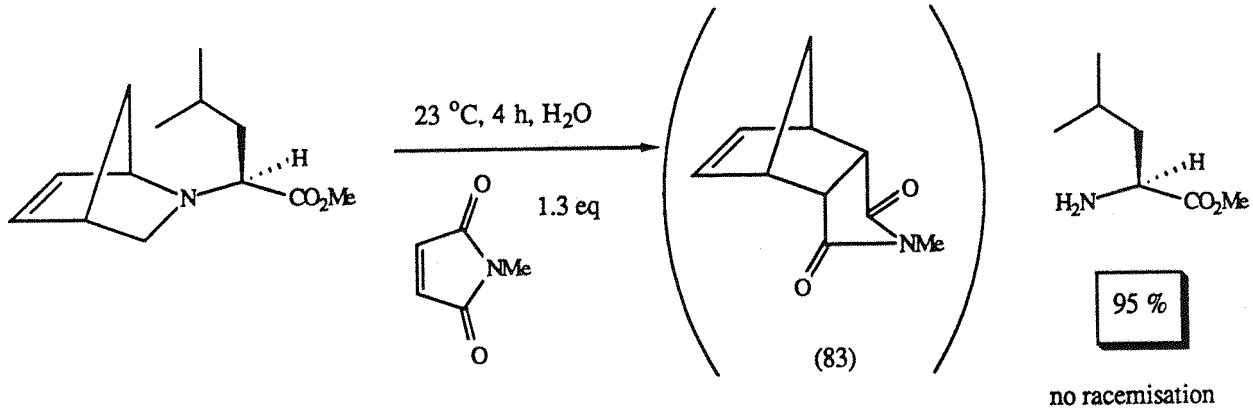
In 1985, Grieco and Larsen reported[114] the use of simple iminium salts as dienophiles in aza Diels-Alder cycloadditions with various dienes in aqueous solution. Each iminium ion was

generated in situ under Mannich-like conditions from the corresponding starting amine and formaldehyde and thereby underwent cycloadditions with excess diene to give cyclic amines, scheme 82. Cyclopentadiene, cyclohexadiene and different substituted butadienes on one side, and benzylamine, methylamine and ammonia on the other side were utilized. The regioselectivity and stereoselectivity observed seemed to confirm a concerted process. These results were applied to the intramolecular mode and thus provided a successful route to lupinine, julandine[115] and δ-coniceine[114] from the dienyl amine (82) and formaldehyde, scheme 82.



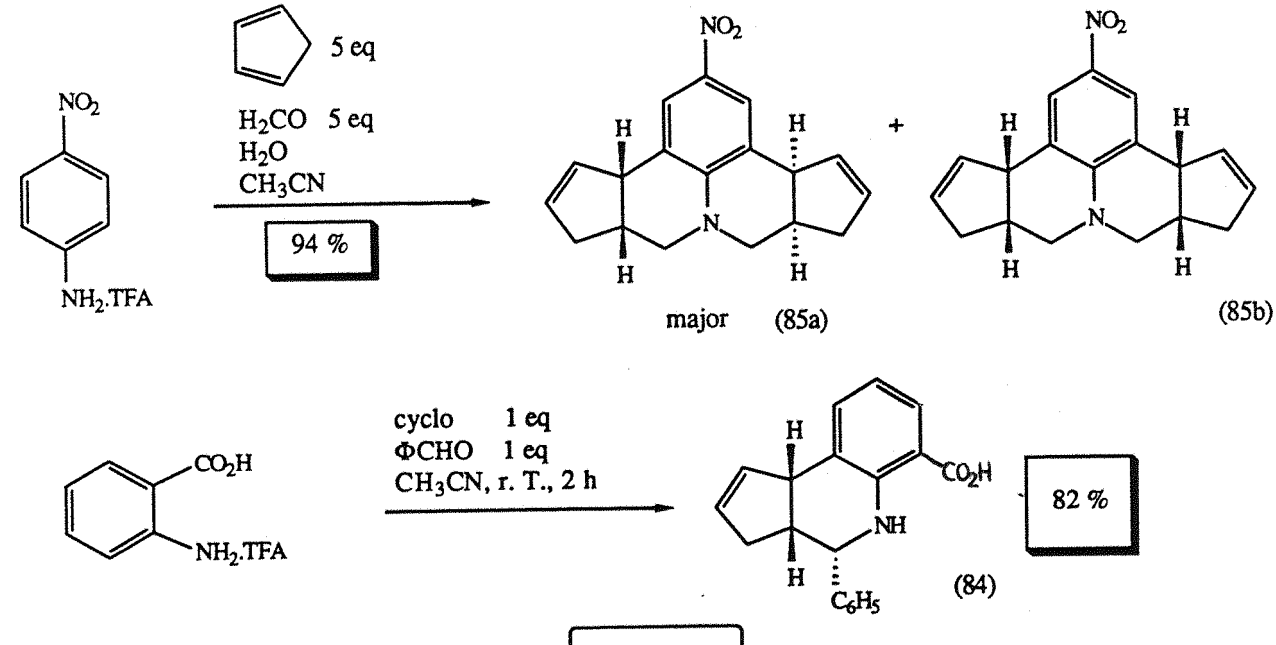
Scheme 82

As a complement to this work, Grieco added[116] in 1987 that these 2-azanorbornenes, obtained above with cyclopentadiene as diene, undergo retro aza Diels-Alder reactions in water at mild temperatures (25-50 °C) and in acid-catalysed conditions (scheme 83). They showed that the presence of N-methylmaleimide was necessary to release in good yield the starting amine, with conservation of configuration for a chiral amine. The tricyclic compound (83) was sometimes afforded alongside.They pointed out that this ability of a heterocycloreversion reaction of azanorbornenes might be exploited to use these species as new protecting groups for primary amines.



Scheme 83

Lastly, Grieco and Bahsas reported[117] in 1988 the use of iminium ions derived from aryl amines and aldehydes as heterodienes in reverse [4+2] cycloadditions with cyclopentadiene as dienophile. The iminium ions were generated in situ from substituted anilines with aqueous formaldehyde or benzaldehyde in acetonitrile in the presence of trifluoroacetic acid. A stereoselective addition took place regioselectively with respect to the dienophile and, according to the excess of aldehyde and cyclopentadiene, led to tetrahydroquinoline based tri- or pentacyclic products (84) and (85) respectively, as summed up in scheme 84.



Scheme 84

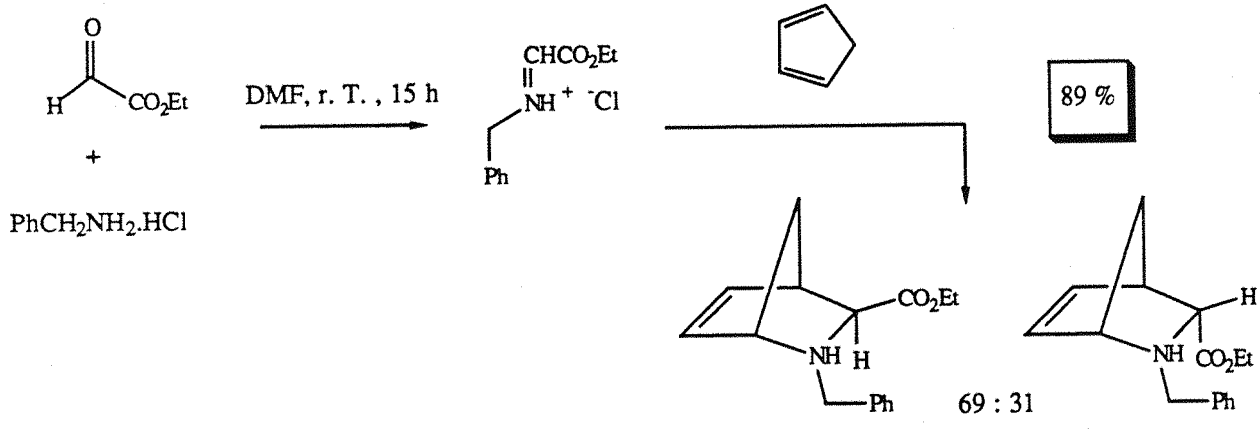
This chemistry of aromatic iminium ions reacting in aza Diels-Alder reactions as dienes in which

two of the four π electrons are provided by the aromatic ring had been scarcely reported before.

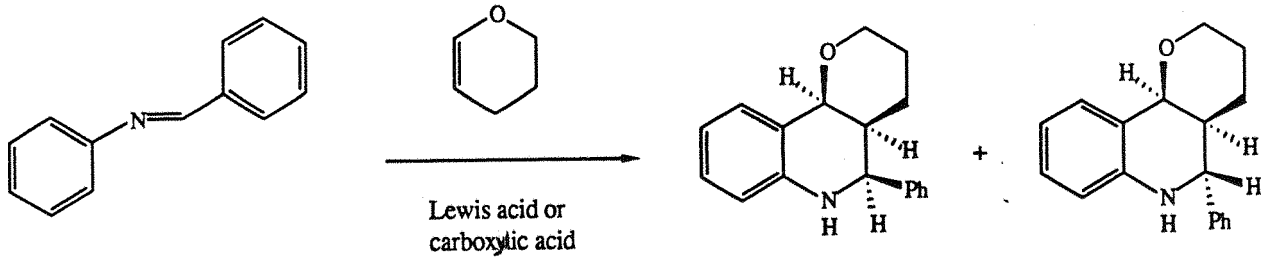
III] Related work.

In line with the work of Grieco affording azanorbornenes, Bailey et al synthesized[118] in 1989 pipecolic acid derivatives via aza Diels-Alder reactions with cyclopentadiene as diene and an iminium ion generated in situ from benzylamine hydrochloride and ethyl glyoxylate (scheme 85).

In relation to the previous discovery of Grieco, Gilchrist et al have further investigated[119] the [4+2] cycloadditions, previously approached by other groups, occurring between 3,4-dihydro-2H-pyran (84) and benzylidene anilines in the presence of several different Lewis acids or carboxylic acids, and hence have confirmed the structures of the isomeric tetrahydroquinolines (85) and (86) as reaction products, scheme 86.



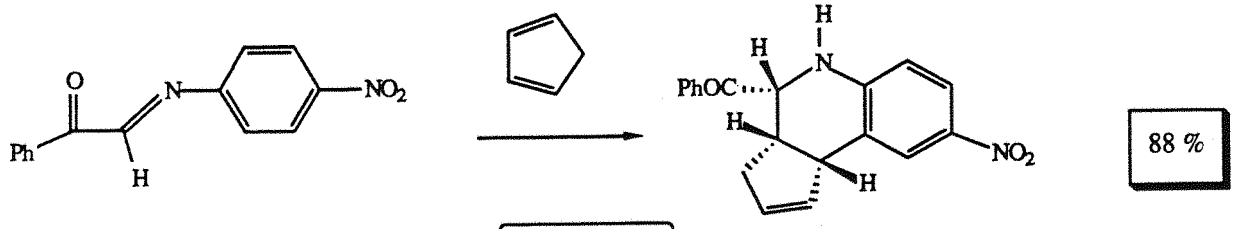
Scheme 85



Scheme 86

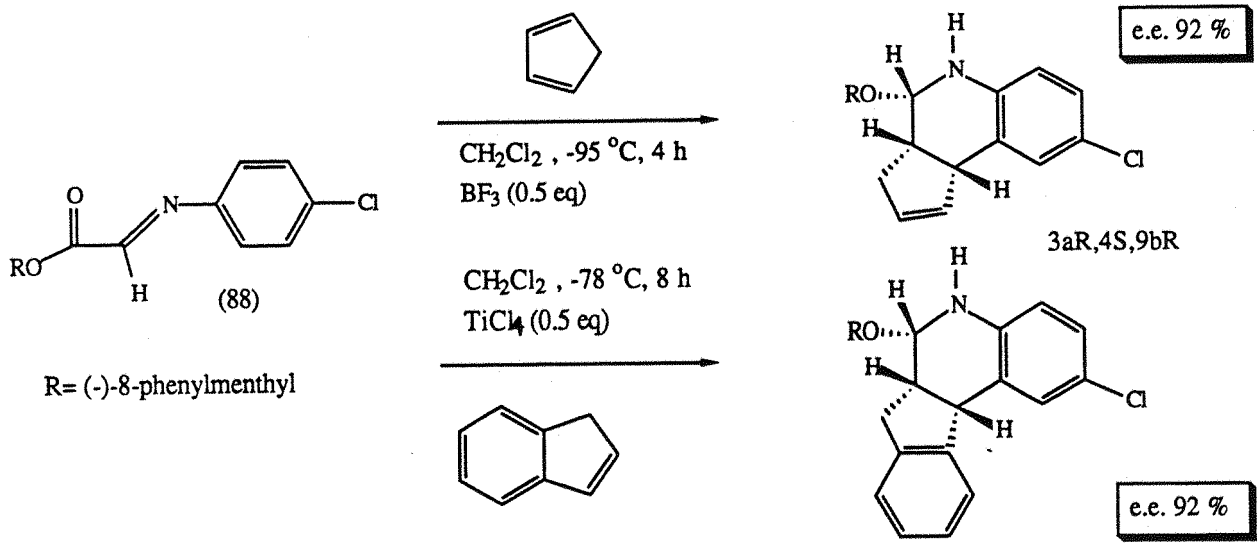
In 1988, Lucchini and Prato reported[120] regio- and stereoselective cycloadditions occurring

between aromatic α-keto-imines derived from aniline as activated dienes and different simple cyclic and acyclic dienic systems as electron-rich dienophiles under Lewis acid catalysis. The usual cis addition was indeed observed as well as the known regiochemistry as regards the dienophile. On the other hand, it was noticed that both ketone substituent and cyclopentadiene unit when used as dienophile were on the same side with respect to the quinoline plane (scheme 87), which confirmed an endo transition state.



Scheme 87

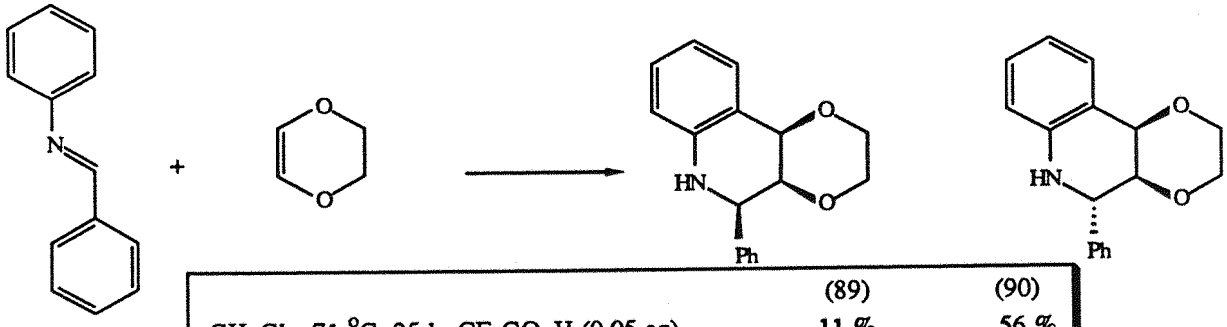
The following year, they completed[121] these first results by using chiral glyoxylate imines such as (88). The diastereoselectivity previously noted thereby corresponded to enantioselectivity. The cyclisations with cyclopentadiene and indene yielded optically active tetrahydroquinolines in the cases mentioned below (scheme 88). Various chiral auxiliaries, solvents (MeCN, PhMe, SO_2, ...) and Lewis acids ($TiCl_4$, $EtAlCl_2$, $SnCl_4$, ...) were utilized. The diastereoisomeric ratios were shown to depend on solvent polarity and temperature.



Scheme 88

Finally, Laszlo reported[122] in 1989 a series of cycloadditions of N-benzylidene anilines to

electron rich Z-vinyl ethers. They led to the two stereoisomers (89) and (90) in a poor diastereoselectivity (scheme 89). Different solvents (Et_2O, CH_3CN, ...), catalysts ($FeCl_3$, KIO/Fe^{3+}, ..) and additives (CF_3CO_2H, tBuOH, NEt_3, ...) were used. A two-step ionic mechanism was suggested.



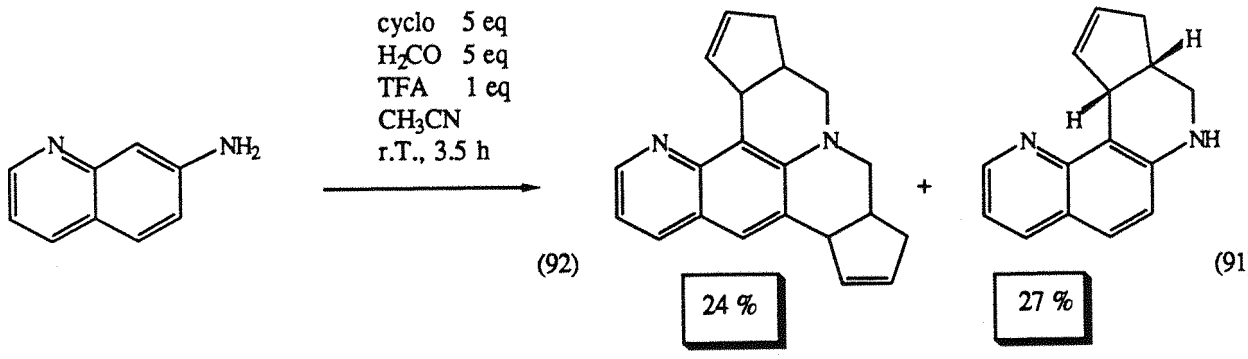
	(89)	(90)
CH_2Cl_2, 71 °C, 25 h, CF_3CO_2H (0.05 eq)	11 %	56 %
Et_2O, 21 °C, 37 h, KIO/Fe^{3+}, CF_3CO_2H (0.05 eq)	58 %	16 %

Scheme 89

[E] OWN OBJECTIVES.

I] Previous results obtained in the group.

In the light of the 1988 Grieco's work which can lead to a wide variety of new heterocyclic compounds, Merriman[123] has undertaken a study of this type of cyclocondensation reaction within a series of aromatic amines (benzenoid and heterocyclic). Using the same reaction conditions as Grieco, he has obtained successful results from 3,6-diamino-acridine with either formaldehyde or benzaldehyde, 4-amino-pyridine with benzaldehyde, and 5- and 7-amino-quinolines with formaldehyde. Styrene and dihydropyran have also shown to be potential dienophiles. The studied imines or Schiff bases have yielded regio- and stereoselectively the monocyclisation or dicyclocondensation (or tetracyclocondensation for 3,6-diamino-acridine) products according to the excess of reagents, as illustrated in scheme 90 respectively with (91) and (92) obtained from 7-amino-quinoline. These experiments have also shown that polymerisation may occur according to the reaction conditions.



Scheme 90

Riviere, by investigating[124] some simple ortho, meta and para substituted anilines as starting amines with formaldehyde and cyclopentadiene, has drawn basic conclusions as regards the ability of the involved aromatic ring to provide two π electrons and thus to undergo the expected cyclisation. The following table (scheme 91) sums up the main results. One can remark that:

-> the conformational effect does not play an important role in the reactions.

-> a strong electron-withdrawing group favors the cycloadditions while yields fall off in the presence of an electron-donating one.

This latter statement can be better understood by considering the probable mechanism of these cyclisations, scheme 92.

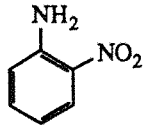
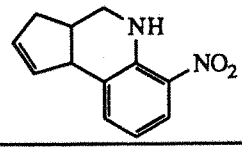
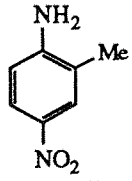
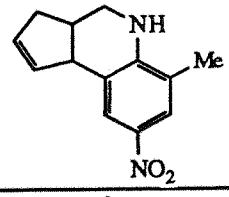
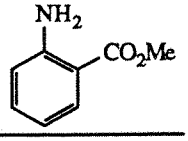
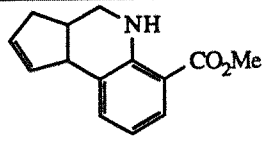
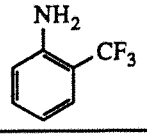
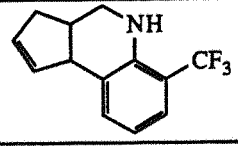
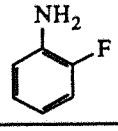
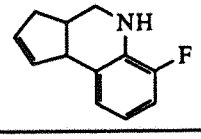
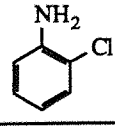
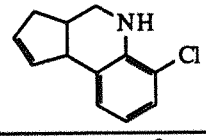
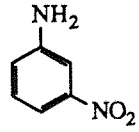
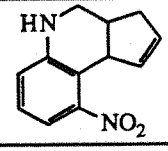
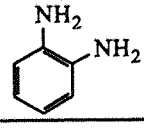
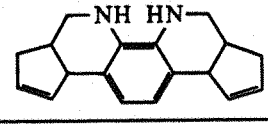
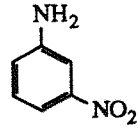
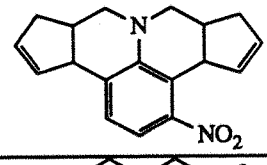
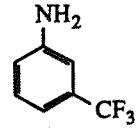
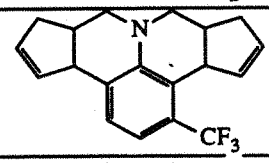
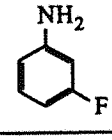
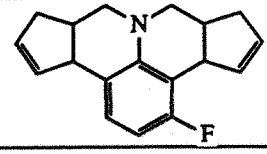
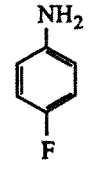
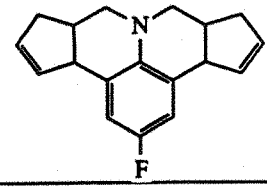
Indeed, at the stage (93) where the imine and cyclopentadiene are likely to be endo to each other (this point will be further discussed later), the electron shift, within the six concerned involved in the cyclisation process, which leads to either a typical transition state (94) or a possible ionic intermediate (95) is all the more favoured that the position ortho to the amine is nucleophilic. The presence of an electron-withdrawing group at the meta or para position with respect to the amine activates the cycloaddition process. In addition, the deactivation of the aromatic ring disfavours any competitive side aromatic substitution. These assessments will be further described in the discussion part (chapter 2).

II] Own objectives.

In view of the previous results performed in the group, it was decided:

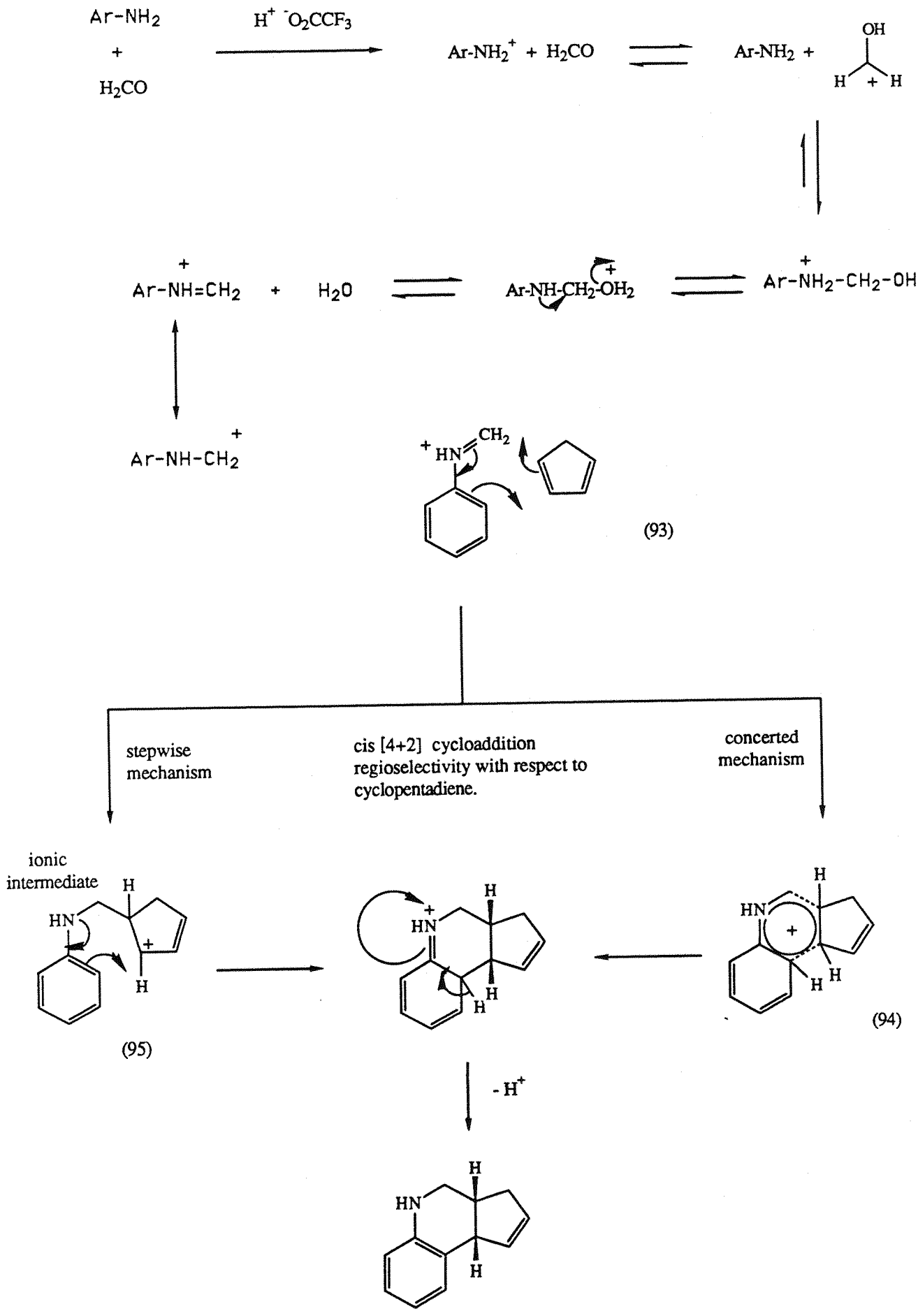
-> to concentrate our attention on cycloadditions with formaldehyde and cyclopentadiene as dienophile.

-> to investigate additions to bicarbocyclic amines - a category not previously studied - related to tetralin, indane and naphthalene, and including amino ketones.

Entry	Substituted aniline	Type[1]	Reaction conditions[2]	Diels-Alder adduct(s)	Yield[3]
1		mono	1 / 1 / 5 / 5 r. T. , 1 h		94 %
2		mono	1 / 1 / 5 / 5 r. T. , 1 h		75 %
3		mono	1 / 1 / 5 / 5 r. T. , 1 h		52 %
4		mono	1 / 1 / 5 / 5 r. T. , 1 h		52 %
5		mono	1 / 1 / 5 / 5 r. T. , 1 h		30 %
6		mono	1 / 1 / 5 / 5 r. T. , 1 h		8 %
7		mono	1 / 1 / 1 / 5 r. T. , 1h		48 %
8		dble mono	1 / 2 / 2 / 2.5 r. T. , 1 h		25 %
9		di	1 / 1 / 5 / 5 r. T. , 1 h		73 %
10		di	1 / 1 / 5 / 5 r. T. , 1 h		66 %
11		di	1 / 1 / 5 / 5 r. T. , 1 h		68 %
12		di	1 / 1 / 5 / 5 r. T. , 1 h		90 %

1] mono= monocyclisation; dble mono= double monocyclisation; di= dicyclisation. 2] respective ratios of starting amine TFA / formaldehyde / cyclopentadiene, reaction temperature, reaction time. 3] after isolation by flash chromatography.

Scheme 91: table of results obtained by Riviere from substituted anilines


Ar-NH2
+
H2CO
H+ -O2CCF3
Ar-NH2+ + H2CO
Ar-NH2 +
OH
H
+
H
Ar-NH=CH2
+
H2O
Ar-NH-CH2-OH2
Ar-NH2-CH2-OH
Ar-NH-CH2
CH2
HN
(93)
stepwise
mechanism
cis [4+2] cycloaddition
regioselectivity with respect to
cyclopentadiene.
concerted
mechanism
ionic
intermediate
(95)
(94)
- H+

Scheme 92

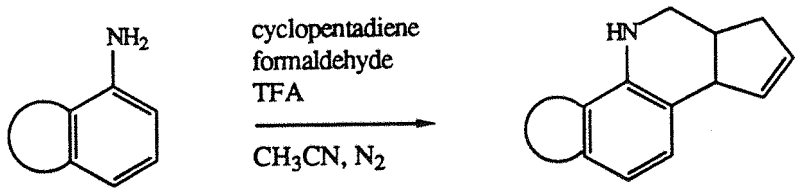
-> to investigate additions to amino-anthraquinones as an extension of the bicyclic amino ketone series to a tricyclic diketonic system.

Some of these reactions were expected to afford azasteroids. Such compounds, as described later, are of considerable interest.

The results are reported and discussed in the second part of this thesis. The chemical features and data are mentioned in the supplementary experimental part (chapter 3).

CHAPTER 2: DISCUSSION

The general aim of this research purpose has been to broaden the previous work of Grieco by studying different types of acid-catalysed cyclocondensation of bi- and tricyclic aromatic amines with formaldehyde and cyclopentadiene in a [4+2] Diels-Alder type process. The following discussion is structured according to the starting amines utilized in our work. The reaction conditions of Grieco (trifluoroacetic acid, aqueous formaldehyde, acetonitrile, nitrogen) have been used in all our cyclisations. The extension of this chemistry from simple aniline derivatives to bi- and tricyclic amines permits the building of new fused ringed systems which, when the amino group is suitably "ortho" with respect to the side ring, have the steroidal skeleton (scheme 93).



Scheme 93

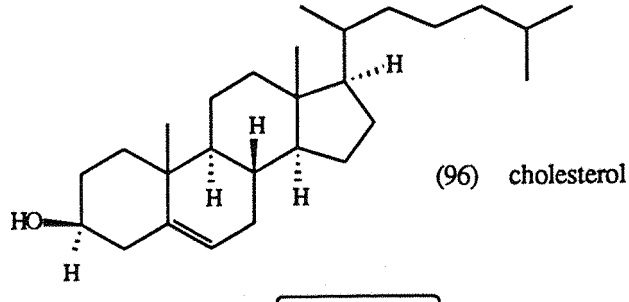
The possibility of a simple one step synthesis of azasteroids is attractive. In the following section the importance of azasteroids is reviewed.

[A] AZASTEROIDS.

I] Steroids: generalities.[125-127]

1] Origin and History.

Among common alcohols of animal and plant origin, the group of C_{27}-C_{29} secondary alcohols show the characteristic of being crystalline solids. Therefore these substances were given the generic name sterols (from Greek stereos= solid). The monosaturated sterol of the formula $C_{27}H_{45}OH$ is the predominant constituent of human gall stones deposited in the bile duct and thus was named cholesterol (96) (from Greek chole= bile), scheme 94.



(96) cholesterol

Scheme 94

Hence, because of their origin (from gall stones) and their sterol like structure as regards the ring system, earlier isolated bile acids were named steroids in about 1920.

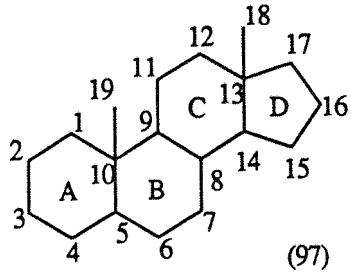
Steroid chemistry underwent a tremendous expansion with discovery of the sex hormones (estradiol, testosterone and progesterone) in 1929-1935 and later of the adrenal cortical hormones (among which the most significant physiologically active species are cortisone and cortisol) in 1935-1938.

But it was only in the fifties that the stereochemistry of steroids was fully elucidated. Moreover,

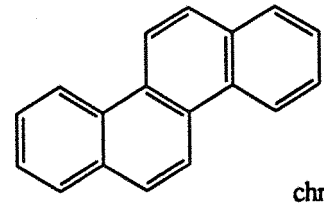
although heteroatoms had been introduced for a long time as substituent groups, in side chains or in side rings of the steroidal tetracyclic skeleton, one can consider that the area of heterocyclic steroids having one or several heteroatoms (O, N, S) in the steroidal nucleus has been investigated from only 1950.

2] Definitions.

Steroids are commonly described as compounds of four or more fused rings showing the same layout as the chrysene ring system, scheme 95. It is considered that any of the rings may be larger or smaller than six-membered, but the basic structure that is most usually found in Nature and chosen as reference for the special nomenclature of steroids is the perhydrocyclopentaphenanthrene nucleus (97) with the first three rings six-membered and the fourth five-membered, scheme 95.



(97)



chrysene

Scheme 95

Heteroatoms may be present anywhere in the skeleton; however, the majority of natural steroids are carbocyclic and saturated products. The main variations which might occur as regards the ring system and consequently ought to be mentioned in naming the compound are the following ones:

-> D-Homo: ring D is expanded to a six-membered ring.

-> A-Nor: ring A is contracted to a five-membered ring.

-> 18-Nor: lacking the C_{13}-methyl group (C_{18}).

-> 19-Nor: lacking the C_{10}-methyl group (C_{19}).

3] The main groups of steroids.

The steroid system performs some of the most fundamental biological functions by providing a wide range of biological activity. Steroids have been classified according to their origin and their structure. The main groups of natural steroids are:

-> sterols and bile acid derivatives and related compounds.

-> the sex hormone derivatives including estrone, testosterone, estradiol, progesterone,

androsterone and androstane.

-> the adrenocortical hormone derivatives including cortisone, cortisol and corticosterone.

-> the genin derivatives.

Minor series of analogues are structurally related to or derived by synthesis from one of the above basic molecule types. They include: estranes, cortexolones, prednisone, prednisolone, ... Finally, some alkaloids possess the steroid skeleton and some steroidal hormones of insects have been isolated (ecdysone).

4] Total synthesis of steroids.[48,128,129]

As underlined earlier, the major difficulty of total synthesis of steroids lies in their stereochemical complexity. Therefore, in synthesis steps must be highly stereoselective. These syntheses may be viewed in terms of the sequence in which rings are added, either as preformed rings or by building up. Hence there are many possibilities of generating the four rings A, B, C and D. For instance:

-> The sequence AB -> ABC -> ABCD has a historical significance because it was utilized to synthesize the sex hormone equilenin in 1939, which was the first total synthesis.

-> The sequence AB + D -> ABD -> ABCD is often illustrated via a Torgov reaction (addition of an anion to an unsaturated system in acid-catalysed conditions).

->The Diels-Alder reaction is often the key step in the sequence AB + D -> ABCD. The chemistry approached in parts [D] and [E] of the introduction and further described in this discussion is related to this area.

Nowadays, two important points of development in steroid total synthesis are asymmetric synthesis and routes based on generation and intramolecular cycloaddition (type Diels-Alder) of ortho-quinodimethanes earlier mentioned in the introduction.

II] Azasteroids.[125-130]

1] Intra / extra nuclear azasteroids.

Azasteroids are compounds in which at least one nitrogen is either an integral part of the steroid nuclear skeleton, or forms part of a side chain, an attached group or a side ring (fused or spiro). Hence, the former category contains the "intranuclear azasteroids" which can be qualified heterocyclic steroids, while the latter contains the "extranuclear azasteroids".

2] Importance.

A number of natural azasteroids have been isolated (see 4]) and have sometimes been used for their bioactivity. In organic synthesis, azasteroids have attracted a great deal of attention for about

forty years for mainly two reasons. First, their preparation represents a challenge to chemists, and often demands or permits the development of new and useful reactions (for instance Torgov reaction). This synthetic and mechanistic interest is associated with the often complex stereochemical features. And secondly, their bioactiviy is promising in many pharmacological areas.

The potential application of azasteroids are numerous. Interest has been shown in the development of a variety of useful agents such as adrenocorticoids, anti-mineralocorticoids, anabolics, oestrogenic, anti-oestrogenic, anti-fertility, cardiac and anti-hypertensive agents, anti-lipemic, central-nervous systems acting, local anaesthetic, anti-microbial and anti- neoplastic agents. Thus structure/activity studies have been made with some interest concerning the position of the nitrogen in the steroidal nucleus, as illustrated in sections 4], 5] and 6].

3] Synthetic aspects.

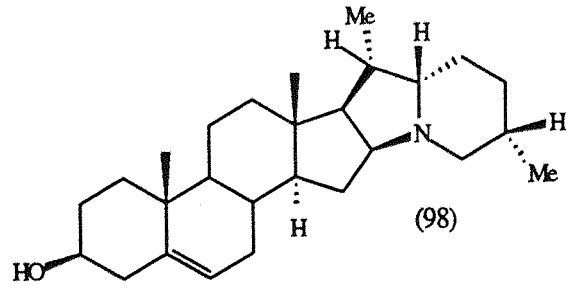
While many naturally occurring steroids have been modified to lead to extra nuclear azasteroids without altering the basic carbon skeleton, few examples of the substitution of carbon by a nitrogen via a ring opening and a subsequent closure in one of the four rings A,B,C or D without any change of ring size have been reported before 1960. It is only from the sixties that many nuclear azasteroids with rings A, B, C six-membered and D five-membered have been synthesized.

The steroidal skeleton containing one or more nitrogens can be totally synthesized by two different strategies: a mono- or bicyclic azasystemsmay be the starting point of the synthesis or one may alternatively construct the azacyclic component of the steroid nucleus by a sequence of synthetic steps.

A few examples of synthetic intranuclear azasteroids according to the position of nitrogen(s) in the ring system are given below (section 6]) after a brief overview about natural azasteroids and synthetic extranuclear azasteroids.

4] Azasteroids of natural origin.[125b,130]

The more prominent are extranuclear azasteroids. Different extranuclear azasteroids related to certain glycosides have been isolated as aglycones released with sugars by acid hydrolysis of these glycosides. Hence, solanidine[125b] (98) (scheme 96) from solanine, tomatidine from tomatine and rubijervine have been reported.

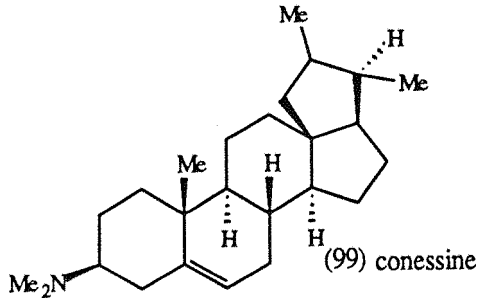


(98)

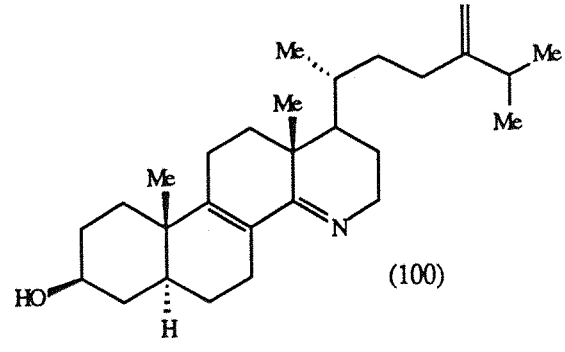
Scheme 96

A group of intranuclear azasteroids from *holarrhena* species based on conarrhimine, conkurchine and funtumine have been used in India for treatment of amoebic dysentery.

Two other *holarrhena* categories of azasteroids are derived from conarrhimine and holarrhimine, the former including conessine[125b] (99) (scheme 97) known for its anti-amoelsic activity and conessidine. Another interesting group such as (100) has shown a high anti-fungal activity[130a].



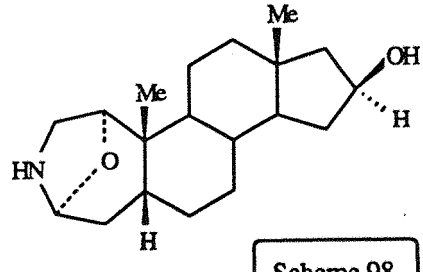
(99) conessine



(100)

Scheme 97

The main intranuclear azasteroids of natural origin have been isolated from salamanders and include samandarine[130a] (101) (scheme 98) which is a central nervous system convulsant and the related moieties samandarone and samamine.



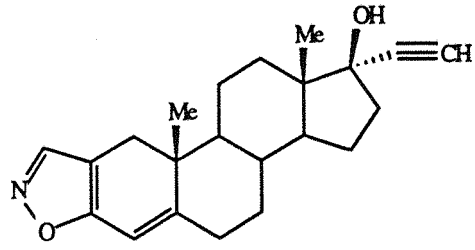
(101) samandarine

Scheme 98

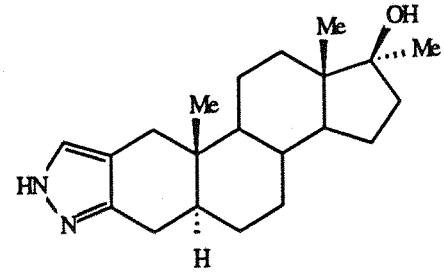
Finally, chelidonine first isolated in 1839 has shown important cytotoxic properties and has been synthesized many times (section 6]).

5] Synthetic extranuclear azasteroids.[130]

Danazol[130j] (102) (scheme 99) discovered in 1963 by Sterling-Winthrop has been a drug of interest mainly for its anti-fertility activity.The same group has also studied the anabolic agents stanozolol[130f] (103) and furazabol[130g] which act on coagulo-fibrinolytic systems and thus may be used clinically.



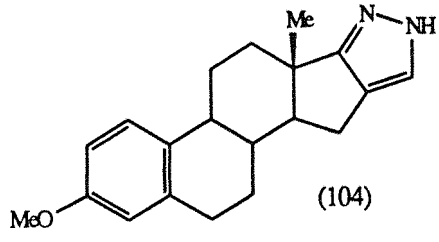
(102) danazol



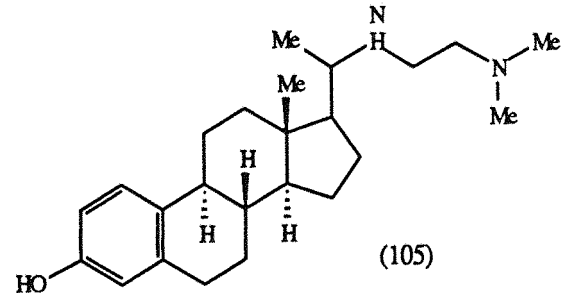
(103) stanozolol

Scheme 99

Pyrazole derivatives like (104) (scheme 100) have shown hypo-cholesterolemic activity equal to that of oestradiol[130m], while (105) has exerted hyper-cholesterolemic effects[128].



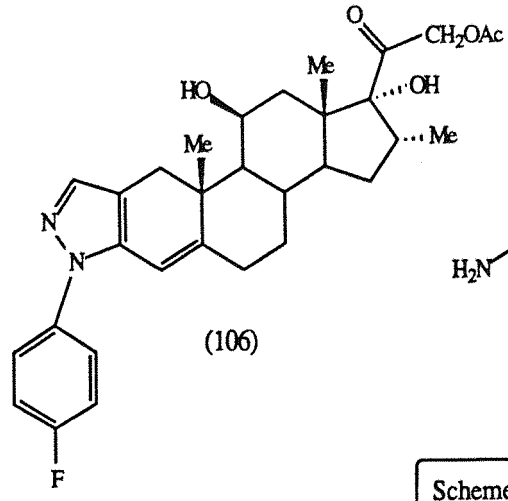
(104)



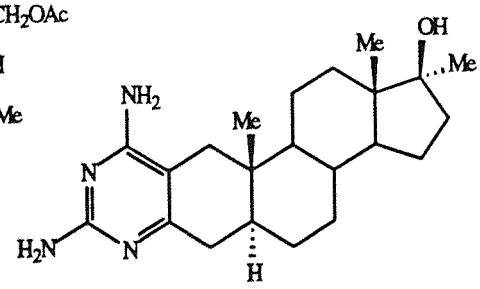
(105)

Scheme 100

A steroidal [3,2-c] pyrazole like (106) (scheme 101) which has the corticosteroid structure has been investigated as a potent anti-inflammatory agent[130d]. Finally, certain steroidal diamino-pyrimidines such as (107) have appeared[130q] interesting for their anti-microbial activity.



(106)



(107)

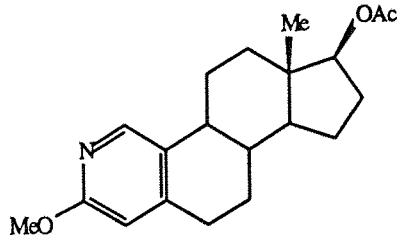
Scheme 101

6] Synthetic intranuclear azasteroids.

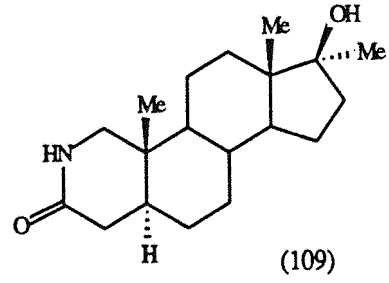
A short list of examples of extranuclear azasteroids prepared by total or partial synthesis is given below according to the position of nitrogen(s) in the tetracyclic system. It covers this area and outlines that only a small number of 9-, 11- and 12-azasteroids have been reported so far in comparison with 4-, 6- and 8-azasteroids.

a/ Nitrogen in ring A (positions 1, 2, 3, 4, 5 and 10).

The 2-azaisosteres (108)[130b] of the natural hormone estradiol and (109)[130e] of the anabolic agent oxandrolone used for muscle development in athletes have been synthesized, scheme 102.



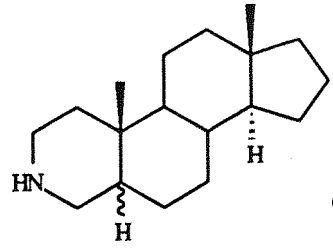
(108)



(109)

Scheme 102

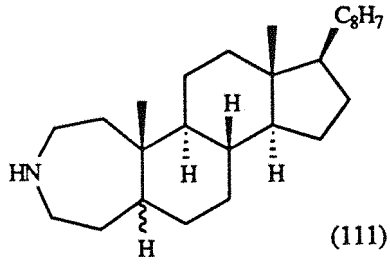
The 3-aza-5α- and 5β-androstanes (110) (scheme 103) were obtained[131] by Shoppee and Krueger in 1961.



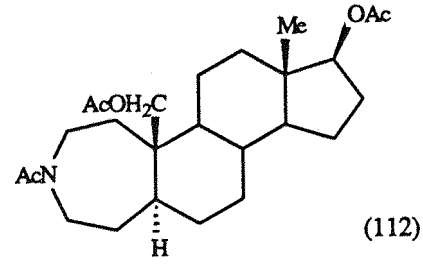
(110)

Scheme 103

Many synthetic 3-azasteroids are characterized by a seven-membered ring A as in 3-aza-A-homo-cholestane (111) prepared by Shoppee and Sly[132] in 1958 and also the anaesthetic agent (112)[130o], scheme 104.



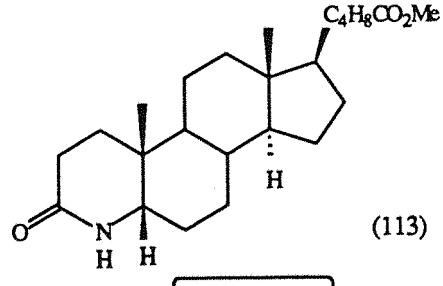
(111)



(112)

Scheme 104

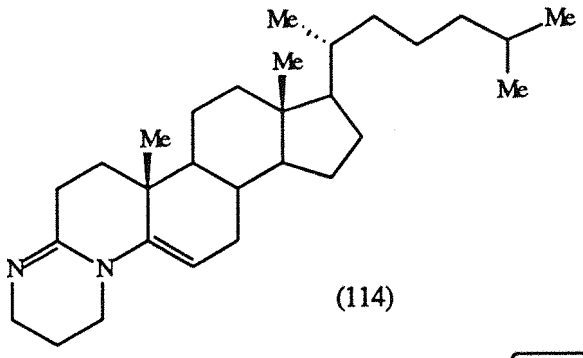
Hara's and Shoppee's groups synthesized around 1960 3-oxo-4-aza-5β-cholanate (113)[133] (scheme 105) and 4-aza-A-homo-androstanes respectively.



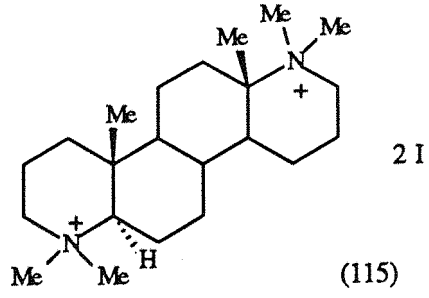
(113)

Scheme 105

Other 4-azasteroids have been more recently reported. Thus (114) has been studied[130l] as a potential hypotensive agent while the chandonium iodide (115) has shown[130n] some neuromuscular blocking effects, scheme 106 .



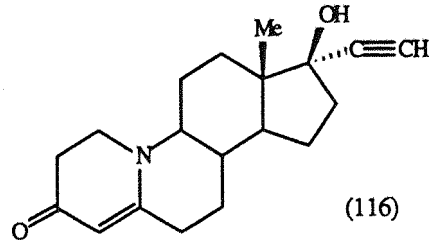
(114)



(115)

Scheme106

Finally, the 10-azasteroid (116) (scheme 107) has shown[130i] an equal activity to progesterone as an anti-LH compound.

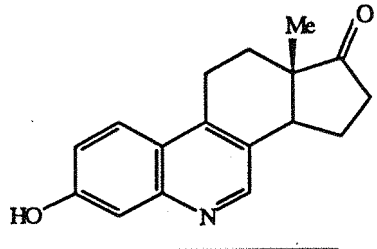


(116)

Scheme 107

b/ Nitrogen in ring B (positions 6, 7, 8 and 9).

Different 6-azaisosteres of natural hormones have been investigated like 6-azaequilenin (117) (scheme 108) or 6-azaestradiol methyl ester.

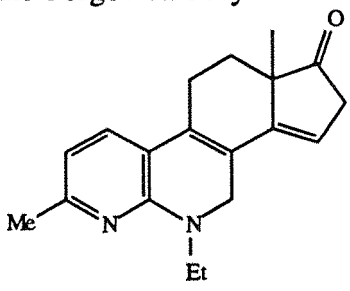


(117)

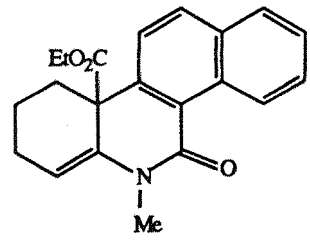
Scheme 108

Artus et al studied[135] in 1973 the synthesis of 4,6-diazasteroids such as (118), scheme 109. In 1976, Ninomiya's group utilized[136] a photocyclisation of enamides leading to benzo[i]-

phenanthridines like (119) related to 6-azasteroids. A number of 6-azasteroids have also been provided via the Torgov carbocyclic steroid synthesis[128].



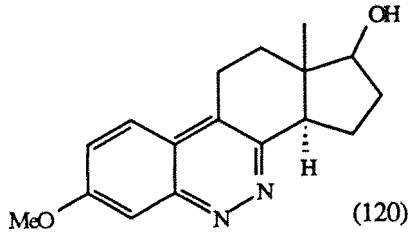
(118)



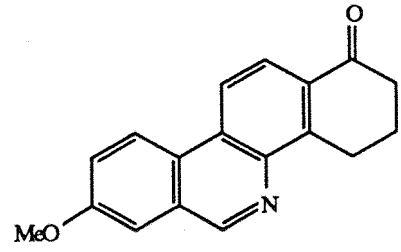
(119)

Scheme 109

Rare 7-azasteroids have been reported. Some analogs of estrogenic hormones like the 6,7-diazasteroid (120) have been prepared[128] by condensations of suitable dienamines, scheme 110. In 1973, 3,4-dihydro-8-methoxy-benzo[c]-phenanthridin-1(2H)-one (121) was obtained[137] via a benzyne cyclisation reaction.



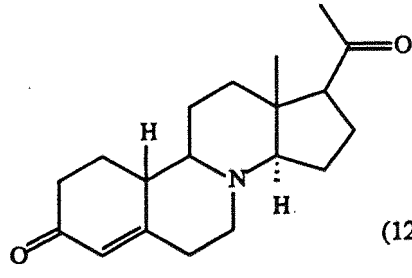
(120)



(121)

Scheme 110

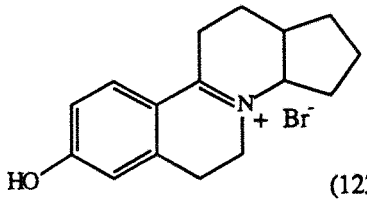
Among others, 8-azaestrogens and 8-aza-19-nor-androgens, 8-azaestrone and 8-aza-19-nor-progesterone (122) (scheme 111) were synthesized in the late sixties by the groups of Brown[138], Meyer[139] and Bowler[140] respectively.



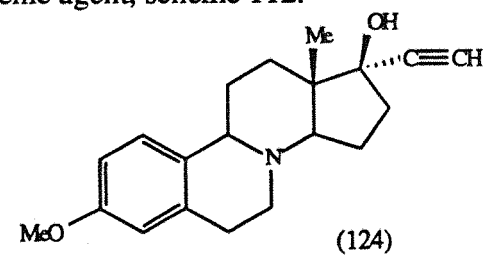
(122)

Scheme 111

A general synthesis of A-aromatic-18-nor-8-azasteroids was demonstrated by Lyle et al [141] in 1975. Besides, some quindonium bromides like (123)[130k] have shown cardiovascular effects, and estrazinol (124)[130h] might be used as an oestrogenic agent, scheme 112.



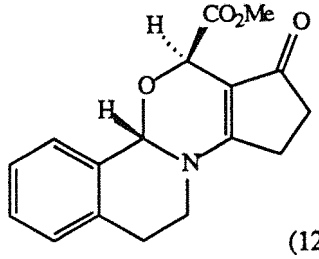
(123)



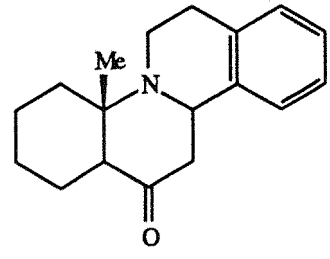
(124)

Scheme 112

Campagna reported[142] in 1986 that several 8-aza-11-oxa-steroid derivatives such as (125) possess good anti-inflammatory, anti-fibrinolytic and membrane stabilizing activities, scheme 113. Finally, an approach to the 9-azasteroid (126) has been developed by Meyer[143], scheme 113.



(125)

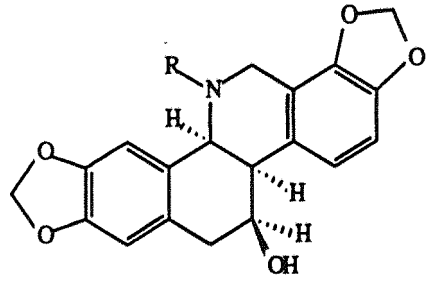


(126)

Scheme 113

c/ Nitrogen in ring C (positions 11, 12, 13 and 14).

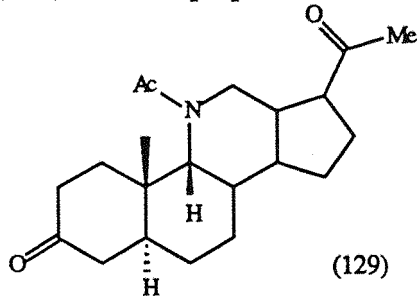
The most well-known 11-azasteroids are probably chelidonine (127) and norchelidonine (128) synthesized many times by different methods[24,144,145], scheme 114.



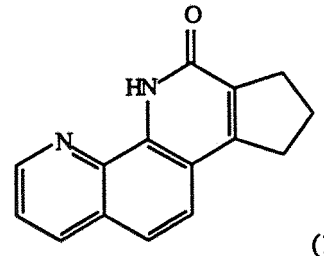
R= Me --> chelidonine (127)
R= H --> norchelidone (128)

Scheme 114

Saturated N-acyl-11-aza-5a-9β-pregnane-3,20-dione (129)[146] (scheme 115) andthe 1,11-diaza-steroid (130)[147] were prepared in the mid-seventies.



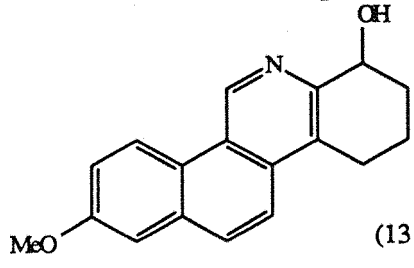
(129)



(130)

Scheme 115

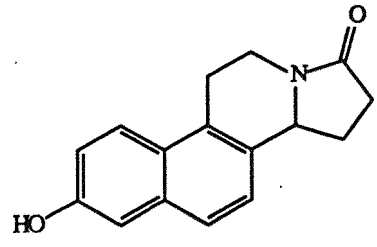
7-Hydroxy-2-methoxy-7,8,9,10-tetrahydrobenzo[i]-phenanthridine (131) has been investigated by Kessar[148] as a potential intermediate for 12-azaequilenine, scheme 116.



(131)

Scheme 116

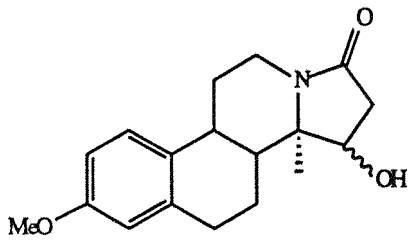
In contrast, the area of 13- and 14-azasteroids has been widely illustrated. Kessar's group has thus prepared 13-aza- (132)[149] and 13-aza-15-thia[150] -18-nor-equilenine, scheme 117. Some 8,13-diazasteroid have shown an analgesic activity.



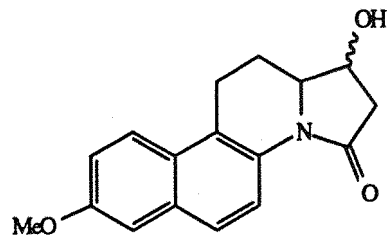
(132)

Scheme 117

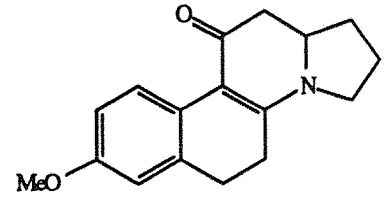
The 13- and 14-azaequilenine skeletons (133) and (134) respectively have been provided by a Diels-Alder reaction[128], while the 14-azasteroid (135) has been approached via an intramolecular cyclisation of enamine esters[128], scheme 118.



(133)



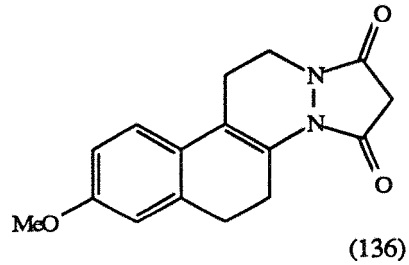
(134)



(135)

Scheme 118

Pandit, Evers and Huisman have developed[128] a pathway to 13,14-diazasteroids such as (136) by a condensation reaction with hydropyridazines, scheme 119.

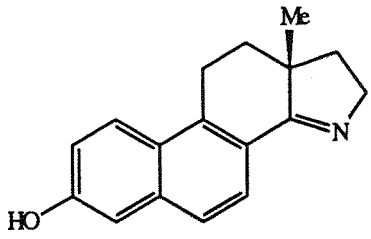


(136)

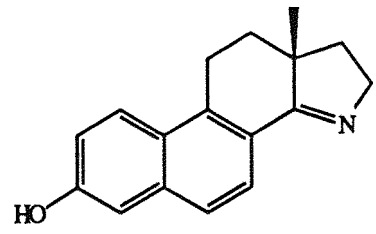
Scheme 119

d/ Nitrogen in ring D (positions 15, 16 and 17).

The synthetic 15-azasteroid (137) has shown[130p] the interesting characteristic of reducing transport into the cells of macromolecular species, proteins, DNA and RNA, while the 15-azasteroid (138), 1,10,11,11a-tetrahydro-11a-methyl-2H-naphth[1,2-g]-indol-7-ol, was reported[151] in 1976 as a potent blocking agent of cell permeability and mitochondrial respiration, scheme 120.



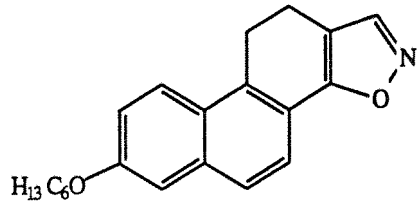
(137)



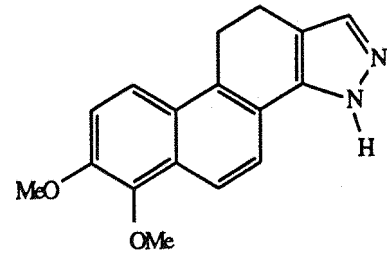
(138)

Scheme 120

Certain pyrazolo and isoxazolo steroids such as the 16-aza-15-oxa-steroid (139) and 15,16-diazasteroid (140)[130p] (and related compounds) possess some antimicrobial activity, scheme 121.



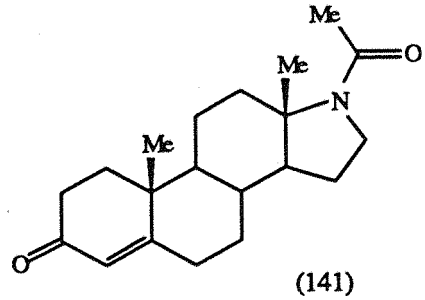
(139)



(140)

Scheme 121

Finally, the isosteres of hormones 17-azaprogesterone (141)[130c] and 16-azaestrone methyl ester have been prepared, scheme 122.



(141)

Scheme 122

[B] PROPOSED PROGRAMME.

The earlier results of Merriman[123] suggest that the chemistry of aza Diels-Alder reactions reported by Grieco et al might be generalized. The efficiency of these reactions appears to be controlled in part by substituent effects. Increased electron deficiency in the azadiene moiety facilitates reaction. Complications in the desired pathway are possible such as secondary cycloaddition reactions and a separate reaction pathway involving electrophilic substitution with formaldehyde.

In the synthetic programme described in this thesis two major amine substrates have been used- bicyclic amines having the naphthalene or indane skeleton and amino-anthraquinones. The objectives in studying cycloadditions based on these substrates have been on the one hand to generalize the aza Diels-Alder reaction and on the other hand to make accessible interesting classes of novel compounds such as azasteroids. In investigating these additions the relative importance of alternative pathways has been assessed.

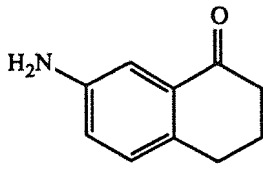
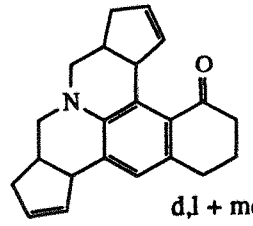
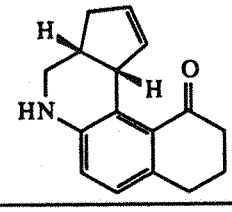
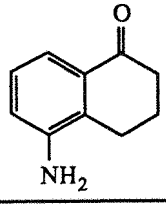
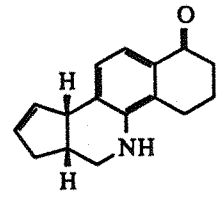
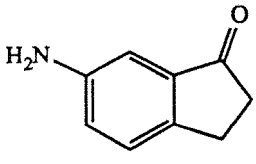
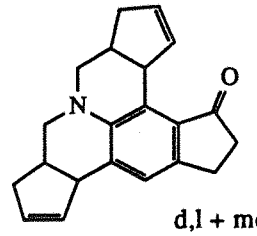
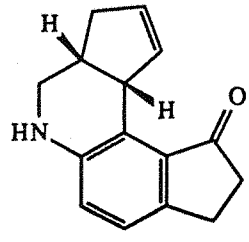
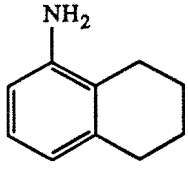
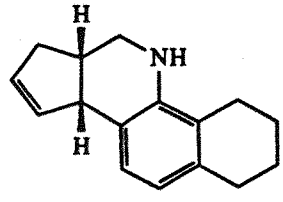
[C] USE OF BICYCLIC AROMATIC AMINES AS SUBSTRATES.

I] Presentation.

The table below (scheme 123) covers all the results obtained in the area of bicyclic aromatic amines related to naphthylamines or indanamines. Two main types of starting amines were investigated: these having an aliphatic side ring (entries 1-17) and those which were fully aromatic (entries 18-23).

Several basic remarks can be already made:
-> reactions from fully aromatic starting amines were less successful than those from amines having an aliphatic side ring.
-> the dicyclisation adducts were afforded in better yields than the examples of monocyclisation.
-> the size of the aliphatic side ring (five or six membered) did not interfere with the outcome of the cyclisations.
-> within the series of amines having an aliphatic side ring, the non ketonic examples underwent the expected cycloadditions either in a lower yield or without regioselectivity compared to the corresponding amino-ketones.

Results obtained with bicyclic aromatic amines are subdivided according to whether the side ring is aliphatic or aromatic. Two model experiments of monocyclistion and dicyclisation will be fully detailed initially. Further examples will then be described more briefly. The relationship of structure of the amine to the efficiency of cyclisation will be analysed, and pathways leading to by-products

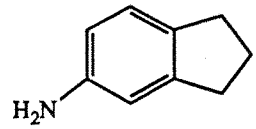
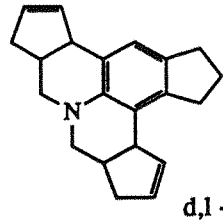
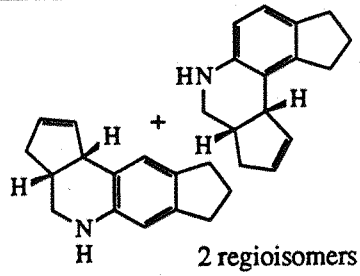
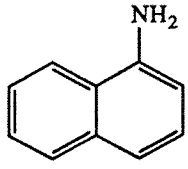
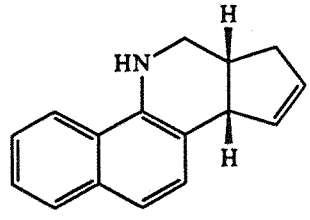
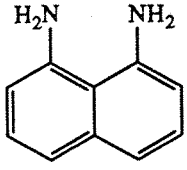
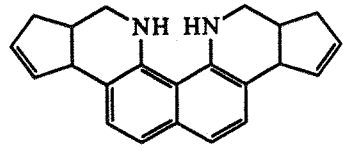
Entry	Starting amine	Type[1]	Reaction conditions[2]	Diels-Alder adduct(s)	Yield[3]
1		di	1 / 1 / 3.4 / 3.4 r. T. , 4.5 h	 d,l + meso	86 % (43 + 12)
2		di	1 / 2 / 2 / 2 r. T. , 1 h		83 % (65 + 18)
3		mono	1 / 1 / 1 / 1 r. T. , 16 h		37 %
4		mono	1 / 1 / 1 / 1 r. T. , 35 min		64 %
5		mono	1 / 1 / 1 / 1 r. T. , 16 h		0 %
6		mono	1 / 1 / 1 / 1 r. T. , 35 min		65 %
7		di	1 / 2 / 2 / 2 r. T. , 1.5 h	 d,l + meso	88 % (74 + 14)
8		di	1 / 2 / 2 / 2 r. T. , 35 min		89 % (59 + 10)
9		mono	1 / 1 / 1 / 1 r. T. , 35 min		39 %
10		mono	1 / 1 / 1 / 1 r. T. , 2 h		45 %
11		mono	1 / 1 / 1 / 2 reflux , 45 min		43 %
12		mono	1 / 1 / 1 / 1 r. T. , 35 min		0 %
13		mono	1 / 1 / 1 / 1 0°C , 20 min		38 %

1] di= dicyclisation ; mono= monocyclisation.

2] respective ratios of starting amine / TFA / formaldehyde / cyclopentadiene
reaction temperature, reaction time.

3] obtained after isolation of the Diels-Alder adduct(s) by flash chromatography. For two separated diastereoisomers d,l and meso, the yields after isolation are indicated (d,l % + meso %) respectively.

Table .../....

Entry	Starting amine	Type[1]	Reaction conditions[2]	Diels-Alder adduct(s)	Yield[3]
14		di	1 / 2 / 2 / 3 r. T. , 15 min	 d,l + meso	29 % (12 + 6)
15		di	1 / 2 / 2 / 3 ~0°C , 2.5 h		71 % (58 + 13)
16		mono	1 / 1 / 1 / 1 0°C , 45 min	 2 regioisomers	9 %
17		mono	1 / 1 / 1 / 1 -10<T<0°C , 4 h		68 %
18		mono	1 / 1 / 5 / 5 r. T. , 3 h		0 %
19		mono	1 / 1 / 1 / 2 r. T. , 35 min		16 %
20		mono	1 / 1 / 1 / 2 0<T<5°C , 35 min		20 %
21		dble mono	1 / 2 / 2 / 2 r. T. , 35 min	 d,l + meso	3 %
22		dble mono	1 / 2 / 2 / 2 0<T<10°C , 10 min		0 %
23		dble mono	1 / 0 / 2 / 3 r. T. , 12 h 40<T<80°C , 7 h		0 %

1] di= dicyclisation ; mono= monocyclisation ; dble mono= double monocyclisation.
2] respective ratios of starting amine / TFA / formaldehyde / cyclopentadiene
reaction temperature, reaction time.
3] obtained after isolation of the Diels-Alder adduct(s) by flash chromatography. For two separated diastereoisomers d,l and meso, the yields after isolation are indicated (d,l % + meso %) respectively.

Scheme 123: table of the results obtained with bicyclic amines.

will be suggested through the particular case of 1-amino-naphthalene.

II] Bicyclic aromatic amines having an aliphatic side ring.

1] Choice of substrates.

As shown in the previous table (scheme 123), the main category of starting amines investigated in this area were aromatic amino ketones having the α-tetralone skeleton or the coresponding five membered nucleus of α-indanone. We focused our attention on 5- and 7-amino-α-tetralones and 6-amino-α-indanone (142), (143) and (144) respectively (scheme 124) which were readily available by nitration of α-tetralone (145) and α-indanone (146) respectively followed by subsequent reduction. Only monocyclisation was likely in the case of 5-amino-α-tetralone while the two other amines could undergo both mono- and dicyclisation processes.

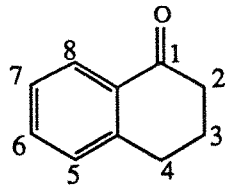
The corresponding non ketonic amines, 1-amino-5,6,7,8-tetrahydro-naphthalene and 5-amino-indane were examined to show the role of a carbonyl group in the side ring.

2] Preparation of the starting amines.

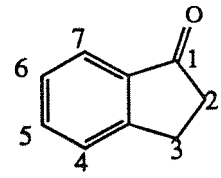
Details of the preparation of starting bicyclic amines are indicated in scheme 124 below. The procedures and analyses of the different species are detailed in the supplementary experimental section (chapter 3).

The nitration of α-tetralone was carried out by using the method of Von Braun[152], in fuming nitric acid at low temperature. This procedure provided 5- and 7-nitro-α-tetralones (147) and (148) (scheme 124) with the latter as major isomer. The electron withdrawing effect of the carbonyl group directed the nitration to the two meta positions. The additional effect of the hydrocarbon chain favouring mainly the para position confirmed the predominant occurrence of the overall electrophilic substitution at the 7-position. 7-Nitro-α-tetralone was partially isolated by simple recrystallization of the crude mixture but flash chromatography was required to separate completely the minor and less polar 5-nitro-isomer. No significant by-product was observed but some starting material was always recovered. The yields of the isolated components ranged from 30 to 70 %. The success and the regiochemical outcome of this procedure seemed to be linked closely to both the potency of the nitric acid and the reaction temperature.

Since the same method had not been applied to the nitration of α-indanone, the procedure described by Ingold and Pigott[153] using concentrated sulphuric acid and potassium nitrate was utilized. The minor 4-nitro-α-indanone (149) was supposed to be afforded in a relative ratio of 1 : 6 with respect to the 6-nitro-isomer (150). However no by-product was isolated alongside



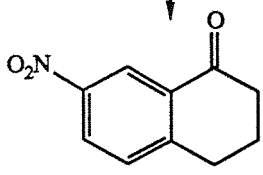
(145)



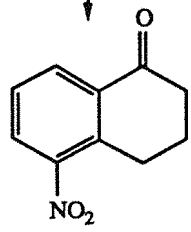
(146)

Fuming HNO_3

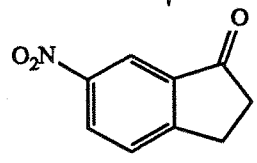
KNO_3, conc. H_2SO_4



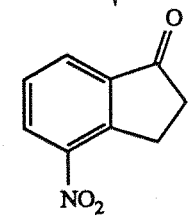
(148)



(147)



(150)

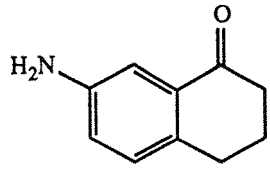


(149)

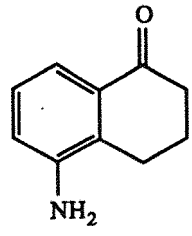
-10<T<-5°C, 1 h 30 min	47 %	+	24 %	=	71 % (66:34)
-12<T<0°C, 2 h 15 min	28 %	+	9 %	=	37 % (75:25)
-12<T<-10°, 1 h 10 min	40 %	+	4 %	=	44 % (90:10)

60 %	+	0 %	0<T<10°C	2 h
71 %	+	0 %	0<T<10°C	4 h 30 min

Fe (4 eq)
AcOH
H_2O
70<T<90°C

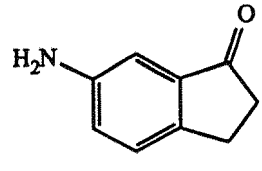


(143)

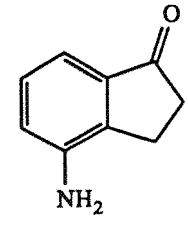


(142)

Fe (4 eq)
AcOH
H_2O
70<T<90°C



(144)



2 h 30 min	78 %
2 h 15 min	87 %
1 h	77 %

1 h 30 min	73 %
50 min	85 %

70 %	1 h 40 min
76 %	2 h 20 min
57 %	55 min

Scheme 124: Preparation of the starting amines

6-nitro-α-indanone and some recovered starting material.

The reductions of all the above nitro compounds to the corresponding amines were carried out with iron powder in glacial acetic acid and water at about 80 °C, as described in the literature[154]. The reduction process required for each molecule of nitro component the transfer of six electrons provided by the reducing agent. Since Fe is oxidized into Fe^{3+} releasing three electrons ($Fe \rightarrow Fe^{3+} + 3\ e^-$), at least two equivalents of iron were necessary with respect to the nitro compound; four equivalents were usually used in our reductions, which led to the amines in high yields (~ 80 %). No by-product such as nitroso intermediates or other derivatives were observed.

Stannous chloride has been often employed with concentrated hydrochloric acid in ethanol as an efficient reducing agent of nitro components[155]. Therefore this procedure was also examined with 7-nitro-α-tetralone and provided the amino derivative in 63 % yield. Apart from the lower yield observed in comparison with the iron-based method, the use of tin afforded complexes which were difficult to break down. The iron-based procedure was preferred for its higher efficiency.

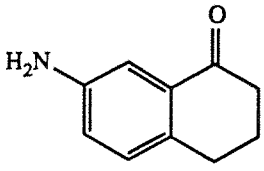
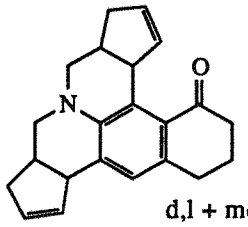
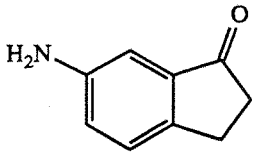
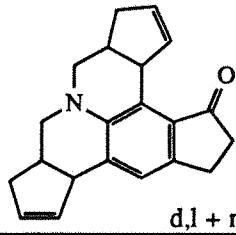
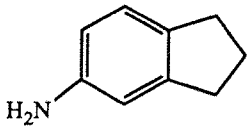
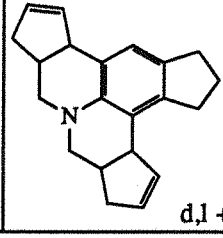
3] Dicyclisations.

The work of Grieco describes mainly dicyclocondensation adducts obtained with formaldehyde, and monocyclisation adducts afforded with benzaldehyde as aldehyde via the in situ generated Schiff base (scheme 84). Therefore amines "meta" with respect to the side ring were investigated first in the dicycloaddition process so as to be able to recognize the two dicyclisation diastereoisomers which might be obtained as by-products when studying the corresponding monocyclisation.

a/ Results.

The results of dicyclisations are summed up in the following table (scheme 125).

In a first attempt of dicyclocondensation of 7-amino-α-tetralone (143) at room temperature, an excess of reagents (3.4 equivalents of formaldehyde and cyclopentadiene) was used along with a 4.5 hour reaction time. Hence two pure compounds less polar than the starting material were fully separated by flash chromatography on silica gel in an 86 % overall yield. Mass spectra of both yellow solids gave the desired molecular ion (M^+(100%)= 317). Thus the major less polar component and the minor more polar component were separated in 43 and 12 % yields (relative ratios 78:22) respectively. They were proved to be the two diastereoisomers (151) and (152) (scheme 126) spectroscopically. The 270 MHz ^1H NMR spectrum showed an aromatic singlet at about 7.0 ppm, three different types of olefinic protons, three or four different types of protons of tertiary carbons and no amino proton. The ^{13}C spectra showed the correct numbers of carbons of

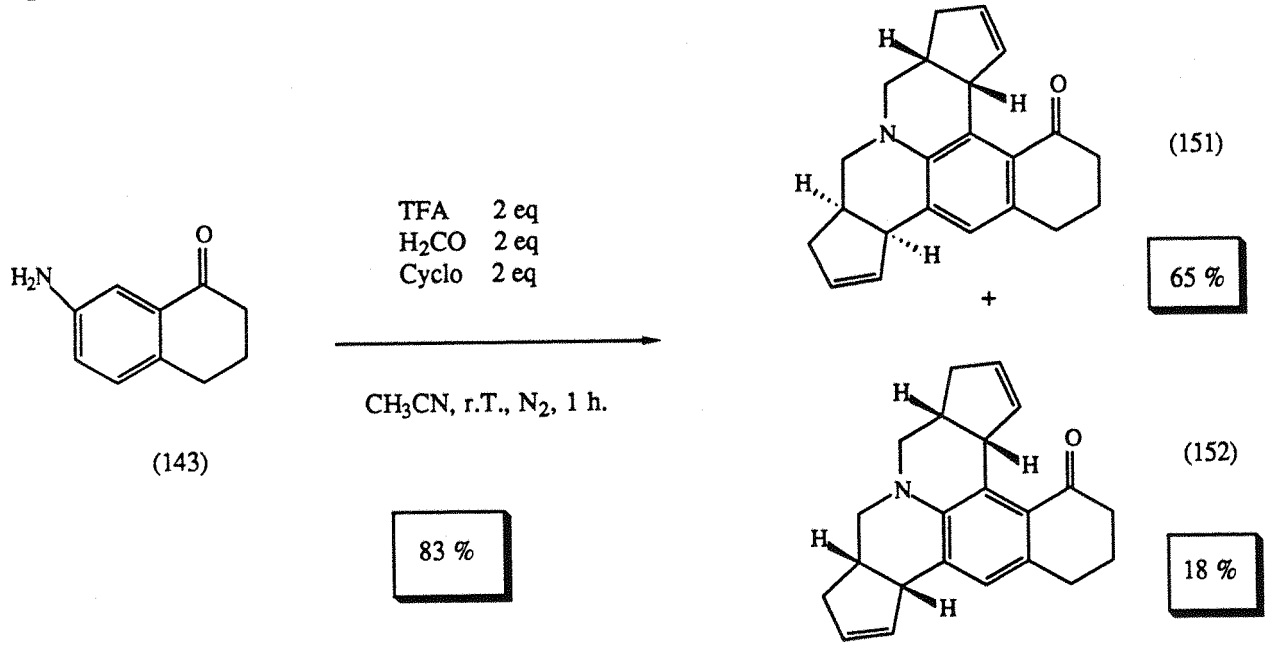
Entry	Starting amine	Reaction conditions[1]	Diels-Alder adducts	Yields[2]			Ratios[3]
				d,l	meso	overall	d,l : meso
1		1 / 1 / 3.4 / 3.4 r. T. , 4.5 h	 d,l + meso	43	12	86	78 : 22
2		1 / 2 / 2 / 2 r. T. , 1 h		65	18	83	78 : 22
3		1 / 2 / 2 / 2 r. T. , 1.5 h	 d,l + meso	74	14	88	84 : 16
4		1 / 2 / 2 / 2 r. T. , 35 min		59	10	89	85 : 15
5		1 / 2 / 2 / 3 r. T. , 15 min	 d,l + meso	12	6	29	66 : 34
6		1 / 2 / 2 / 3 ~0°C , 2.5 h		58	13	71	82 : 18

1] Respective ratios of starting amine / TFA / formaldehyde / cyclopentadiene
reaction temperature, reaction time.
2] Overall yield after isolation by flash chromatography; yield of each diastereoisomer after isolation.
3] Calculated from the separated diastereoisomers.

Scheme 125: tables of the results of dicyclisation from bicyclic amines.

each category with compatible chemical shifts while the IR spectra had peaks around 2800-3100 cm^{-1} for C-H, a strong peak at about 1670 cm^{-1} for C=O and no broad band at about 3300 cm^{-1} for N-H. On likely steric grounds, the major fraction was assigned to the "d,l" isomer (151) and the minor to the "meso" (152). This point will be further discussed later, but one can here mention that Grieco had proven such a distribution by single-crystal X-ray analysis of the pentacyclic adducts afforded from simple anilines.

This reaction was further studied to find out wether such a good result could be achieved by observing a far shorter reaction time and by avoiding the use of excess of reagents. Hence the dicyclisation of 7-amino-α-tetralone with TFA, formaldehyde and cyclopentadiene was carried out in respective ratios 1/2/2/2 at room temperature for 1 hour and provided in 83 % overall yield the same diastereoisomers (151) and (152) which were completely separated in 65 % and 18 % respective yields (relative ratios 78:22).

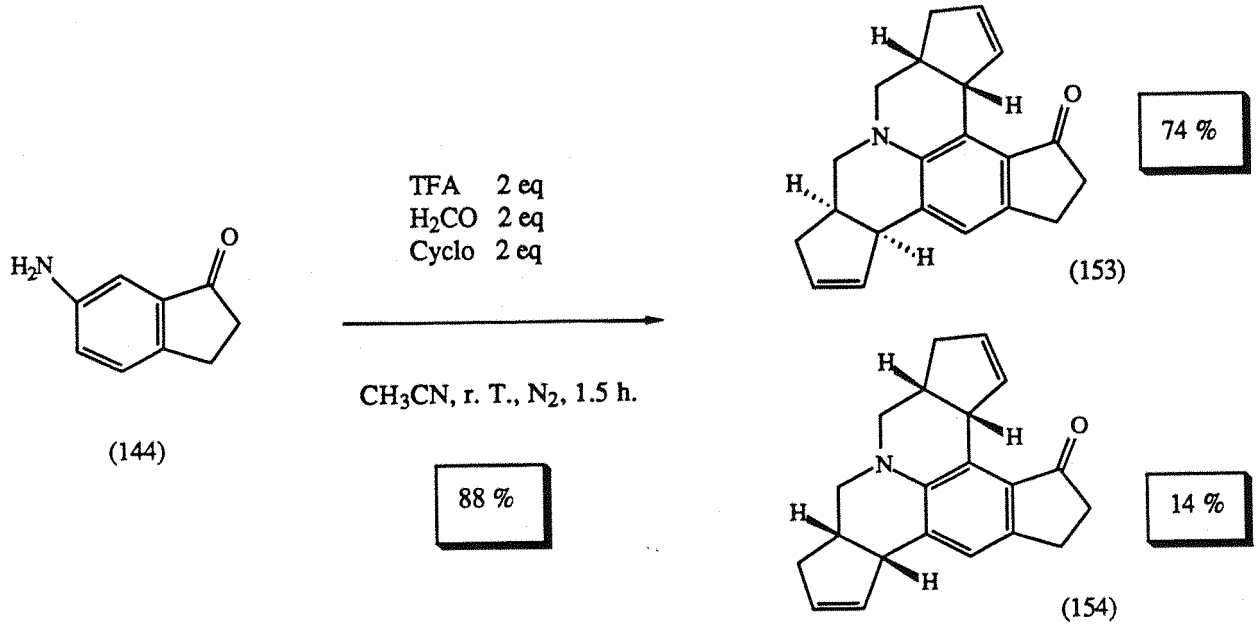


Scheme 126

The dicyclisation of 6-amino-α-indanone (144) was approached under the same successful conditions as those for 7-amino-α-tetralone, with TFA/formaldehyde/cyclopentadiene in respective ratios 1/2/2/2 at room temperature for 1.5 hour. It led in 88 % overall yield to the two diatereoisomers d,l (153) and meso (154) (scheme 127) which were fully separated in 74 % and 14 % respective ratios (relative ratios 84:16).

A further experiment carried out under the similar conditions but using a shorter reaction time (

35 minutes) provided in 89 % overall yield the same two ketonic julolidines (153) and (154) separated in 59 and 10 % yields respectively (relative ratios 85:15), which confirmed the high reactivity of the dicyclisation process from amino-ketones.



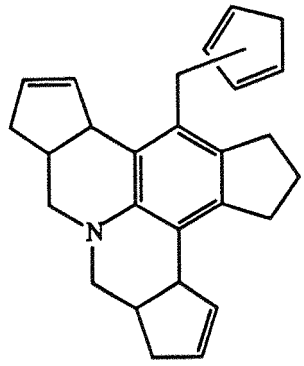
Scheme 127

The investigation of the same double cyclisation of the related 5-amino-indane appeared very attractive for a better understanding of the potential role of the carbonyl group in these cyclisations.

In a first attempt, the double cyclocondensation of 5-amino-indane (155) (scheme 129) was carried out with TFA/formaldehyde/cyclopentadiene in respective ratios 1/2/2/3 at room temperature and with a very short reaction time. Flash chromatography of the crude reaction product which had quickly turned dark green allowed the separation of four main fractions. The two less polar compounds were unambiguously assigned to the diastereoisomers d,l (156) and meso (157) (scheme 129) separated in 12 and 6 % yields respectively. The third fraction was a mixture of both, which implied a poor 29 % overall yield. Surprisingly, a fourth fraction was isolated in 9 % yield. In view of its mass spectrum (367 (100%), 303 (7), 289 (18)), a further reaction of the dicyclisation adducts (M^+(100%)= 289) involving one equivalent of formaldehyde and one equivalent of cyclopentadiene was suspected to have occurred at the free aromatic position. Therefore the structure (158) (scheme 128) was proposed for the isolated by-product.

Unfortunately, no clear 270 MHz ^1H spectrum was obtained and consequently no conclusion could be stated with regard to the presence or not of an aromatic singlet.

(158)

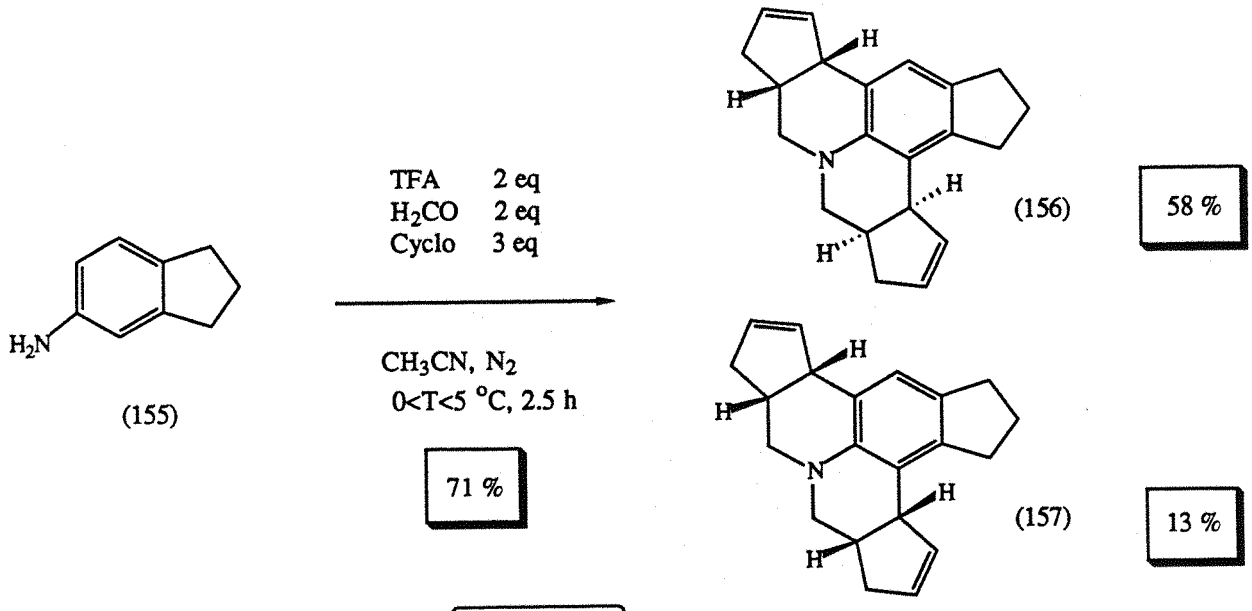


M= 367

Scheme 128

Hence the assignment of structure to this fourth fraction is based only on mass spectral evidence. The suggestion of further reaction by electrophilic attack on the one hand and of decomposition of the crude reaction product on the other hand could explain the rather poor yield of the diastereoisomers (156) and (157).

By a change to less forcing reaction conditions - same ratios of reagents, 2.5 hours but at lower temperature (~0 °C) - the formation of unwanted by-products was largely avoided and the adducts (156) and (157) were completely separated in 58 % and 13 % yields respectively (relative ratios 82:18) giving a 71 % overall yield. Temperature seemed thus to have played a quite selective role in the course of the reaction.



Scheme 129

b/ Conclusion.

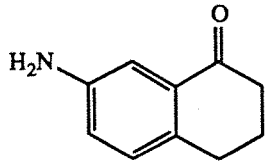
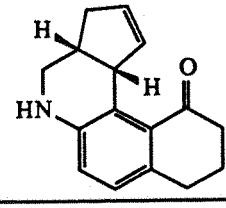
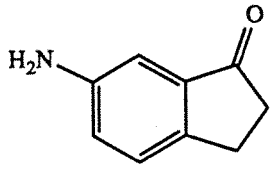
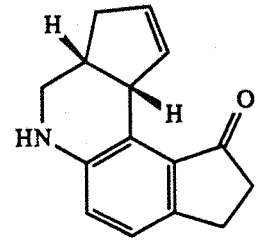
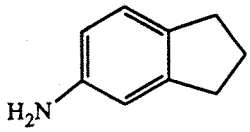
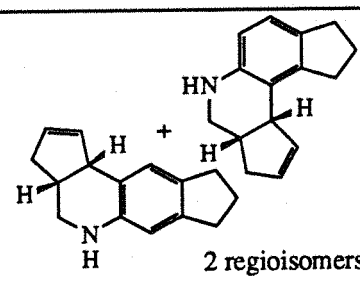
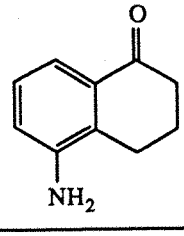
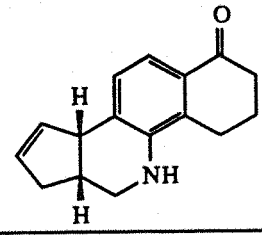
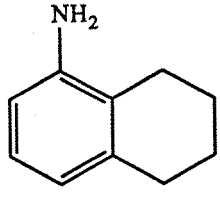
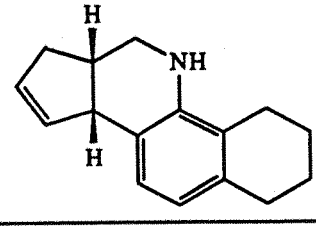
These first examples of double cyclocondensation permitted us to generalize to bicyclic starting amines having an aliphatic side ring the results previously observed by Grieco with simple substituted anilines, with yields ranging from 70 to 90 %. They are smooth reactions providing two diastereoisomers d,l and meso in about 80:20 relative ratios. The amino-ketones gave substantially higher yields than the simple amino-indane. This may be attributed to the effect of the electron withdrawing carbonyl functionality which inhibits further reaction. Such an effect will be described in greater detail in the general conclusion after this discussion.

4] Monocyclisations.

The results of monocyclisations are shown below (scheme 130).

The reactions where the dicyclisation process could compete with the desired monocyclisation mode (entries 1-7) are first reported. The monocyclisations of the amines "ortho" to the side ring (entries 8-11) are discussed in a later section.

a/ Monocyclisations of 7-amino-α-tetralone, 6-amino-α-indanone and 5-amino-indane.

Entry	Starting amine	Reaction conditions[1]	Monocyclisation adduct(s)	Yield[2]
1		1 / 1 / 1 / 1 r. T. , 16 h		37 %
2		1 / 1 / 1 / 1 r. T. , 35 min		64 %
3		1 / 1 / 1 / 1 r. T. , 35 min		39 %
4		1 / 1 / 1 / 1 r. T. , 2 h		45 %
5		1 / 1 / 1 / 2 reflux, 45 min		44 %
6		1 / 1 / 1 / 1 0°C , 45 min	 2 regioisomers	9 %
7		1 / 1 / 1 / 1 -10<T<0°C , 4 h		68 %
8		1 / 1 / 5 / 5 r. T. , 16 h		0 %
9		1 / 1 / 1 / 1 r. T. , 35 min		65 %
10		1 / 1 / 1 / 1 r. T. , 35 min		0 %
11		1 / 1 / 1 / 1 0°C , 20 min		38 %

1] respective ratios of starting amine / TFA / formaldehyde / cyclopentadiene
reaction temperature, reaction time.

2] after isolation by flash chromatography.

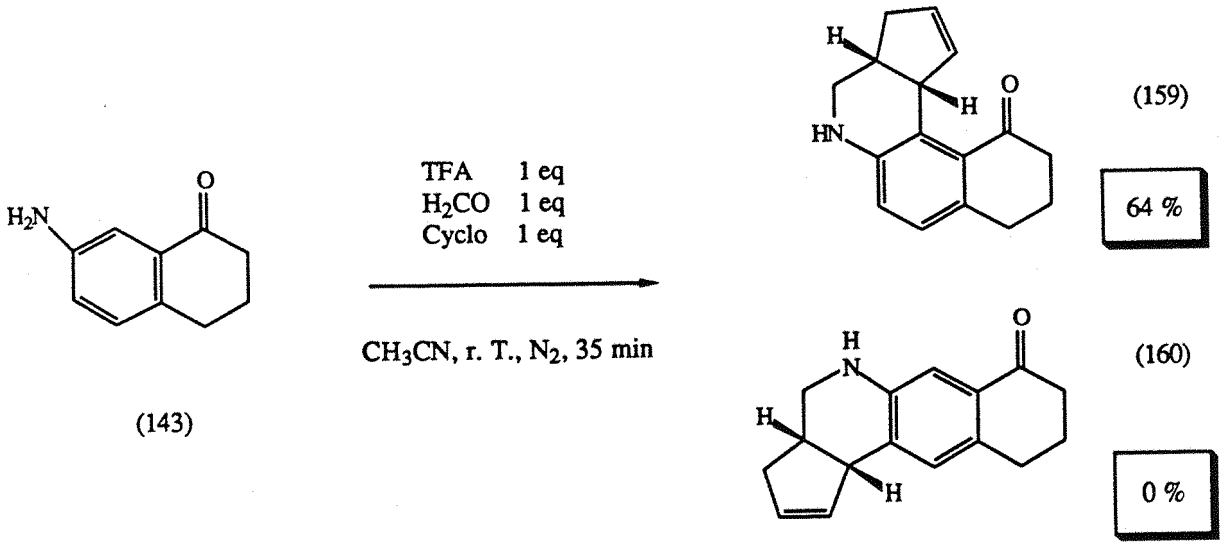
Scheme 130: table of the results of monocyclisation from bicyclic amines having an aliphatic side ring.

The high reactivity of the second cyclocondensation in the presence of excess formaldehyde was demonstrated earlier. Therefore these three reactions were studied with stoichiometric quantities of reagents.

In a first attempt, reaction of 7-amino-α-tetralone (143) with TFA/formaldehyde/cyclopentadiene in respective ratios 1/1/1/1 at room temperature for 16 hours gave two main fractions which were separated and characterized. The less polar fraction was shown by means of comparative t.l.c. and mass spectrum (M^+(100%)= 317) to correspond to a mixture of the two previously reported products of double cyclisation (151) and (152) (scheme 126). These adducts were obtained in 5 % yield. The other more polar compound was unambiguously confirmed to be the regioisomer (159) (scheme 131) isolated in 38 % yield. M^+(100%)= 239, the two clear doublets at 6.69 ppm and 6.90 ppm in the 270 MHz ^1H NMR spectrum and the absence of two significant aromatic singlets which would have corresponded to (160) proved the regioselectivity shown in the monocyclisation process. Besides, the amino group appeared at 3.67 ppm while the N-H vibration was observed at 3340 cm^{-1} in the IR spectrum.

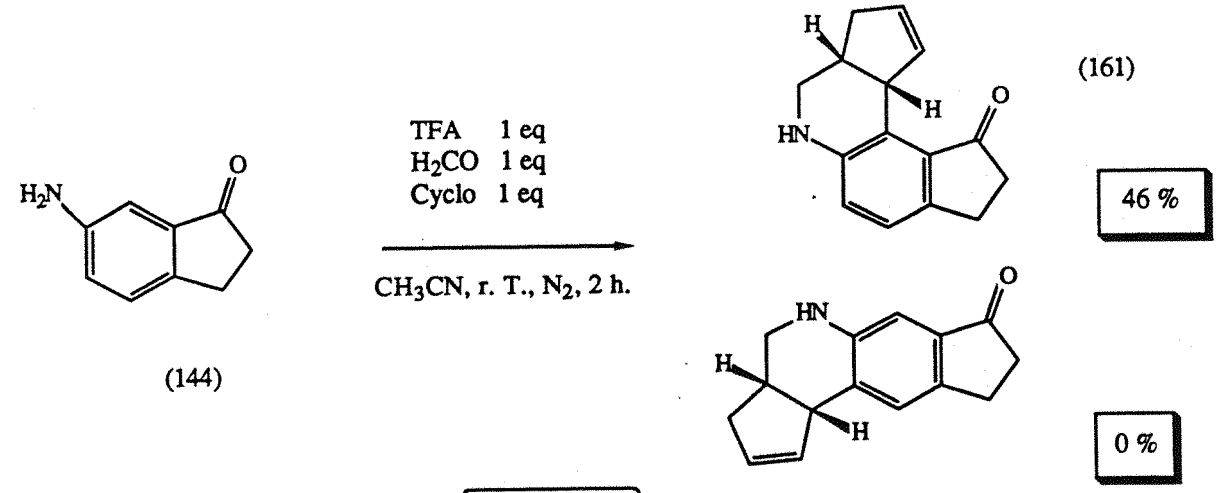
Since a small quantity of starting amine was recovered (<10 %) and the dicyclisation adducts were also obtained in a poor yield, it might be suspected that the poor result was mainly due to further substitution at the free aromatic positions favored by the long reaction time. Indeed, several spots with Rf values lower than that of 7-amino-α-tetralone were clearly noticed on t.l.c. but these compounds were not isolated.

In view of these remarks, the reaction was repeated under the same conditions but using a 35 minute reaction time. Thus (159) was isolated in 64 % yield. some starting material and double condensation products were again observed on t.l.c. .



Scheme 131

Similar behaviour and results were expected from 6-amino-α-indanone (144). The monocyclisation carried out with stoichiometric ratios of reagents at room temperature for 2 hours led to four main fractions among which the two less polar were confirmed (t.l.c., mass spectra) to be the previously investigated dicyclocondensation adducts (153) and (154) (scheme 127) isolated in 19 % and 3 % yields respectively. The major fraction separated was characterized spectroscopically as the regioisomer (161) (scheme 132) and isolated in 46 % yield (M^+(100%)= 225, two clear doublets at 7.07 ppm and 6.80 ppm, the amino proton at 3.89 ppm). Finally the more polar fraction was some recovered starting amine (19 %).



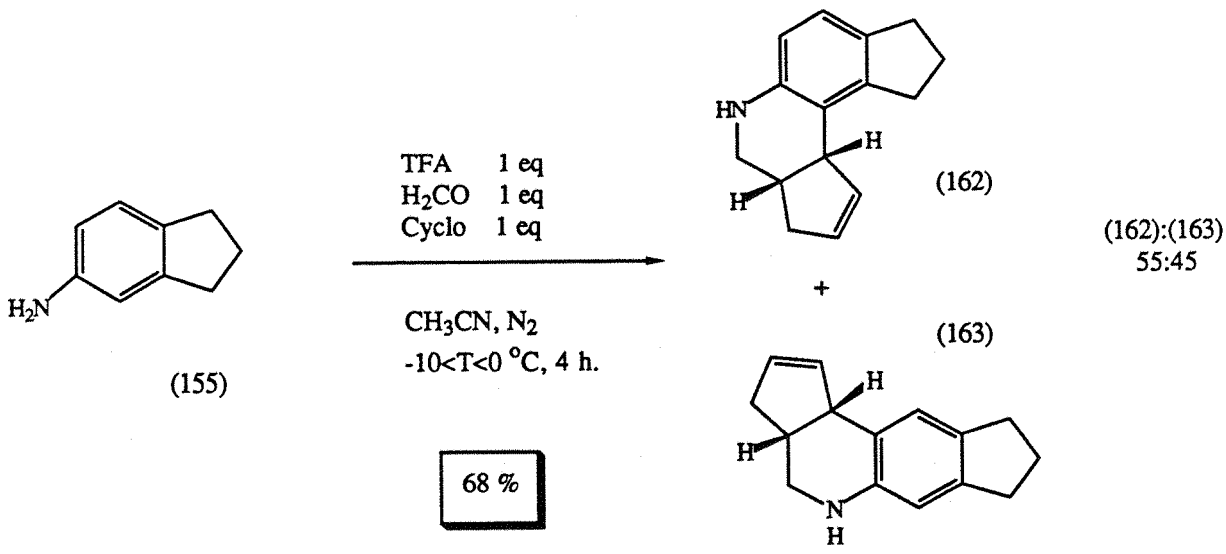
Scheme 132

As in the case of the corresponding dicyclisation, the above experiment was carried out with a heterogenous mixture of the amine salt which was very insoluble in acetonitrile. Considering the previous yields, it was possible that the salt of the monocyclisation adduct was more soluble in acetonitrile than the salt of the starting amine. Hence a second cyclisation might be favoured. Therefore the reaction was repeated with the same ratios of reagents but by warming (25-55 ^{o}C) in 35 minute reaction time. Despite the higher temperature, the initial salt was not fully dissolved. Thus (161) was obtained in 39 % yield while starting amine was recovered in 18 % yield. In a last attempt, the monocyclisation was carried out in 45 minutes at reflux (70-80 ^{o}C) with respective ratios 1/1/1/2 for starting amine, TFA, formaldehyde and cyclopentadiene. In these conditions, the initial amine/TFA salt was completely dissolved. However the desired compound (161) was provided in only a similar yield (44 %).

On the whole, 6-amino-α-indanone behaved like 7-amino-α-tetralone in the monocyclisation process as far as the regioselectivity of the cycloaddition and the reactivity are concerned. In contrast, the reaction course and competitiveness appeared more complex in the former case. It might be explained in terms of relative solubilities of the different salts present in the reaction mixture at room temperature.

The monocyclisation of 5-amino-indane (155) (scheme 133) was carried out with TFA, formaldehyde and cyclopentadiene in respective ratios 1/1/1/1 for 45 minutes at 0 ^{o}C so as to disfavour any further substitution already observed in the dicyclisation process. A pure fraction less polar than starting amine was fully isolated in 9 % yield along with the dicyclisation adducts (2 %). While the mass spectrum of the new compound showed the desired molecular ion (M^{+}(100%)= 211), the clean 270 MHz ^{1}H and 68 MHz ^{13}C NMR spectra revealed it to be the mixture of the two regioisomers (162) and (163) (scheme 133) in relative ratios 57:43 respectively (deduced from the integration curve). Indeed, two aromatic singlets, two aromatic doublets, four distinct types of olefinic protons and twice as many peaks in the ^{13}C spectrum as carbons were noticed. A lower reaction temperature and a longer reaction time could be supposed to disfavour the second cyclocondensation and to improve the regioselectivity of the addition.

The second experiment was carried out again in stoichiometric ratios of reagents but between -10 and 0 ^{o}C for 4 hours. The same oily mixture of (162) and (163) was obtained in 68 % overall yield in relative ratios 55:45 respectively. Further attempts to separate the two regioisomers by chromatography failed.

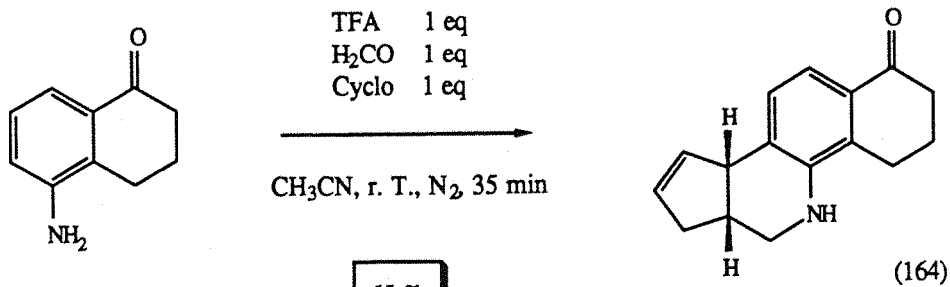


Scheme 133

b/ Monocyclisations of 5-amino-α-tetralone and 1-amino-5,6,7,8-tetrahydro-naphthalene: obtention of 11-azasteroids.

The comparative study of these two cases differing from each other by the presence or not of a carbonyl group in the side ring permitted us to settle whether this functionality activated the simple monocyclisation mode which leads to only one isomer.

The monocyclisation of 5-amino-α-tetralone (142) (scheme 134) was investigated under conditions already known to be successful with the 7-amino-isomer, that is to say with TFA/formaldehyde/cyclopentadiene in ratios 1/1/1/1 at room temperature for 35 minutes. It yielded a crystalline compound whose structure was unambiguously determined and assigned to (164) (scheme 134) by usual analyses (M^+(100%)=239). The desired adduct was completely separated in 65 % yield. Among other features, the two aromatic doublets appeared at 7.48 ppm and 7.15 ppm while they were at 6.90 ppm and 6.69 ppm in the case of the monocyclisation product of 7-amino-α-tetralone. This difference is quite in accordance with the position of the strongly electron-withdrawing carbonyl group wih respect to the aromatic protons.



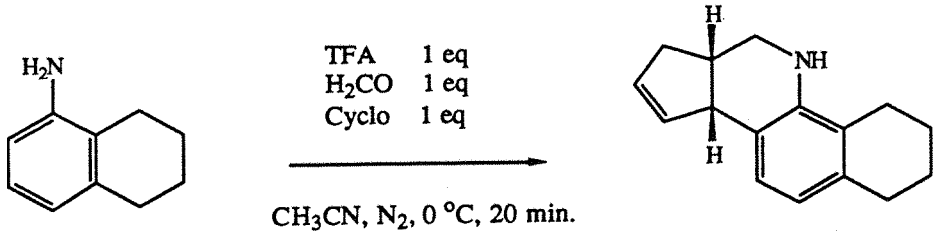
(142) (164)

Scheme 134

The same reaction carried out with a large excess of formaldehyde and cyclopentadiene (5 equivalents) at roomtemperature and for 16 hours led to the isolation of three fractions less polar than starting amine but surprisingly none of them corresponded to (164) on t.l.c. . The complex mass spectra (252 (100%), 317 (10-20), 239 (90)) confirmed the occurrence of further reaction with formaldehyde.

The monocyclisation of 1-amino-5,6,7,8-tetrahydo-naphthalene (165) (scheme 135) was first approached in the classical conditions, with TFA, formaldehyde and cyclopentadiene in stoichiometric ratios at room temperature for 35 minutes. Several spots of equal intensity and more polar than starting amine could be observed on t.l.c., but none of these components was isolated. As in the case of 5-amino-indane, a lower reaction temperature was considered likely to favour the formation of the cycloadducts at the expense of polar by-products.

Therefore, the reaction was repeated but at 0 ^{o}C and for 20 minutes. A minor compound, less polar than the starting material, was fully separated and assigned to the desired structure (166) (scheme 135) in view of its mass spectrum (M^{+}(100%)= 225) and clear ^{1}H and ^{13}C NMR spectra. Some starting amine was recovered in a significant quantity (25 %). No further experiment to improve the poor yield thus obtained (38 %) by using an even lower temperature and a longer reaction time was attempted.



(165) (166)

38 %

Scheme 135

c/ Conclusion.

In view of these monocyclisation results, one could state the strong regiochemical control exerted by a carbonyl group in the side ring as far as the "meta" amines are concerned. Indeed, while the cycloaddition occurred in a regioselective fashion with 7-amino-α-tetralone and 6-amino-α-indanone, the two possible isomers were equally provided by 5-amino-indane.

This functionality seems also to control reactivity. But this assessment requires a further explanation. In the same reaction conditions (stoichiometric ratios, room temperature, ~35 minutes), 6-amino-α-indanone and 5-amino-indane led to quite different yields (scheme 130: entry 3, 39 % and entry 6, 9 % respectively); the same variation was also shown by the "ortho" amines, 5-amino-α-tetralone and 1-amino-5,6,7,8- tetrahydro-naphthalene (entry 9, 65 % and entry 10, 0 % respectively). On the other hand, a decrease of the reaction temperature afforded respectable yields for both 5-amino-indane (entry 7, 68 %) and 1-amino-5,6,7,8-tetrahydro-naphthalene (entry 11, 38 %). These results show that the carbonyl group, by disfavouring any side reaction at room temperature (and activating one cyclisation position for 7-amino-α-tetralone and 6-amino-α-indanone), did increase the reactivity of the monocyclisation mode. It was not observed with non-ketonic amines and consequently by-products were afforded in a major way. But the desired reactivity could as well be obtained by carrying out these reactions at low temperature, as illustrated by 5-amino-indane and 1-amino-5,6,7,8-tetrahydro-naphthalene.

Finally, the dicyclisation adducts were always provided in a minor quantity along with the monocyclisation adduct despite the stoichiometry of reagents observed.

III] Fully aromatic bicyclic amines.

1] Introduction.

The investigation of amino-naphthalenes constituted the closest analogy to the aniline series previously reported. 1-Amino-naphthalene (167) (scheme 137) had the advantage with respect to the 2-amino-isomer of inability to undergo the dicyclisation mode already described. In addition, 2-amino-naphthalene is highly carcinogenic and unsuitable for study. This choice permitted an interesting comparison with the quinoline series developed by Merriman[123] and in particular with 5-amino-quinoline (168) (scheme 138). Moreover, the cyclisation from 1-amino-naphthalene allowed an overall view of the types of by-products which can be afforded in our reactions at the expense of the Diels-Alder adducts. Possible structures for these undesired species will be described. Finally, the related 1,8-diamine (224) (scheme 162) was studied in view of the likely utility of the product.

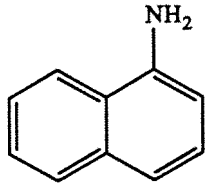
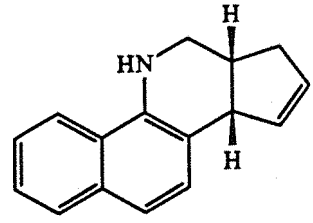
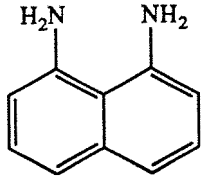
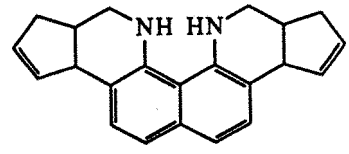
The different results obtained with 1-amino-naphthalene (167) and 1,8-diamino-naphthalene (224) are indicated in the following table (scheme 136).

2] Monocyclisation of 1-amino-naphthalene.

a/ Results.

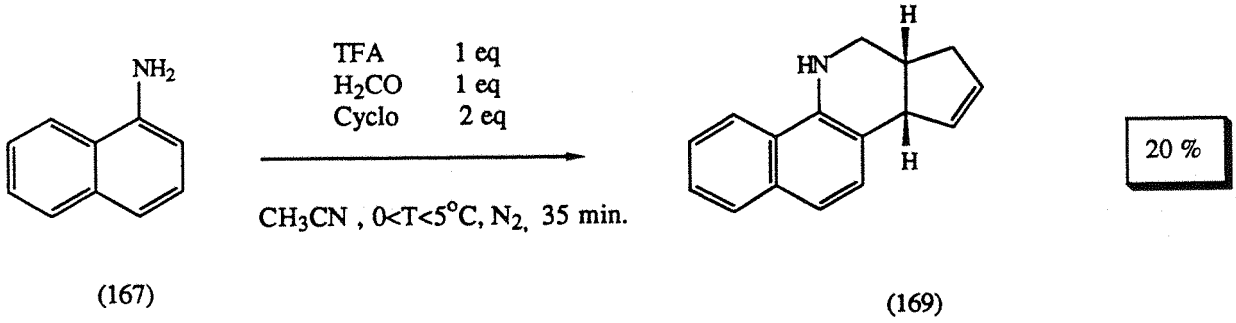
The first attempt of monocyclocondensation of 1-amino-naphthalene (167) (scheme 137) was studied under conditions already known as being successful for 5-amino-quinoline (168) (scheme 138), with ratios 1/1/5/5 for starting amine, formaldehyde and cyclopentadiene respectively at room temperature for 3 hours. Two components were obtained in addition to minor impurities and were partially separated as brown solids. Surprisingly, all these reaction products were more polar than the starting amine. The mass spectra of the two isolated fractions showed 234 (100%), 454 (75) for one fraction and 234 (100%), 482 (16), 468 (83), 454 (55), 248 (47) for the other one, while the Diels-Alder cycloadduct (169) should have shown M^+(100%)= 221.

Therefore, cyclisation of 1-amino-naphthalene was repeated with TFA, formaldehyde and cyclopentadiene in respective ratios 1/1/1/2 at different temperatures and with a shorter reaction time (35 minutes). A non polar compound was afforded along with the same undesired polar products and assigned to the expected structure (169) (scheme137) on the basis of usual spectroscopic analyses (M^+(100%)= 221, clear 270 MHz ^{1}H NMR spectrum). It was hence isolated in 16 % yield from an experiment at room temperature and in 20 % yield from an experiment at about 0 °C.

Entry	Starting amine	Type[1]	Reaction conditions[2]	Diels-Alder adduct(s)	Yield[3]
1		mono	1 / 1 / 5 / 5 r. T. , 3 h		0 %
2		mono	1 / 1 / 1 / 2 r. T. , 35 min		16 %
3		mono	1 / 1 / 1 / 2 0<T<5°C , 35 min		20 %
4		dble mono	1 / 2 / 2 / 2 r. T. , 35 min		3 %
5		dble mono	1 / 2 / 2 / 2 0<T<10°C , 10 min		0 %
6		dble mono	1 / 0 / 2 / 3 r. T. , 12 h 40<T<80°C , 7 h	d,l + meso	0 %

1] mono= monocyclisation ; dble mono= double monocyclisation.
2] respective ratios of starting amine / TFA / formaldehyde / cyclopentadiene
reaction temperature, reaction time.
3] after isolation by flash chromatography.

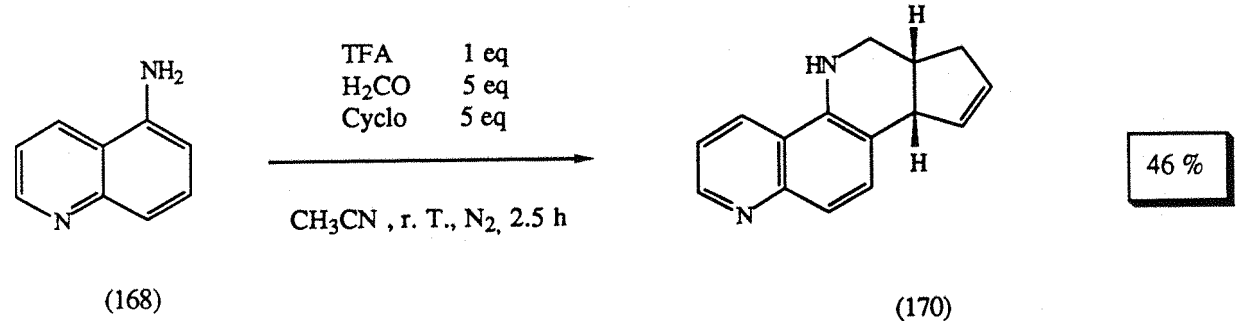
Scheme 136: Table of the results obtained from fully aromatic bicyclic amines.



(167) (169)

Scheme 137

These two last results represented an appreciable improvement. Nevertheless, they had to be compared to the case of 5-amino-quinoline (168) (scheme 138) which had afforded the desired tetracyclic 7*H* -cyclopenta[1,2-*i*]-5,6,6a,9a-tetrahydro-1,7-phenanthroline (170) in 46 % yield with a large excess of formaldehyde and cyclopentadiene[123].



(168) (170)

Scheme 138

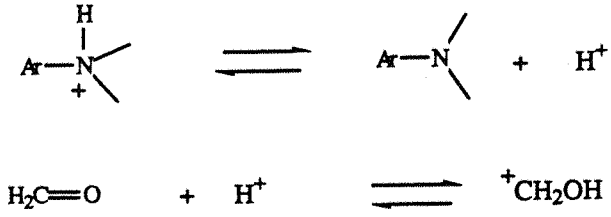
The difference in behaviour between 1-amino-naphthalene and 5-amino-quinoline lies in the ability of the nitrogen atom in the aromatic ring of the latter to decrease strongly the reactivity at the para position with respect to the amino group by its electron attracting effect and consequently to diminish further reaction.

b/ Comments on the formation of by-products.

The formation of polar by-products in most of our reported cyclisations is rationalized on the basis of the presence of the ionic form $^{+}CH_2OH$ of formaldehyde due to acid catalysis with TFA.

Apart from its expected tendency to form iminium ions with the investigated amines, these cations show also a good ability to indergo electrophilic aromatic substitutions at the most activated positions; and this second alternative is all the more favoured when an excess of formaldehyde is used. The main uncertainty lies in the positon at which the substitution might occur.

Although TFA was not utilized in "catalytic" quantity (more than one equivalent was used), one can assume that, in our cyclisations, at any moment the amine and free formaldehyde are only partially protonated, which is expressed by the following system of equilibria (scheme 139):

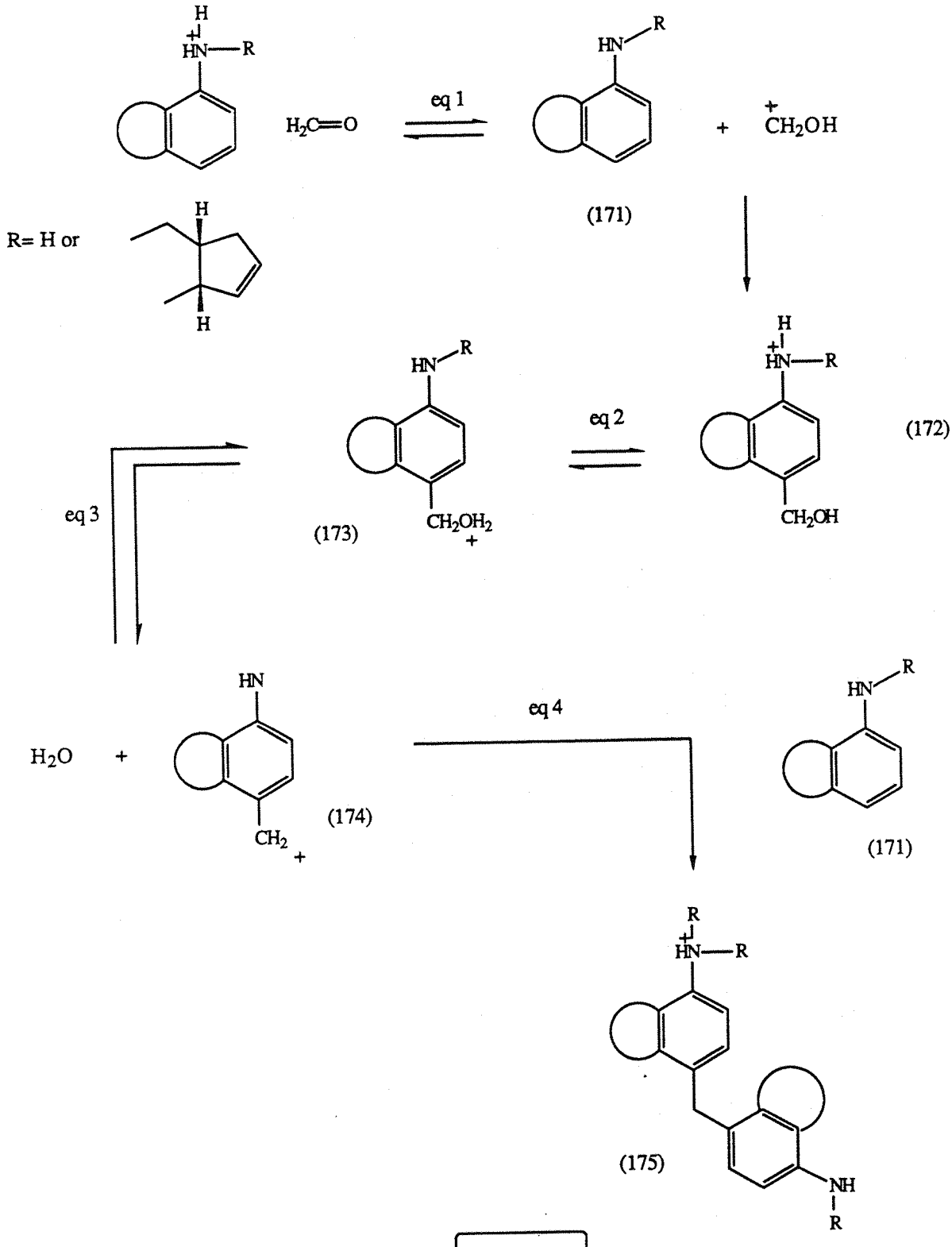


Scheme 139

As demonstrated earlier, the reactions competing as far as the "meta" amines are concerned are the monocyclisation and dicyclisation processes. If "ortho" amines are considered, only the monocyclisation mode is possible. The likely mechanism for the formation of by-products of type (175) is shown in scheme 140.

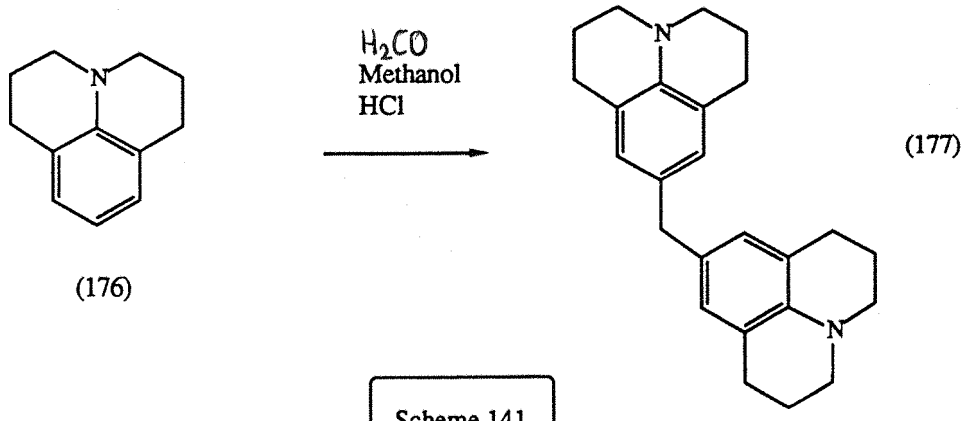
When non protonated, the "ortho" amine activates the ring and particularly the para and ortho positions by its mesomeric effect, while the protonated form deactivates it. Hence, any aromatic substitution takes place definitely from the former one. One can also fairly estimate that the expected cycloaddition occurs before a side substitution, which consequently blocks the ortho position with repect to the amino group.

On the whole, when favoured by the reaction conditions, a further substitution of $^{+}CH_2OH$ may be observed mainly at the para position of a neutral amine (171), mostly the cyclisation adduct, which is expressed by the equation 1 (scheme 140). Likewise, the intermediate alcohol (172) is protonated according to the equation 2. The form (173) can next release water (equation 3) and yield the reactive aryl cation (174) which shows the same ability to undergo aromatic substitution on activated aromatic position; therefore a second molecule of the neutral amine (171) is likely to be involved in this side process according to the equation 4, which leads to a dimer of type (175) predominantly para-para disubstituted.


H
HN—R
H2C=O
eq 1
HN—R
+ CH2OH
(171)
R= H or
H
H
eq 2
(172)
eq 3
(173)
CH2OH2
+
CH2OH
HN
H2O +
(174)
CH2
+
eq 4
HN—R
(171)
R
HN—R
(175)
NH
R

Scheme 140

This type of junction at the para position can be illustrated by examples from the literature. For instance, Barker and Halles[156] reported that julolidine (176) (scheme 141) yielded under acid catalysis conditions with formaldehyde di-2,3,6,7-tetrahydro-1*H*, 5*H* -benzo[ij]quinolizin-9-yl-methane (177).



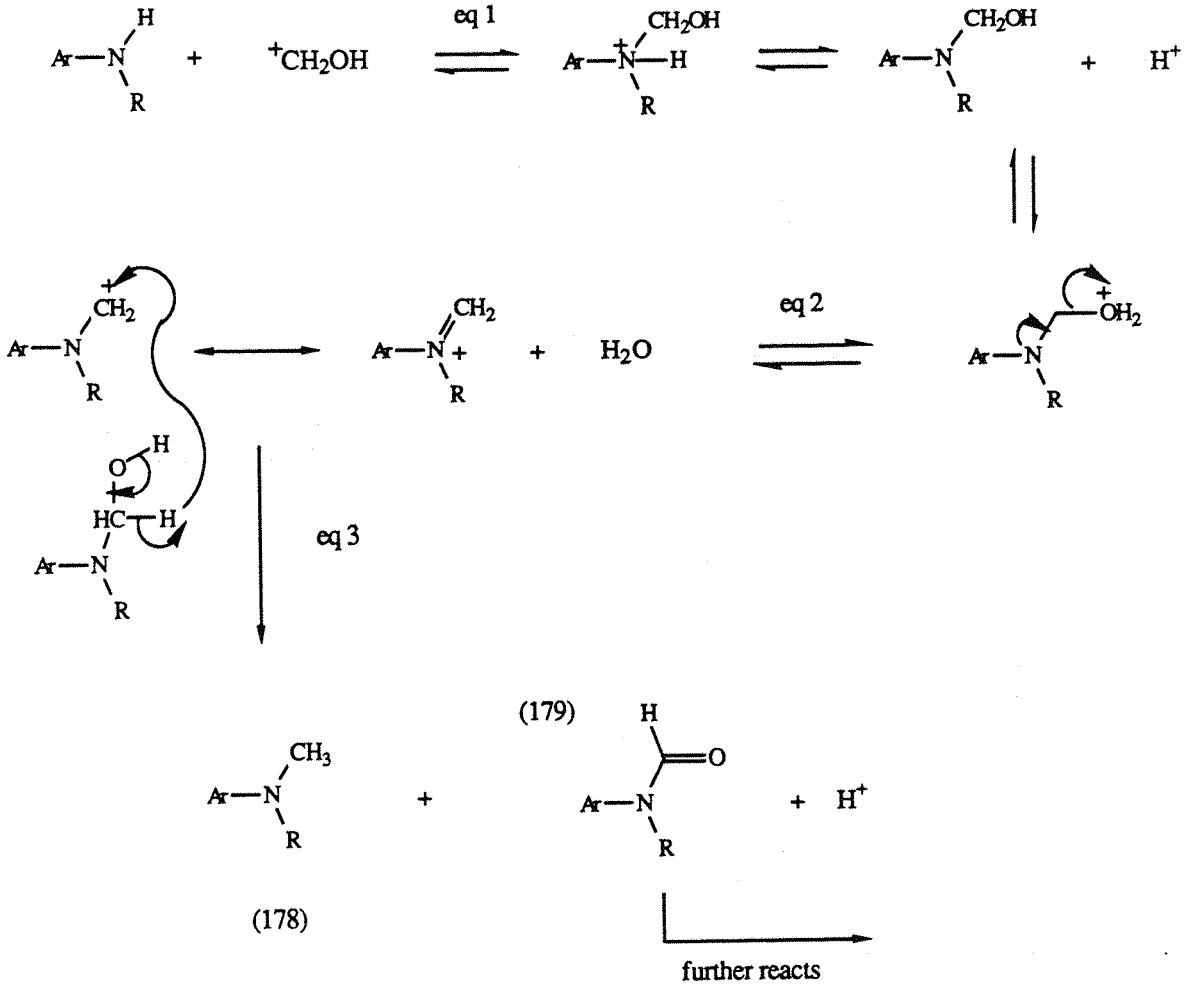
(176) (177)

Scheme 141

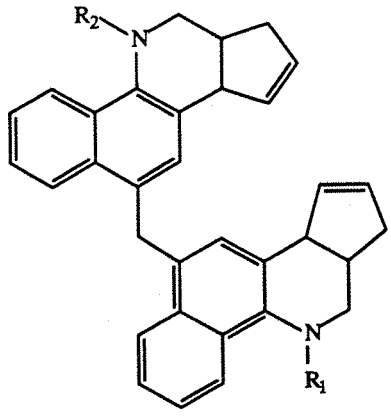
The overall side substitution process described in scheme 140 involved a move of the initial equilibrium (equation 1). It might be avoided by choosing suitable reaction conditions such as:
-> use of stoichiometric ratios of amine and formaldehyde.
-> investigation of amines having a strongly electron deficient group in the para position or a highly favourable cyclisation process, as observed in the tetralone, indanone and anthraquinone series.
-> variation of reaction temperature, reaction time and dilution according to the studied case.

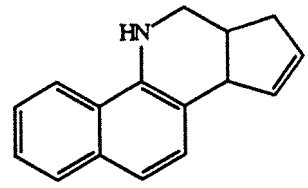
A second type of side reaction might take place, the addition of the amino group (mainly the cyclisation adduct) to the cation $^{+}CH_2OH$ (equation 1, scheme 142). Such a step might lead to N-methylamines (178) and amides (179) via hydride transfer processes as in the equations 2 and 3. In line with the previous developments were suggested the structures (180) and (181) (scheme 143) to explain the mass spectra of the two polar fractions isolated in the first approach of the monocyclisation of 1-amino-naphthalene.

Substitution on the second aromatic ring of 1-amino-naphthalene might take place, probably at the position 5. However, this ring is likely to be far less activated. Finally, it was not unprobable that (181) and (182) had the same Rf values and that the second fraction was a mixture of both compounds.



Scheme 142





(169) M= 221

(180) R_1=R_2=H M= 454
(181) R_1=R_2=Me M= 482
(182) R_1=Me, R_2=H M= 468

Scheme 143

3] Double monocyclisation of 1,8-diamino-naphthalene.

a/ Interest of the Diels-Alder adducts.

In spite of the low yield obtained with 1-amino-naphthalene, it seemed to us interesting to investigate the corresponding symmetric aromatic diamine, 1,8-diamino-naphthalene (224) (scheme 162). Indeed, this double momocyclisation was expected to provide the two diastereoisomers d,l and meso, separable and with probably the former as the major isomer. The d,l enantiomers (225) (scheme 162) possess a C_2 symmetry axis and C_2 chiral auxiliaries have been of high interest for a few years.

The Diels-Alder adducts also show a highly nucleophilic area between the two nitrogens atoms. Such a diamino system might exhibit the ability of trapping certain metal cations according to their size and the stability of the binding. More than one equivalent of ligand with respect to the cation may be required. Although the oxygen-based trapping agents (crown-ethers, cryptands) have been more numerous, various nitrogen-based ligand/metal cation complexes have been reported for decades. A number of them are chelates, the most well-known of which are porphyrins[157].

The reaction of phenylenediamine investigated by Riviere (scheme 91, entry 8) led to similar compounds showing the same potential applications[124]. Certain anthraquinone derivatives (section [D]) will show the same features.

An overview of recent uses of nitrogen-based C_2 chiral auxiliaries and a brief illustration of nitrogen-based ligand/metal cation complexes through a few recent examples are given below.

1) Nitrogen-based C_2 chiral auxiliaries.

α] Chiral auxiliaries.

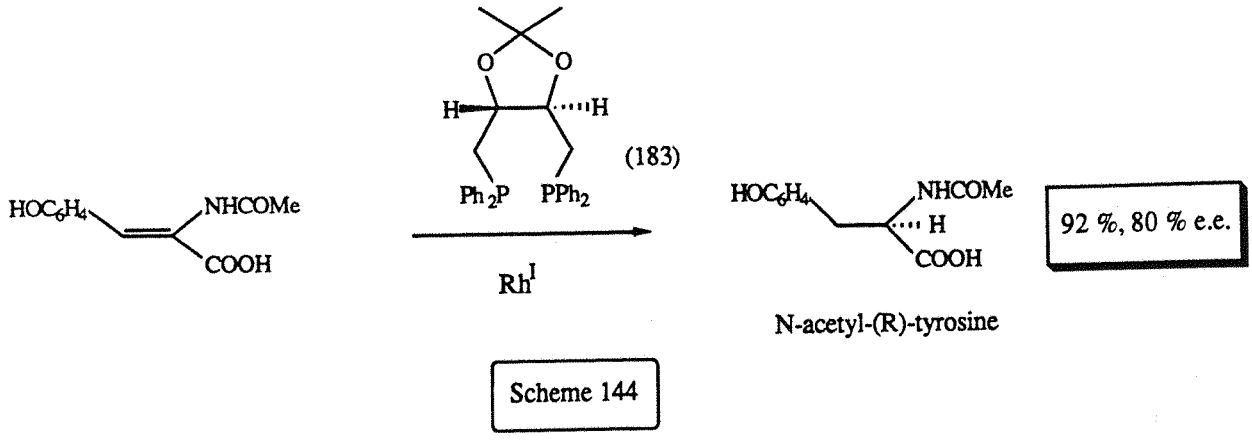
The aim of asymmetric induction in a chemical transformation is to provide the reaction product with absolute stereochemical control, that is to say with total diastereoselectivity and enantioselectivity. The construction of complex bioactive molecules requires control of stereochemistry at each synthetic step. Therefore, the application of asymmetric induction in enantioselective routes has constituted an important area of research for a decade[158-162]. While intramolecular asymmetric induction in which the chiral agent is borne by one of the reagents (see asymmetric induction in Diels-Alder reaction in the introduction) has been widely investigated, the transfer of the chiral information in an intermolecular mode is just being approached. This latter type of asymmetric induction occurs between a starting material, a reagent and an external chiral auxiliary commonly named ligand. Sometimes, a catalyst often derived from a metal is required to form a transition or intermediate complex starting material/reagent/ligand /catalyst leading next to an enantiomeric or diastereoisomeric excess. Structures of the complexes are mainly conjectural as clear structural evidence has rarely been obtained. However such complexes can function as catalysts.

β] C_2 chiral auxiliaries: history.

Many recent examples have shown that the presence of a C_2 symmetry axis in a chiral auxiliary could enhance the selectivity as far as the different possible transition states are concerned. A C_2 symmetric species lacks mirror symmetry and consequently is a dissymmetric molecule.

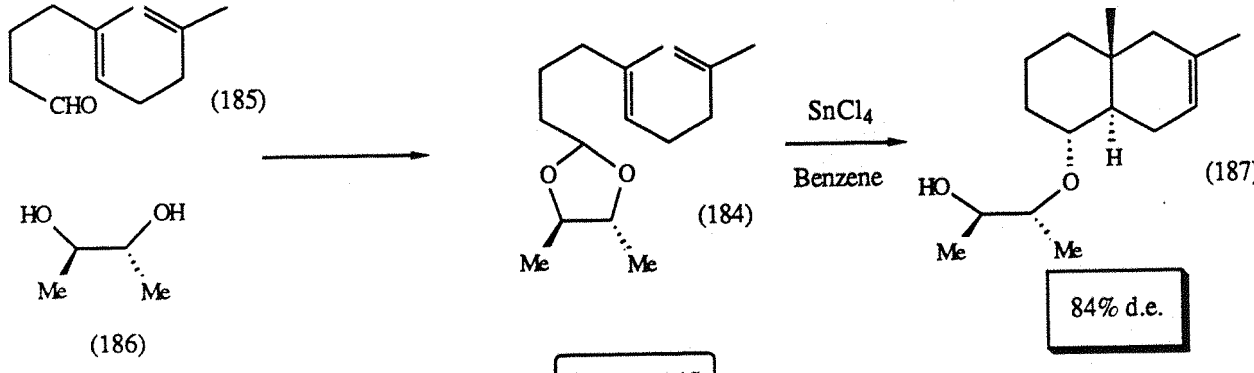
A number of highly enantioselective reactions using C_2 chiral ligands of various nature have been reported over the last few years[159]. The first successful applications of C_2 chiral molecules in an asymmetric induction process were reported in the seventies.

In 1972, Kagan[163] described asymmetric catalytic reductions with the hydrogenation agent (-)-Diop (183), 2,3-o-isopropylidene-2,3-dihydroxy-1,4-bis(diphenyl-phosphino)butane, and $Rh^{(I)}$ through transition metal complexes, scheme 144. It opened the area of C_2 chiral phosphines which has been reviewed recently[161].



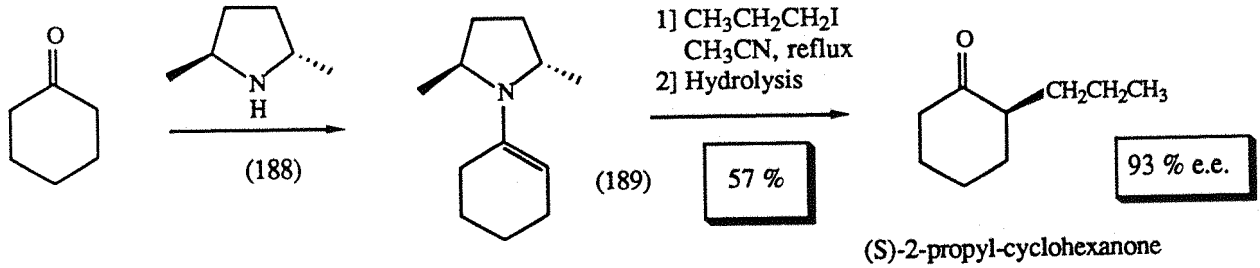
Scheme 144

Johnson used[164] in 1976 optically active acetal (184) (scheme 145) derived from the aldehyde (185) and (-)-2,5-butanediol (186) to form diastereoselectively the decalin system (187). Many oxygen based C_2 symmetry ligands (other diols, crown ethers) have been applied since in asymmetric synthesis[158,159].



Scheme 145

A year later, Whitesell utilized[165] the (+)-2,5-dimethyl-pyrrolidine (188) (scheme 146) to alkylate cyclohexanone via the enamine intermediate (189) in a highly enantioselective mode.



Scheme 146

A variety of C_2 chiral amines or diamines have been described and used in asymmetric induction via a starting material/reagent/ligand(/catalyst) complex containing one or more equivalents of ligand. The most significant results reported in the last three years are mentioned in the following section.

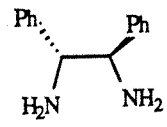
γ] Nitrogen-based C_2 chiral auxiliaries.

1- "Stien" related auxiliaries.

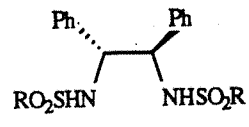
C_2 chiral 1,2-diaminoethane derivatives have appeared as powerful controllers in enantioselective synthesis through a series of successful applications in different types of reaction[160]. It is mainly the group of Corey which has been developing this promising chemistry.

The basic structures are the (R,R) and (S,S) forms of 1,2-diamino-1,2-diphenylethane, stilbene-diamine or "stien" (190) (scheme 147). They can readily be converted to sulfonamides (191) of the (R,R)- and (S,S)- series. Finally, some aluminium- (192) and boron- (193) based Lewis acids can be prepared from each enantiomer and used as catalysts in various chemical transformations.

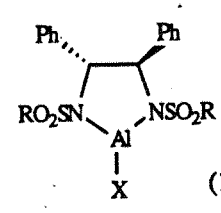
Series (R,R):



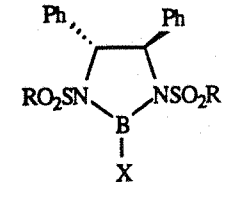
(190)



(191)



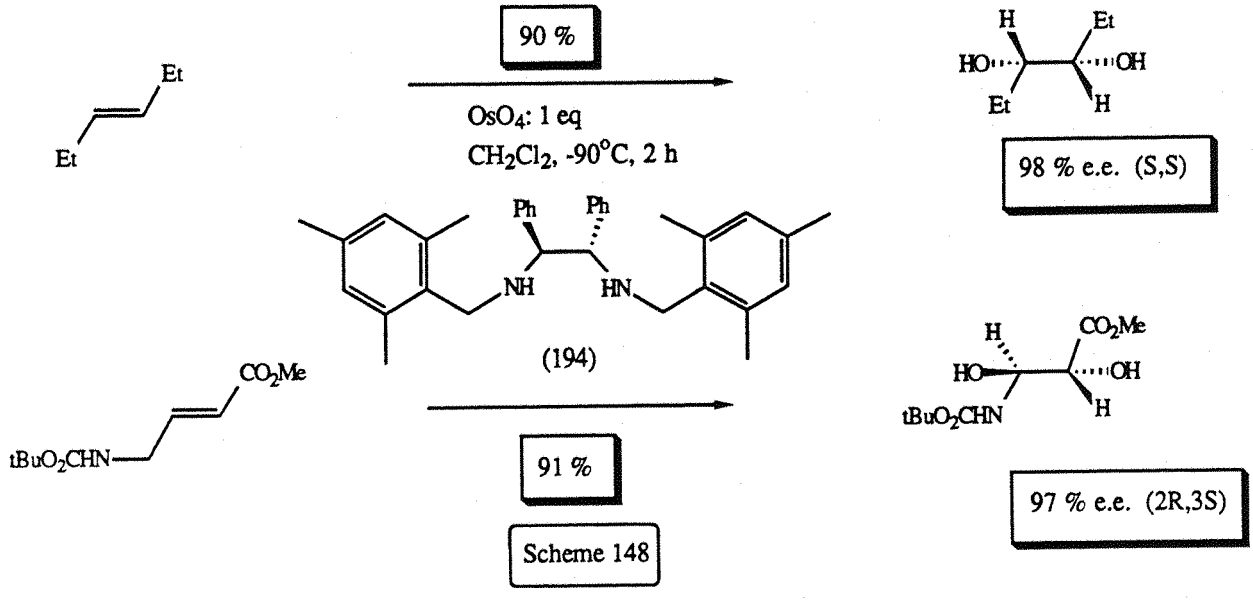
(192)



(193)

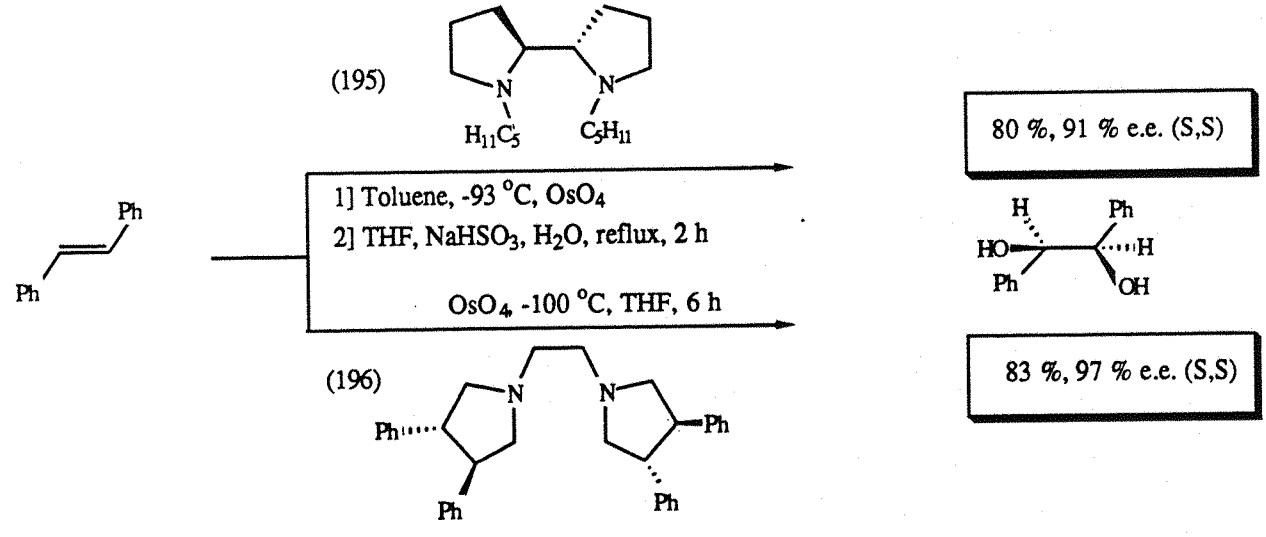
Scheme 147

The enantioselective dihydroxylation of terminal E-1,2-disubstituted olefins by an osmium tetraoxide-based chiral complex has been investigated by Corey, Tomioka and Hirama mainly. Hence, Corey obtained[166] in 1989 impressive enantioselectivity with the simple (-)-(S,S)-stien derivative (194) (scheme 148), 1,2-diphenyl-1,2-bis[2,4,6-trimethyl-benzyl-amino]ethane.



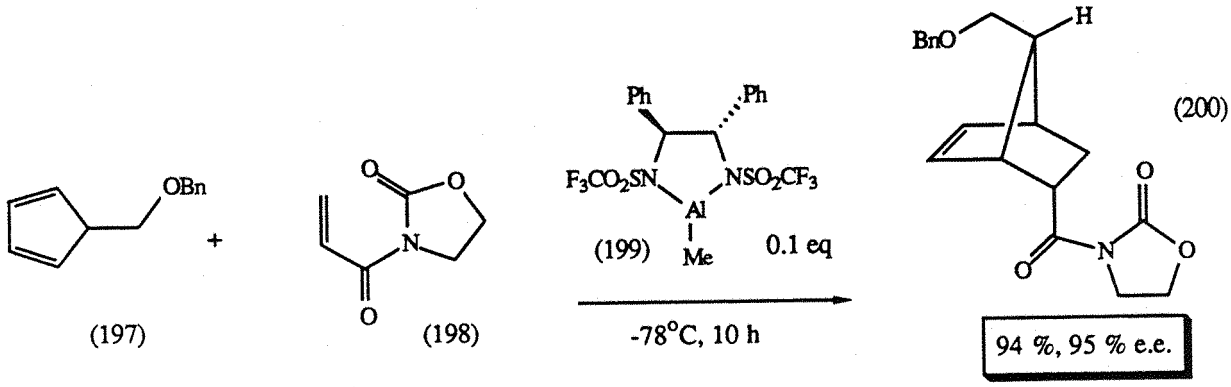
Scheme 148

Hirama has studied this reaction[167] with the (S,S)-stien related bicyclic ligand (195) (scheme 149) while Tomioka has used[168] the bicyclic 1,2-diamino-ethane derivative (196). Both of them have observed similar high enantioselectivity.



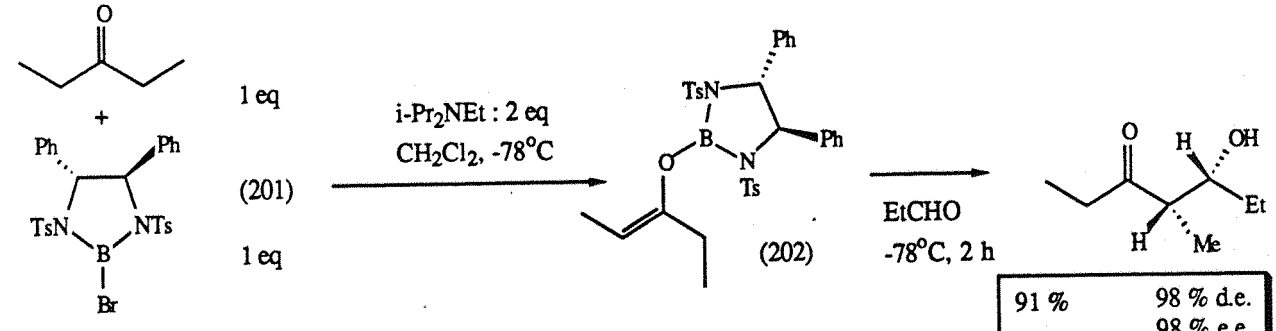
Scheme 149

Corey has recently applied different chiral aluminium and boron complexes to different reactions. Hence the Diels-Alder reaction of 5-((benzyloxy)methyl)-1,3-cyclopentadiene (197) (scheme 150) and the acrylyloxazolidinone (198) with the (S,S)-ligand (199) has provided the intermediate (200) which is of high interest for the synthesis of optically pure prostaglandins[169].



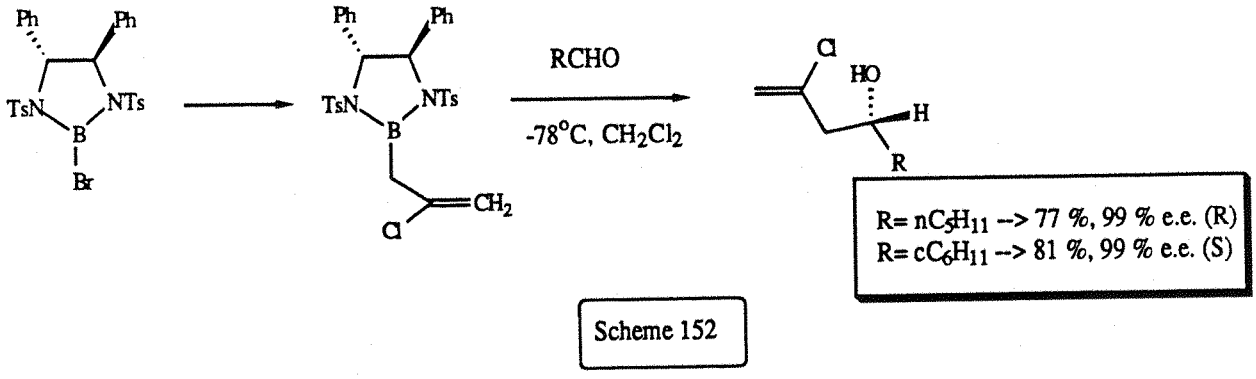
Scheme 150

A related (R,R) boran derivative (201) (scheme 151) has permitted impressive diastereo- and enantioselective aldol reactions via Z-boran enolates such as (202) derived from 3-pentanone[169].



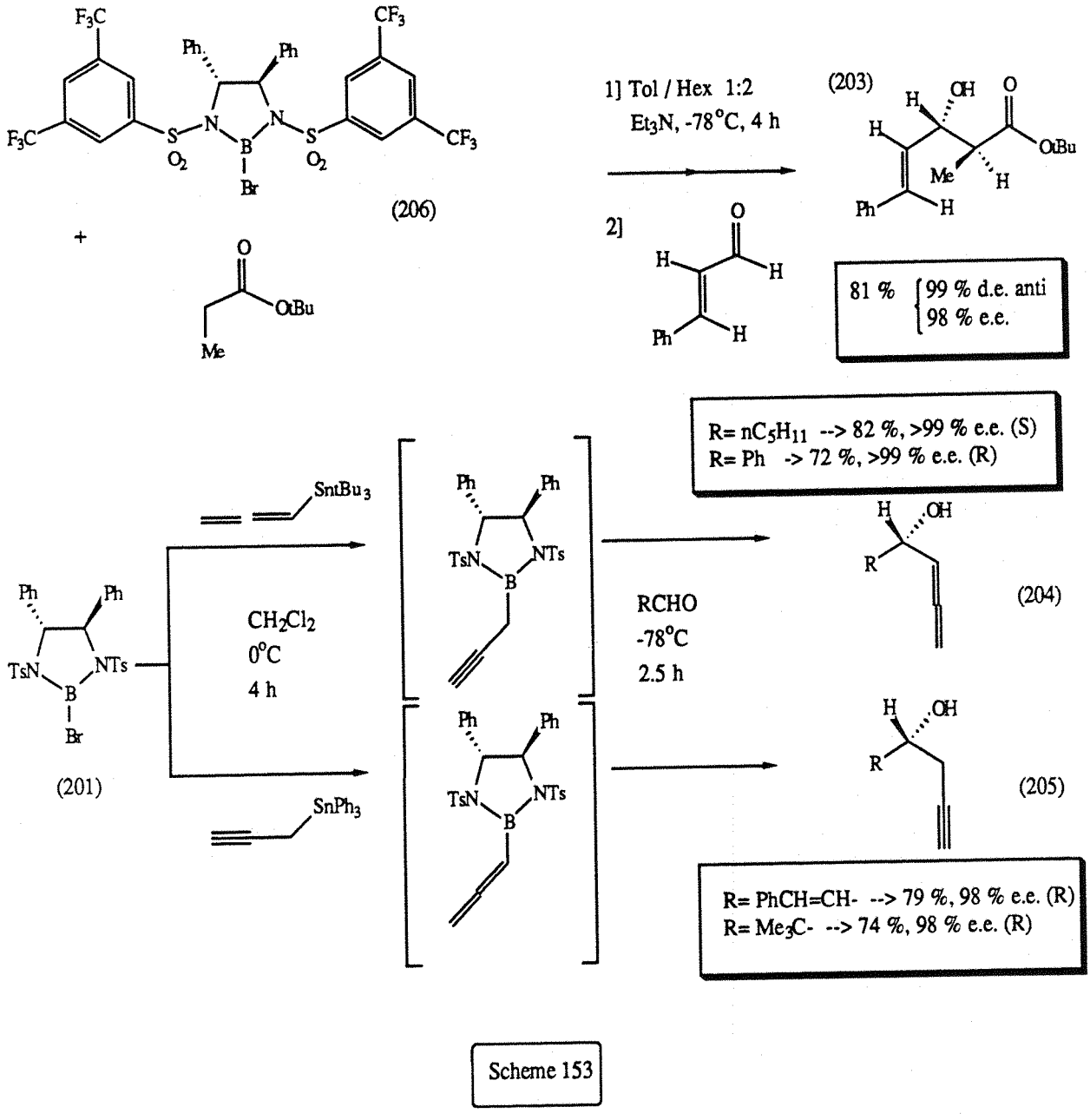
Scheme 151

The same stien derivative has also been employed by Corey[170] in asymmetric addition of substituted allyl groups to aldehydes as illustrated by the following example, scheme 152.



Scheme 152

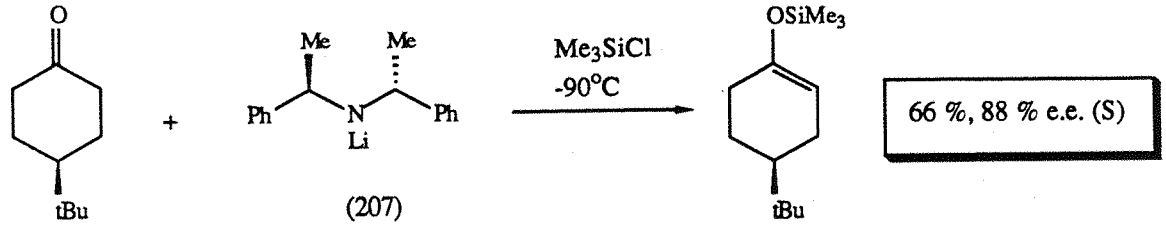
Finally, two very recent applications have concerned an enantioselective nucleophilic addition to aldehydes to form secondary alcohols[171,172] (202) (scheme 153) and an enantioselective synthesis of chiral propa-1,2-dienyl (204) and propargyl (205) carbinols[173]. The new (R,R)-stien allyl boran (206) has been utilized in the former example with propionate esters and various aldehydes leading to syn- or anti-aldol products, while the earlier mentioned (R,R)-bromo-boran (201) has been the chirality controller in the latter example.



Scheme 153

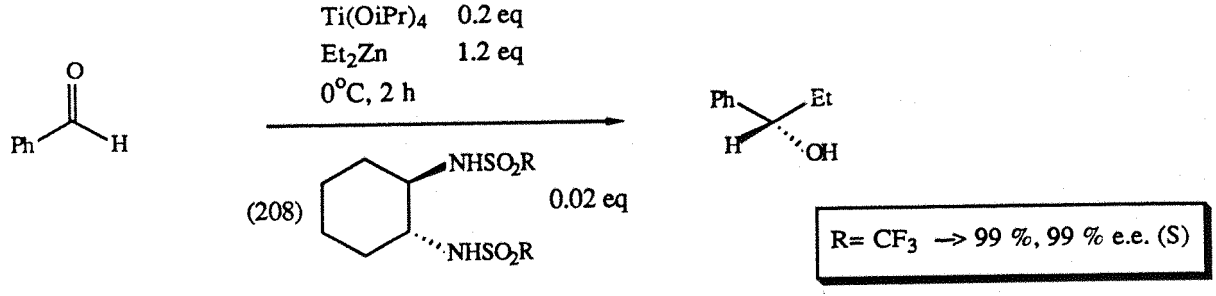
2- Other auxiliaries.

The (R,R)-lithium amide (207) (scheme 154) has been often used in numerous reactions but it has not always undergone a high enantioselectivity[174-176]. Recently, Simpkins has shown[177] it permitted an asymmetric deprotonation of certain prochiral ketones to give enol ethers in enantiomeric excess.



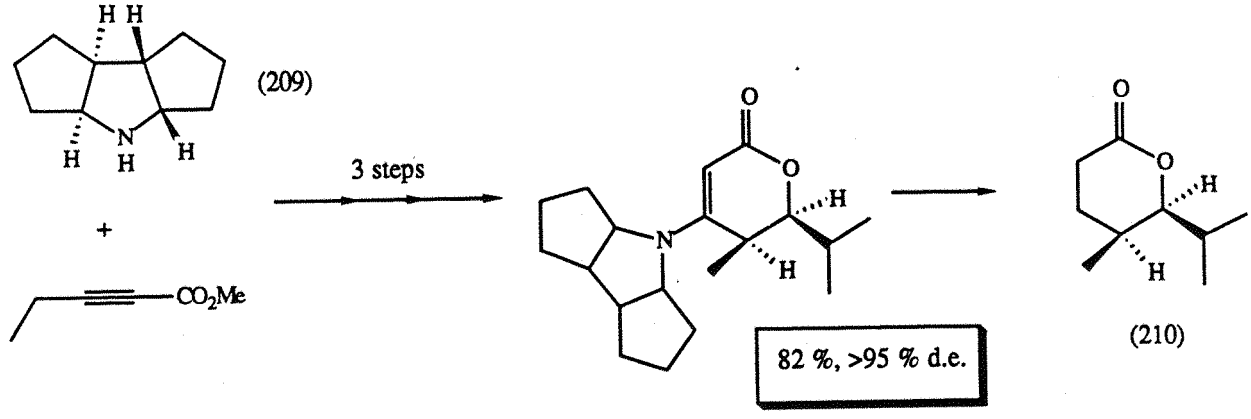
Scheme 154

The amides (208) (scheme 155) have constituted a group of highly potent catalysts for controlling the enantioselectivity in additions of the diethylzinc-orthotitanate complex to benzaldehyde[178], as illustrated by the following example.



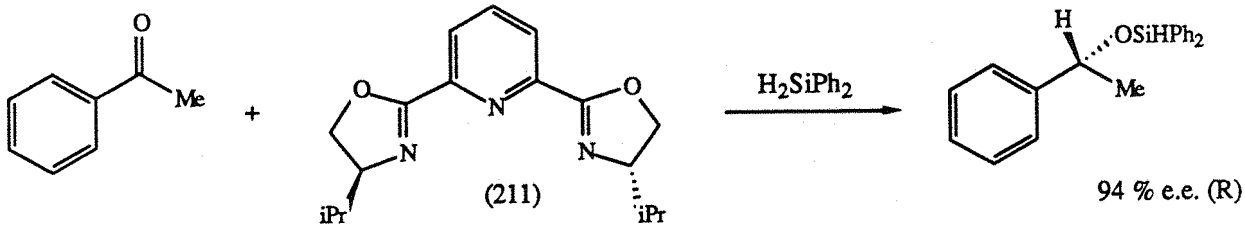
Scheme 155

The C_2 chiral tricyclic amine (209) (scheme 156) was first synthesized in 1988 by Whitesell and applied[179] to the formation of the lactone (210).



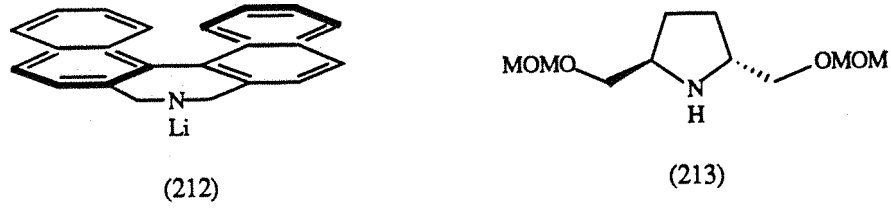
Scheme 156

The chiral pyridine (211) (scheme 157) has been employed[180] as a ligand in rhodium-catalysed asymmetric hydrosilylation of acetophenone.



Scheme 157

Finally, the lithium amide (212) (scheme 158), 3,5-dihydro-*4H* -dinaphthyl [2,1-c:1',2'-e] azepine, and (2R,5R)-2,5-bis(methoxy-methoxy-methyl) pyrrolidine (213) were earlier reported (in 1986) in asymmetric Michael addition to methyl crotonate[181] (up to 97 % d.e.) and asymmetric dialkylation of α-cyano acetic acid[182] (up to 90 % d.e.) respectively.



(212) (213)

Scheme 158

2) Nitrogen-based chelates.

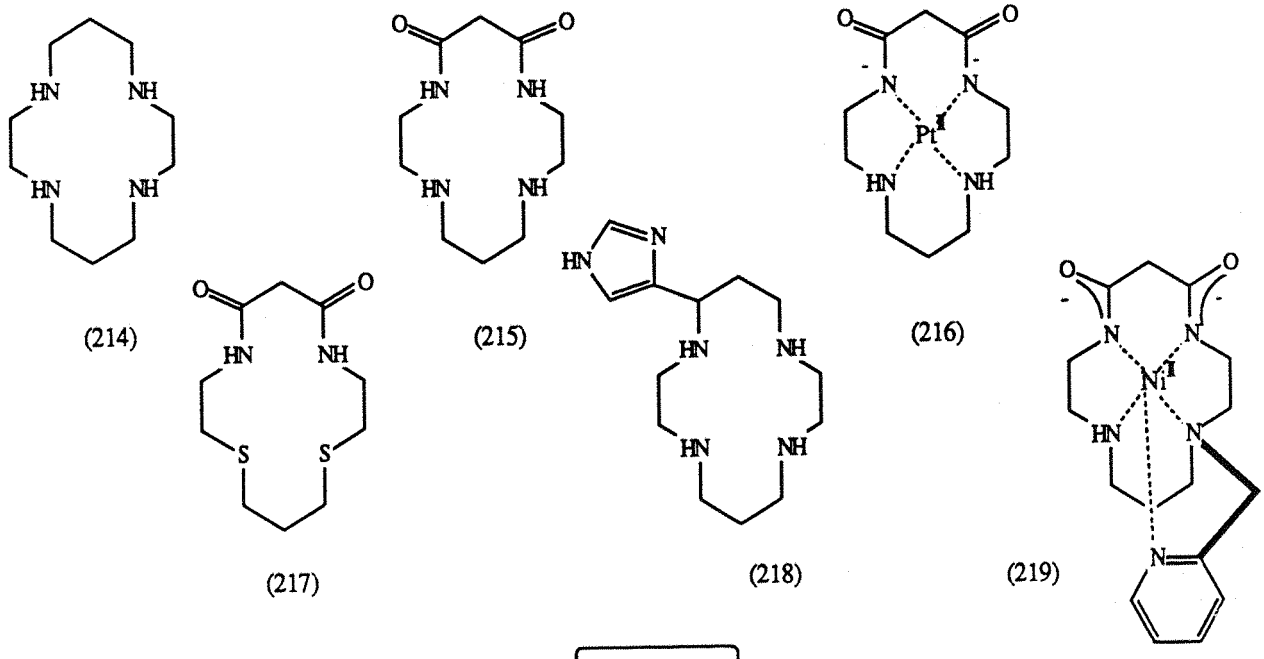
Macrocyclic polyamines are an important group of ligands for complexing cations. The simplest member has been cyclam (214) (scheme 159) but various functionalizations have been developed and reviewed by Kimura[183]. Strategies can involve:

-> conversion of amines into amides which leads to dioxocyclam (215). It complexes more especially Cu^{II}, Co^{II} and Ni^{II}. Its dianionic form (216) binds Pt^{II}.

-> replacement of some nitrogen donors for suphur donors as shown by (217). Likewise, its $(N^-)_2S_2$ derivative has appeared as a selective ligand for noble metal ions such as Pt^{II} and Pd^{II}.

-> attachment of intramolecular pendant donors such as pyridinyl or pyrrazolyl substituents which

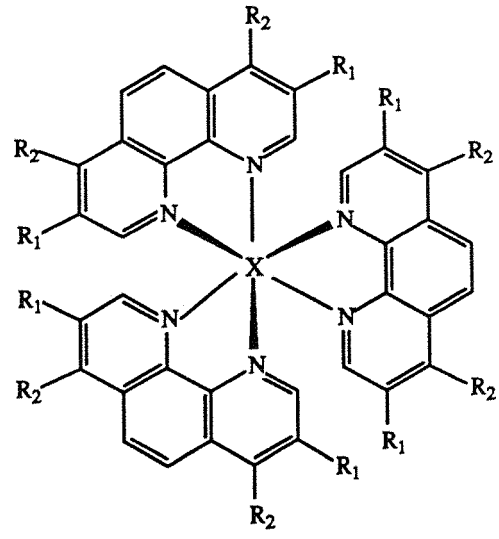
may be linked either to a carbon atom α to a nitrogen atom as illustrated by (218) or to a nitrogen atom as shown by the $(N^-)_2$ dioxocyclam (219) (Ni^{II} trapping agent).



Scheme 159

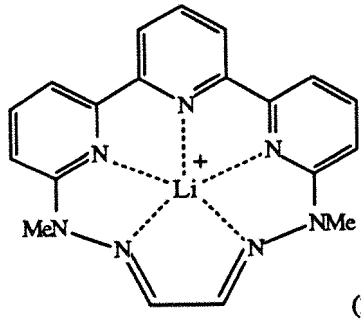
Barton has shown[184] that three molecules of certain phenanthroline derivatives may bind metal cations and particularly transition metal cations such as Co, Rh and Ru ((220), (221) and (222) respectively, scheme 160) by means of six nitrogen donors. Now these chiral transition metal complexes have been shown to bind to the DNA strand at certain sites. Hence, because of their very structure, they target specific DNA sites.

	X	R_1	R_2	Name
(220)	Co	H	H	$Co(phen)_3^{3+}$
(221)	Rh	H	Ph	$Rh(DIP)_3^{3+}$
(222)	Ru	Me	Me	$Ru(TMP)_3^{2+}$



Scheme 160

The macrocyclic 1,6-dimethyl-1,2,5,6-tetra-aza-[6.0.0]pyridinophane-2,4- diene (223) (scheme 161) has been reported[185] as forming a complex with alkali metal cations and more especially with Li^+. Seven nitrogen atoms are present in the planar pentadentate ligand but only the five nitrogen donors 1,2,4,5 and 7 link to Li^+ as the cation is exactly within the pentagonal plane thus obtained.



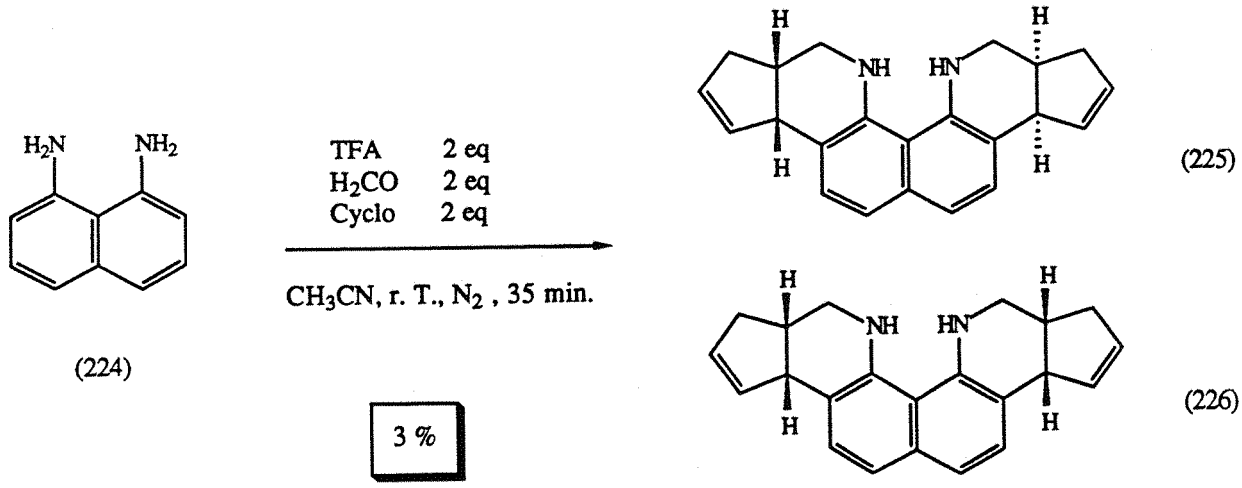
(223)

Scheme 161

b/ Results.

The double monocyclisation of 1,8-diamino-naphthalene (224) (scheme 162) carried out with TFA, formaldehyde and cyclopentadiene in the respective ratios 1/2/2/3 at room temperature for 35 minutes afforded a non polar reddish solid whose mass spectrum (M^+(100%)= 314) and 270 MHz ^1H NMR spectrum undoubtedly confirmed the desired structures (225) and/or (226) of the

diastereoisomers d,l and meso respectively. However, a very poor 3 % yield was obtained.



Scheme 162

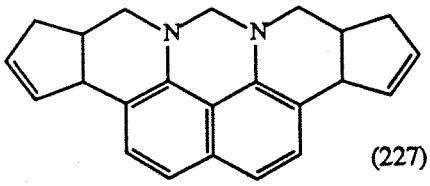
We had suspected that the seven-ringed system (227) (scheme 163) after further reaction with formaldehyde between the close two nitrogen atoms might also be afforded. On the other hand, many polar compounds were observed along with an important polymeric black solid removed with difficulty by filtration. Indeed, the process leading to by-products in the 1-amino-naphthalene case was all the more favoured here by the symmetrical diamino system; the same "dimerization" could take place at the two activated para positions which yielded eventually a polymer. Moreover, the starting amine was very impure.

The attempt of improvement of the yield using purified 1,8-diamino-naphthalene failed. The experiment using the same ratios of reagents but between 0 and 10 °C in 10 minutes did not allow the desired adduct(s) to be recovered. Finally, a further experiment was carried out without TFA in order to avoid the formation of $^{+}CH_2OH$ for 19 hours (including 7 hours at 40-80 °C). Likewise, no amelioration in the reaction outcome was observed.

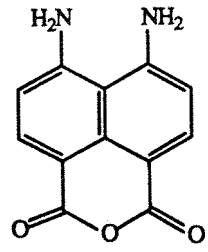
4] Conclusion.

The two fully aromatic amines reported above were clearly less successful than the other bicyclic amines having an aliphatic side ring. Their behaviour would likely be similar if the para positions were either blocked or deactivated by an electron deficient group or a nitrogen atom at a suitable position in the bicyclic skeleton (as with 5- and 7-amino-quinolines). The investigation of 1,8-diamino-naphthalene derivatives such as 4,5-diamino-1,8-naphthalic anhydride (228) (scheme

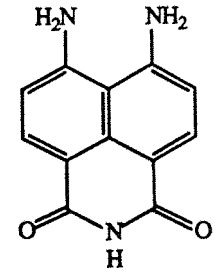
163) or 4,5-diamino-1,8-naphthalimide (229) might provide the d,l isomer in high yield.



(227)



(228)



(229)

Scheme 163

IV] Conclusion concerning bicyclic amines.

The chemistry based on aniline derivatives reported by Grieco and developed by Riviere was further extended to bicyclic amines with an aliphatic or aromatic fused ring. The tetralin- and indane-based amines yielded the expected adducts in the range 38-68 % in the monocyclisation mode and in the range 71-90 % in the dicyclisation mode. The double effect of a carbonyl group as far as the reactivity and the regioselectivity are concerned was put into light mainly in the monocyclisation process (see conclusion in previous section II] 4] c/). But this functionality does interfere also in the dicyclisation process in view of the difference of yields observed with amino-ketones (~88 %) and 5-amino- indane (71 %). The role of a carbonyl group in the side ring needs to be further studied with starting material where the amine and the carbonyl are ortho to each other.

While Grieco had investigated para-substituted anilines whereby no side reaction was able to take place (para position blocked), the study of meta-nitro-aniline in both monocyclisation (see table 91, entry 7, 48 %) and dicyclisation (entry 9, 73 %) modes effected by Riviere is closer to the cases of our two amino-ketones (where the carbonyl group is also meta with respect to the amine); one can consequently notice the correlation existing between the two types of starting amines.

The investigated fully aromatic bicyclic amines having no electron-withdrawing atom (in the basic skeleton) or substituent clearly led to poorer yields even at lower temperature because of the occurrence of further reaction (see suggested mechanism in previous section III] 2] b/). A deactivation of the para position with respect to the amino group is required in order to obtain better results from these naphthylamines.

[D] USE OF TRICYCLIC AROMATIC AMINES AS SUBSTRATES: INVESTIGATION OF AMINO-ANTHRAQUINONES.

I] Choice of the anthraquinone skeleton.

The investigation of different types of bicyclic aromatic amines in Diels-Alder cyclocondensations with formaldehyde and cyclopentadiene suggested an activating and regioselective role of a carbonyl group in the side ring. Therefore, instead of studying various categories of tricyclic aromatic amines as starting materials (fully aromatic or not, five- or six-membered rings, presence of heteroatoms in the nucleus, several possible positions for the amino group, ...), which would have constituted too broad on purpose, we decided to extend the tetralone and indanone series to the corresponding tricyclic aromatic amino-ketones and chose to investigate the anthraquinone skeleton.

Indeed, the quinonoid nucleus was to show the same activation and regioselectivity in the cyclisations from "meta" (with respect to one carbonyl group) amino derivatives (2-amino-anthraquinone) as those observed with 7-amino-α-tetralone and 6-amino-α-indanone. It permitted a thorough investigation in a second system of the influence of remote carbonyl groups upon the cyclisation; these "ortho" amino derivatives (1-amino-, 1,4- and 1,5-diamino- anthraquinones), leading to 11-azasteroids, were to exhibit the same activation as that reported by Riviere with his ortho-substituted anilines by an electron-withdrawing group. Moreover, in both types of cyclisation, a strong deactivation of the free aromatic positions was to be observed because of the second carbonyl group, as in the case of 5-amino-α-tetralone. Finally, when the second aromatic ring did not bear any amino group, no undesired further reaction of formaldehyde was supposed to occur there to a noticable extent, thanks to the overall strong deactivation effect of the carbonyl groups.

II] Features and applications of amino-anthraquinone derivatives.

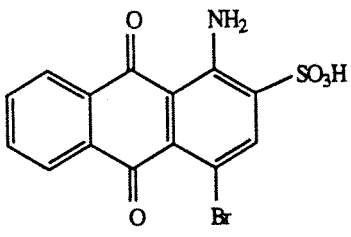
Anthraquinone-based species have shown a variety of interesting features. Within this series, amino-anthraquinone derivatives have appeared as the group of highest interest because of the broad range of potential applications. They have been widely used as dyes for decades. Their electrochemistry and more particularly their cyclovoltammetric behaviour has been investigated and has shown interesting reversibility which might prove to be the foundation of electrochromic devices. Certain amino-anthaquinones have been revealed as anti-cancer agents. Finally anthraquinone poly-ethers having at least one oxygen atom "ortho" to one of the two carbonyls have been reported as showing the ability to transport some metal cations. Hence access to a series of novel anthraquinones would be interesting for a number of reasons.

1] Amino-anthraquinone derivatives as dyestuffs.[186-188]

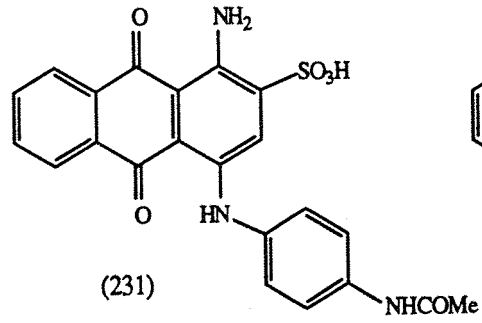
Amino-anthraquinone derivatives have constituted for about fifty years one of the leading class of dyestuffs. These have been almost exclusively 1,4-diamino-anthraquinone derivatives. Their prominent colour is blue but the shades range from bluish violet to bluish green according to the substitutents. They have been widely used in various areas (mainly in textiles) because these molecules, besides the quality of the colour, usually show the following required features: affinity for the support (often fibers), wet fastness, fastness to light (stability to light) and leveling qualities. Finally, these anthraquinone based compounds have been employed in the four main categories of dyes: acid dyes (for textile), vat dyes, reactive dyes and pigments (for inks and coating compositions). The importance of amino-anthraquinones as dyestuffs are illustrated below.

a/ Acid amino-anthraquinone dyes.[186a,187a]

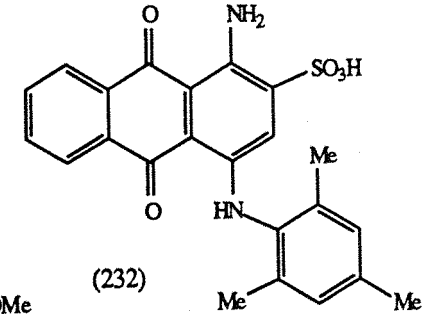
A broad variety of these dyestuffs are afforded by simple condensation (mostly carried out in aqueous solution) of 1-amino-4-bromoanthraquinone-2-sulfonic acid (bromaminic acid) (230) (scheme 164), with various amines. The coplanar condensation with the aromatic amine p-amino-acetanilide led to Anthralan Blue G (231) while Alizarine Sky Blue BS (232) has been synthesized with mesidine as the amine in a non coplanar manner due to the o,o'-disubstitution. Diamines have also been used to lead to dyes such as (233).



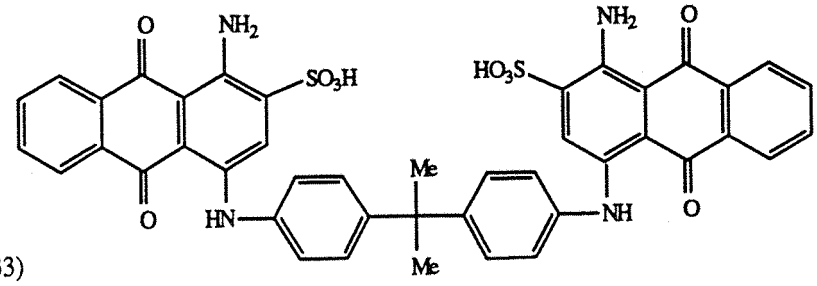
(230)



(231)



(232)

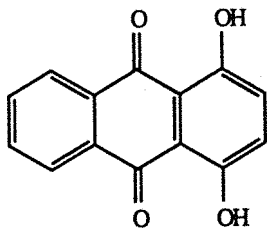


(233)

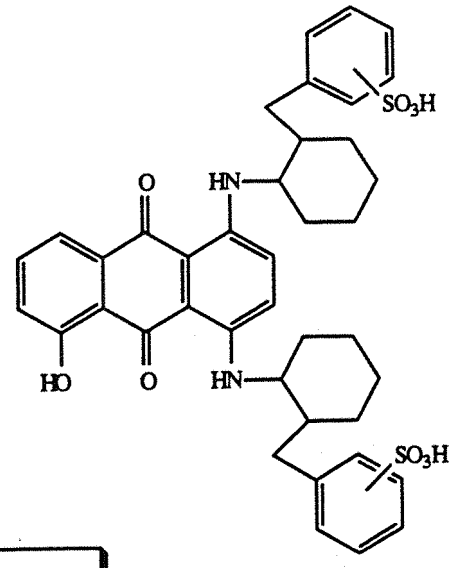
Supranol fast blue GG

Scheme 164

A second wide group of acid dyes have been synthesized by sulfonation of a dye base. Most of the obtained dyes are symmetrically substituted 1,4-diamino-anthraquinones provided commonly by condensation of 1,4-dihydroxy-anthraquinone, quinizarin (234) (scheme 165) with aliphatic, cycloaliphatic (example (235)) or aromatic amines, followed by a subsequent sulfonation. The anthraquinone nucleus may bear additional substituents (-OH, -Br, -Cl, -SO_3H, ...).



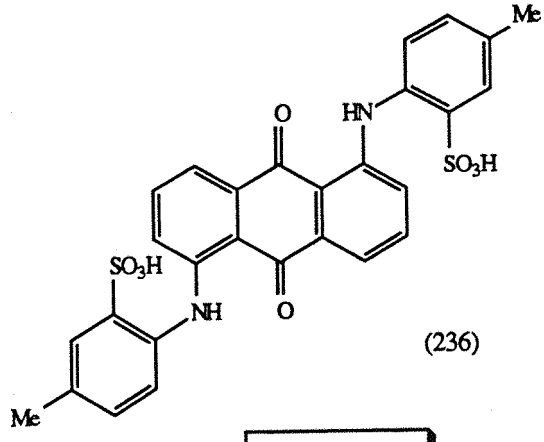
(234)



(235)

Scheme 165

Finally, compound (236) (scheme 166) has been one of the scarce 1,5-diamino derivative utilized (as one of the constituents of Anthraquinone violet).



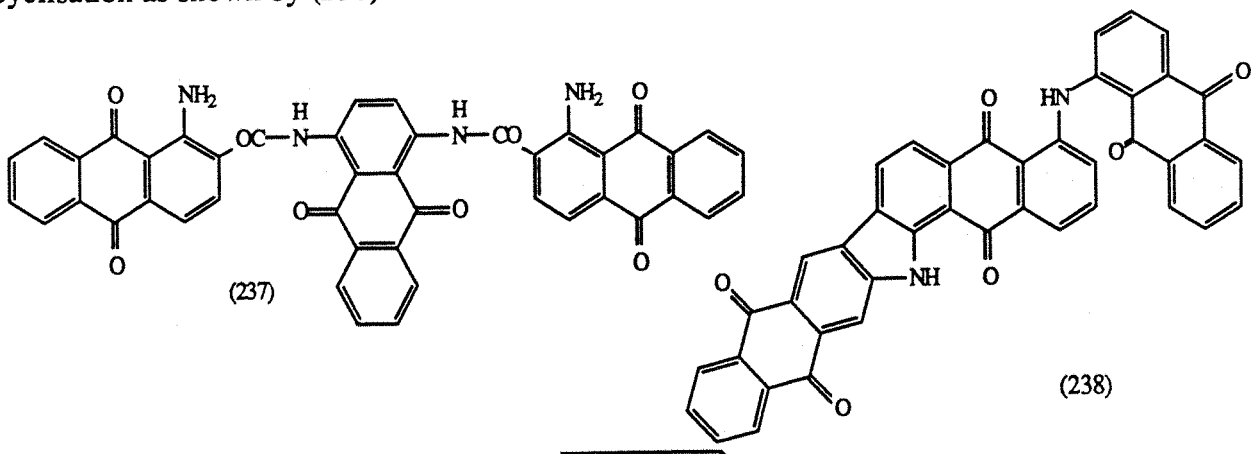
(236)

Scheme 166

b/ Amino-anthraquinonoid vat dyes[186b-c,187b]

They have constituted one of the leading group of vat dyes for cotton and other cellulosic fibers. Most of them have been species containing two or three similar or different basic anthraquinone unities, often acyl-amido-anthraquinones, linked either directly by intermolecular condensation as illustrated by Indanthrene Rubine GR (237) (scheme 167) or through a junction reagent such as imidazoles, oxazoles, thiazoles, triazoles or oxadiazoles. Certain direct condensations have thus led to "anthrimides" derivatives (1,1' or 1,2'-dianthraquinonylamines) and carbazoles after further

cyclisation as shown by (238).

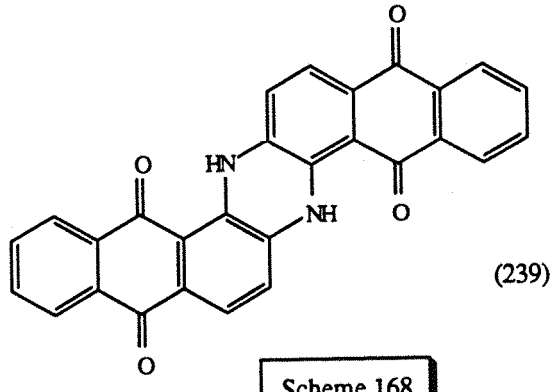


(237)

(238)

Scheme 167

The indanthrone derivatives have formed a major category of anthraquinone vat dyes. Indanthrone (239) (scheme 168) is derived fromthe condensation of two molecules of 1- or 2-amino-anthraquinone in a complex mechanism. It has been applied on textile but also as a blue pigment.



(239)

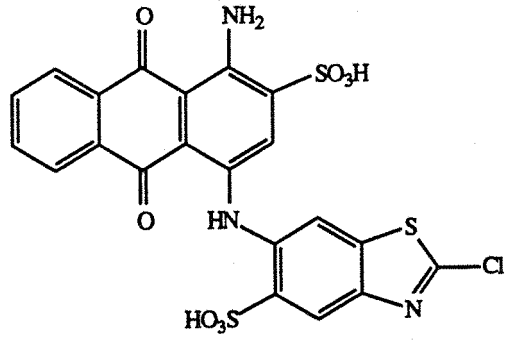
Scheme 168

c/ Amino-anthraquinonoid reactive dyes.[188a,b]

A "reactive dye" usually designates a dye applicable to cotton. A reactive dye must contain either a leaving group X able to be displaced by a hydroxyl of cellulose (dye-X + cell-O^- —> dye-O-cell + X^-) or an activated C=C to which a hydroxyl may add (dye-$CH=CH_2$ + cell-OH —> dye-CH_2-CH_2-O-cell).

The amino-anthraquinonoid reactive dyestuffs have been often soluble in water. Most of them have been 1-amino-4-arylamino-anthraquinone-2-sulfonic acid derivatives in which the aryl

substituent is an aromatic system containing at least one reactive group as in the single example (240) below, scheme 169.

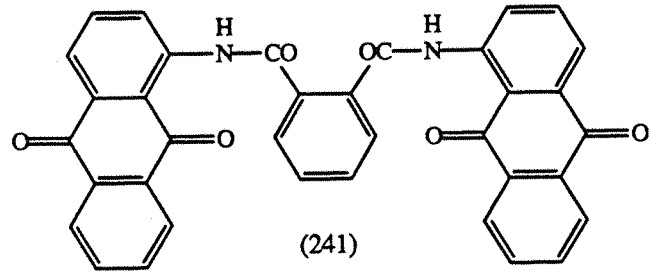


(240)

Scheme 169

d/ Amino-anthraquinonoid pigments.[187c]

Pigments must be insoluble in water and in the organic solvent in which they are to be used. Pigments are often utilized in suspension in suitable liquids and are hence employed mainly in printing inks and coating compositions. A number of amino-anthraquinonoid vat dyes have been converted into pigments (when not solubilized or made unsoluble) such as Acylamino yellow (241) (scheme 170).



(241)

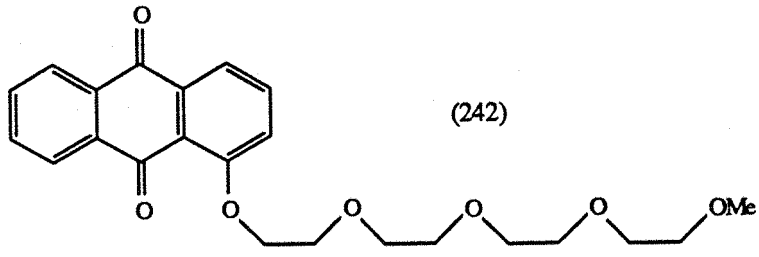
Scheme 170

2] Anthraquinonoid cation carriers.

The main results mentioned here have been reported by the group of Echegoyen and Gokel. They have demonstrated and applied the ability of transporting metal cations (Li^+, Na^+, K^+) exhibited by the reduced forms of anthraquinone-based podands and lariat ethers (a polyethyleneoxy or crown-ether type macrocyclic side-chain attached to the anthraquinone nucleus). The following results have been obtained by means of cyclicvoltammetry, atomic absorption spectrophotometry

and electron spin resonance.

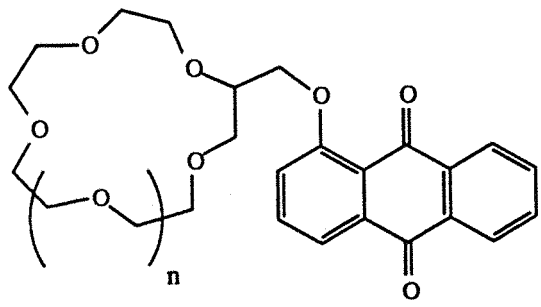
It was first shown[189] in 1986 that the transport of Li^+ through an organic model membrane (containing 0.1 M nBu_4NClO_4 and 2 mM of (242) in CH_2Cl_2) dramatically changed according to the potential applied at the working electrode. While (242) (scheme 171) appeared in its neutral form as a weak carrier, an important enhancement of transport of Li^+ (transport rate up to 2.2 x 10^{-7} mol/h) was observed with its anionic form $(242)^-$ after one single electron reduction. The obtained ligand/cation complex was thus neutral.



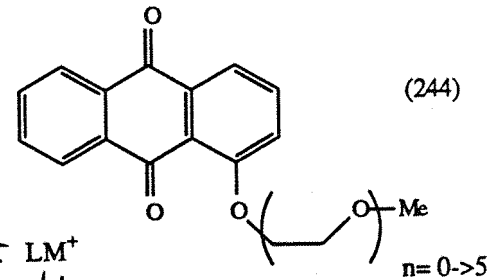
(242)

Scheme 171

The electrochemical switching process was then further investigated[190-192] and the chain effect in geometric and electronic cooperativity between the anionic or dianionic anthraquinone substituted podand of type (244) or lariat ether of type (243) was examined (scheme 172). Distinct new redox waves were observed from one (step 1') and, according to the case (with Na^+, K^+), two (step 2') electron transfer processes when a range 0-1 equivalent of cation was used, as shown in scheme 172.

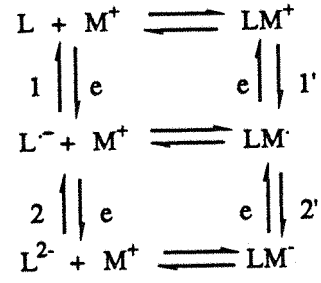


(243)



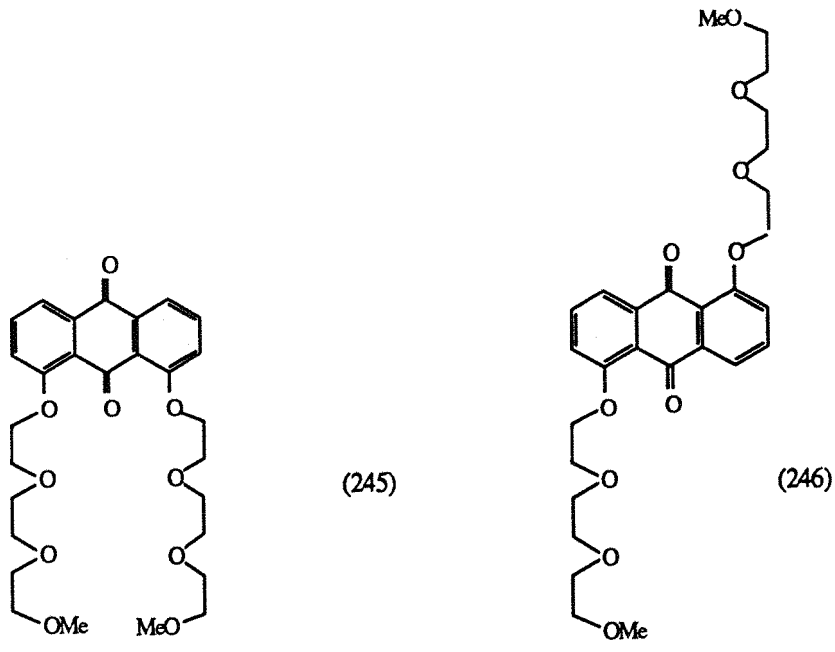
(244)

n= 0->5



Scheme 172

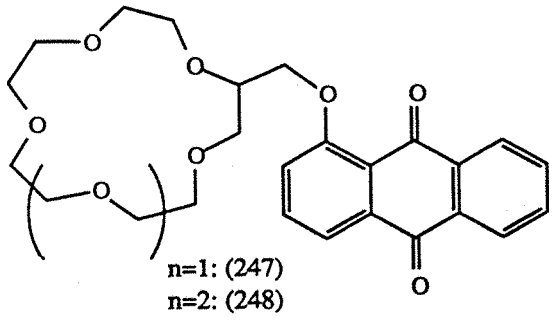
The same electronichemical study of the symmetrical bibracchial podands (corresponding to (244) with n= 3) "syn" (245) (scheme 173) and "anti" (246) in their mono- and dianionic states led in 1988 to further progress[193]. Reduced "anti" podand strongly bound successively two cations, one on each side, while cation was bound at one side of the anthraquinone in the 1:1 complex. Two Na^+ cations were also attached on the same side of the "syn". The binding enhancement obtained with the "anti" podand and Li^+ (for the one electron reduction wave) was one of the largest observed with any lariat or podand in a switching process ($\Delta E^{1-1'} = 0.46$ V).

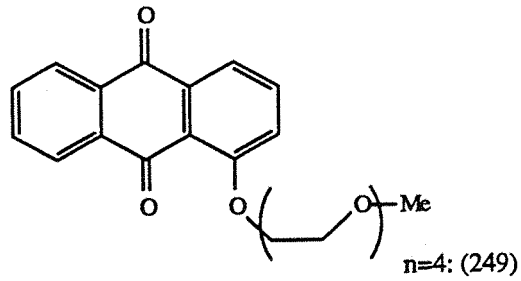


(245) (246)

Scheme 173

Finally, the first electrochemically switched "on/off" activation/deactivation process was reported[194] in 1989. The previously studied reduction was completed by the reverse oxidation of the anionic ligand/metal cation complex at the receiving phase, thus releasing cation. Thereby the cation transport is electrochemically controlled. The best results were noticed with the lariat ethers (247) and (248) and the podand (249) (scheme 174) as ligands and Na^+ as cation using a bulk liquid membrane (containing 40 ml of 0.5-2 mM ligand and 0.1 M $nBuNClO_4$ in CH_2Cl_2).



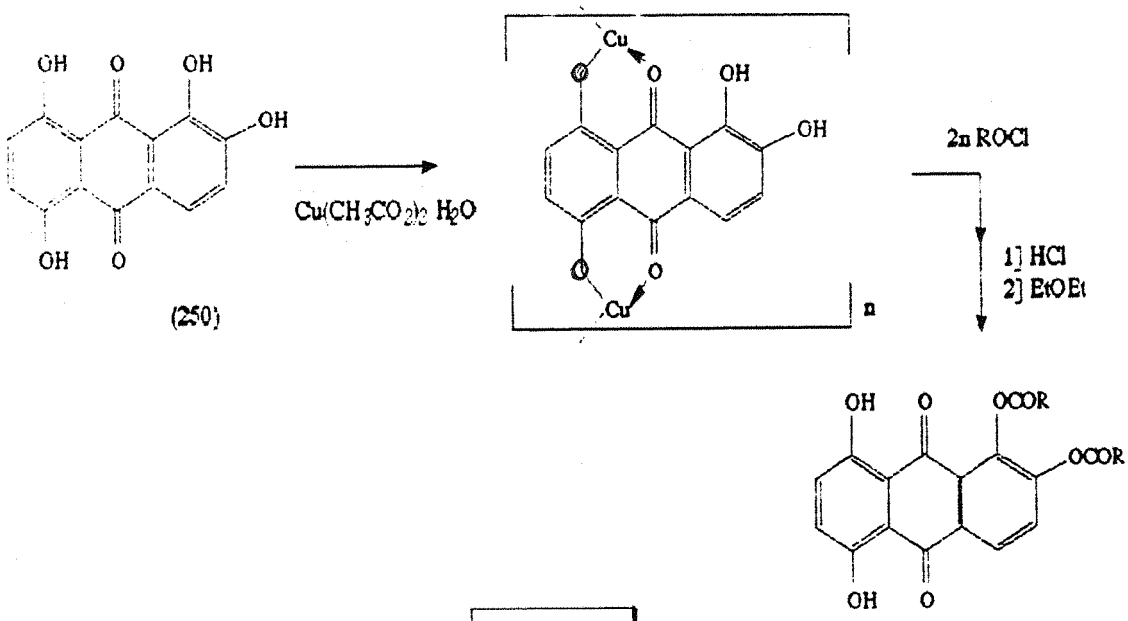


Carrier	Cation	Neutral	Reduced	Reduced/oxidized
(247)	Na^+	6.9×10^{-2}	1.3×10^{-1}	3.4×10^{-1}
(248)	Na^+	9.7×10^{-2}	1.4×10^{-1}	2.3×10^{-1}
(249)	Na^+	2.1×10^{-2}	1.4×10^{-2}	5.4×10^{-2}

Transport rate constants (h^{-1})

Scheme 174

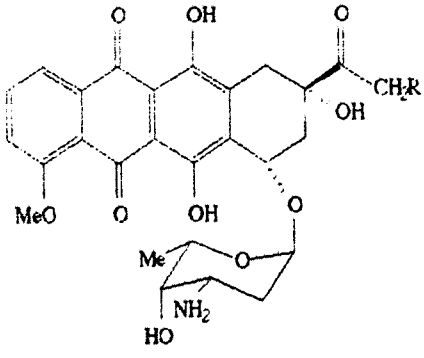
As a significantly different example, Papageorgiou reported[195] in 1986 a metal chelation occurring between Cu^{II} and two molecules of certain polyhydroxy-anthraquinones which involved a carbonyl oxygen atom and a hydroxyl group "ortho" with respect to it. This particularity allowed the selective esterification of chrysazin, alizarin and quinolizarin (250) (scheme 175).



Scheme 175

3] Amino-anthraquinone-based anti-cancer agents.[196-198]

The anti-tumor compounds anthracyclines are currently utilized in the treatment of neoplastic deseases. One of the most potent is doxorubicin[196] (251) (scheme 176) commonly named adriamycin. On the other hand, these anthracyclines exhibit toxic effects including cardiotoxicity. Therefore new anthracycline derivatives which have no severe side-effect has constituted an important area of research.



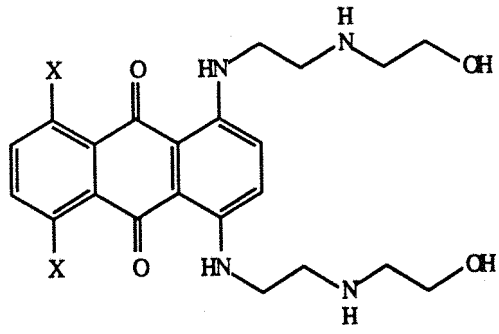
R= OH –> doxorubicin (251)

R= H –> daunorubicin (252)

Scheme 176

Now anthraquinones[197,198] show a lower tendency to be reduced by enzymatic species and consequently a lower toxicity than doxorubicin and daunorubicin (252). Hence, mitoxantrone (253)

(scheme 177), by exhibiting significant anti-tumor activity, has appeared as a good anti-neoplastic agent. It is now employed clinically for the treatment of human cancers. Mitoxantrone and ametantrone (254) intercalate with DNA thanks to the two basic side-chains.



X= OH --> mitoxantrone (253)

X= H --> ametantrone (254)

Scheme 177

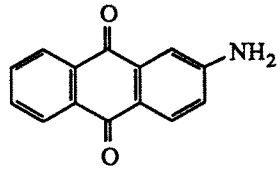
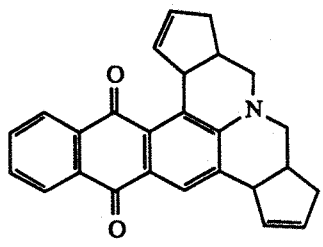
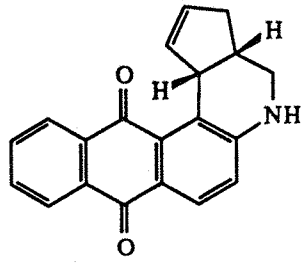
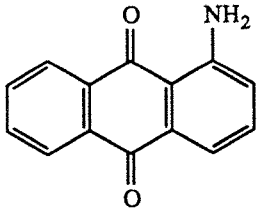
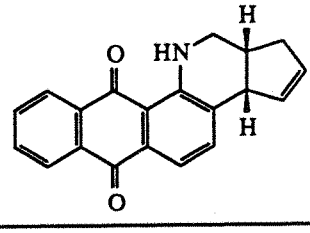
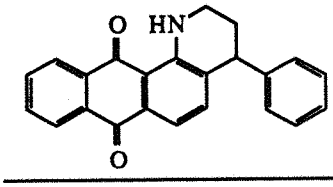
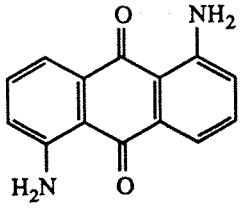
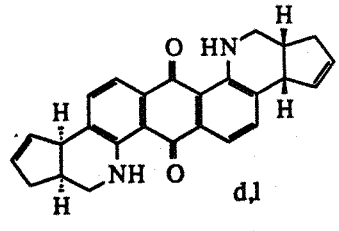
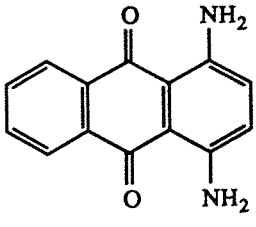
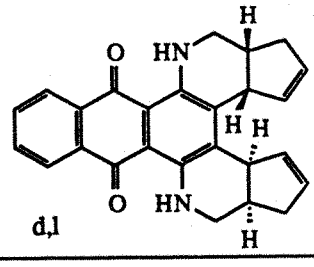
It has been confirmed[197] that the complexation of anthracyclines and anthracenediones with metals permits not only their absorption by organism but also a decrease in the undesired toxicity. Mitoxantrone and ametantrone form complexes with one Pd^{II} ion per molecule. The binding seems to take place with the two nitrogen atoms on the other side-chain on C_8. These metal-anthraquinone complexes (and metal-anthracycline complexes) constitute a novel category of anti-cancer agent whose interaction with DNA is different from that of the free drugs. The properties of these anti-cancer agents have been examined according to the nature of the complexed metal ion.

III] Results.

The 1-, 2-amino-, 1,4- and 1,5-diamino-anthraquinones which are commercialized were studied. The 2,6-diamino-derivative was not investigated because it could undergo the mono-, double mono-, di- and double dicyclisation processes and thus lead in a non selective course to a variety of adducts. 1,8-Diamino-anthraquinone was not available commercially. One must mention here that the d,l diastereoisomers derived from the 1,4- and 1,5-diamines possess a C_2 symmetry axis and a symmetry centre respectively (see previous section [C] III] 3] a/ 1)) about C_2 chiral auxiliaries).

The results observed in the monocyclisation (entries 3-8), double monocyclisation (entries 9-12) and dicyclisation (entries 1-2) reactions are listed below (scheme178).

1] Mono- and dicylisations of 2-amino-anthraquinone.

Entry	Starting amine	Type[1]	Reaction conditions[2]	Diels-Alder adduct(s)	Yield[3]
1		di	1 / 2 / 5 / 5 r. T. , 1 h 40 min		54 %
2		di	1 / 3 / 3 / 3 r. T. , 45 min	d,l + meso	96 %
3		mono	1 / 1 / 1 / 1 r. T. , 25 min		0 %
4		mono	1 / 3 / 1 / 2 r. T. , 45 min		55 %
5		mono	1 / 3 / 1 / 2 reflux, 45 min		74 %
6		mono	1 / 1 / 1 / 1 r. T. , 35 min		33 %
7		mono	1 / 1 / 2 / 2 r. T. , 45 min		95 %
8		mono	1 / 1 / 4 / 4 r. T. , 2 h 15 min reflux, 45 min		86 %
9		dble mono	1 / 2 / 4 / 4 r. T. , 1 h 40 min		42 %
10		dble mono	1 / 2 / 2 / 3 0°C, 10 min	d,l	18 %
11		dble mono	1 / 2 / 4 / 4 r. T. , 1.5 min		13 %
12		dble mono	1 / 2 / 2 / 3 r. T. , 25 min	d,l	43 %

1] di= dicyclisation ; mono= monocyclisation ; dble mono= double monocyclisation.
2] respective ratios of starting amine / TFA / formaldehyde / cyclopentadiene (styrene for entry 8) reaction temperature, reaction time.
3] obtained after isolation of the Diels-Alder adduct(s) by flash chromatography.

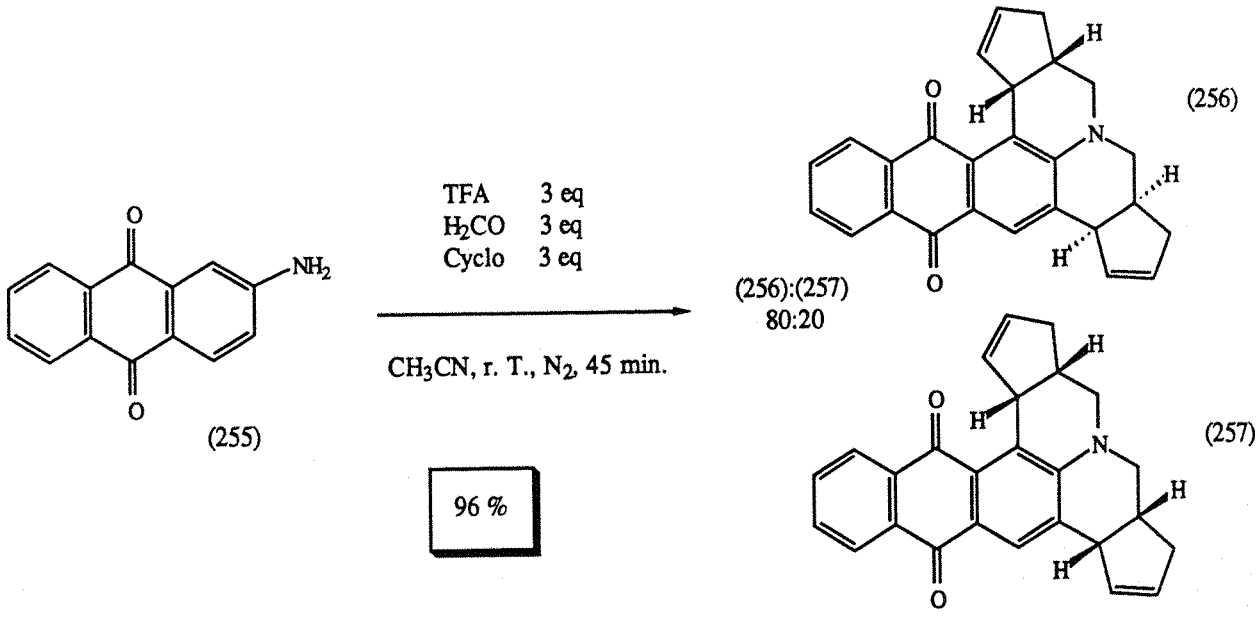
Scheme 178: table of the results obtained with the amino-anthraquinones.

a/ Dicyclisation.

The dicyclisation process was to provide the diastereoisomers d,l and meso in an overall yield higher than those observed in the previously investigated dicyclocondensations of bicyclic amines (71-89 %).

In a first experiment, the dicyclisation of 2-amino-anthraquinone (255) (scheme 179) was carried out with TFA/formaldehyde/cyclopentadiene in respective ratios 1/2/5/5 at room temperature for 1 hour 40 minutes. It afforded a red major component after separation by flash chromatography on alumina (in the anthraquinone series, the columns were run on alumina for a better separation). The mass spectrum (M^+(100%)= 379) and the IR spectrum (no N-H stretching) confirmed the desired structure(s) (256) and/or (257) thus isolated in 54 % yield. Despite the use of a large excess of reagents, it was unlikely that some further reaction on the two aromatic rings constituted the main explanation for the moderate yield. On the other hand, the starting material utilized was very impure (technical) and the crude reaction product pre-adsorbed on alumina tended to stick on it while running the column. This latter difficulty was noticed with all the amino-anthraquinones investigated.

Therefore the reaction was repeated from purified (by flash chromatography) starting material as a brown powder with a small excess of TFA, formaldehyde and cyclopentadiene (respective ratios 1/3/3/3), a shorter reaction time (45 minutes) and at room temperature. Under these conditions, a major compound was completely separated along with a slightly more polar fraction. The mass spectrum (M^+(100%)= 379) and the 270 MHz ^1H NMR spectrum (singlet at 8.06 ppm, two multiplets at 8.19 and 7.69 ppm, no amino proton) confirmed the skeleton of a dicyclisation adduct hence obtained in 96 % yield. The ^{13}C spectrum unambiguously revealed it to be a mixture of the two diastereoisomers d,l (256) and meso (257) since many peaks were doubled. Again on steric grounds, the d,l was considered as the more favoured rather than the meso (the relative ratios 80:20 were deduced from spectra). Hence, contrary to what we hoped, the minor fraction which was also a red solid was not the meso isomer.



Scheme 179

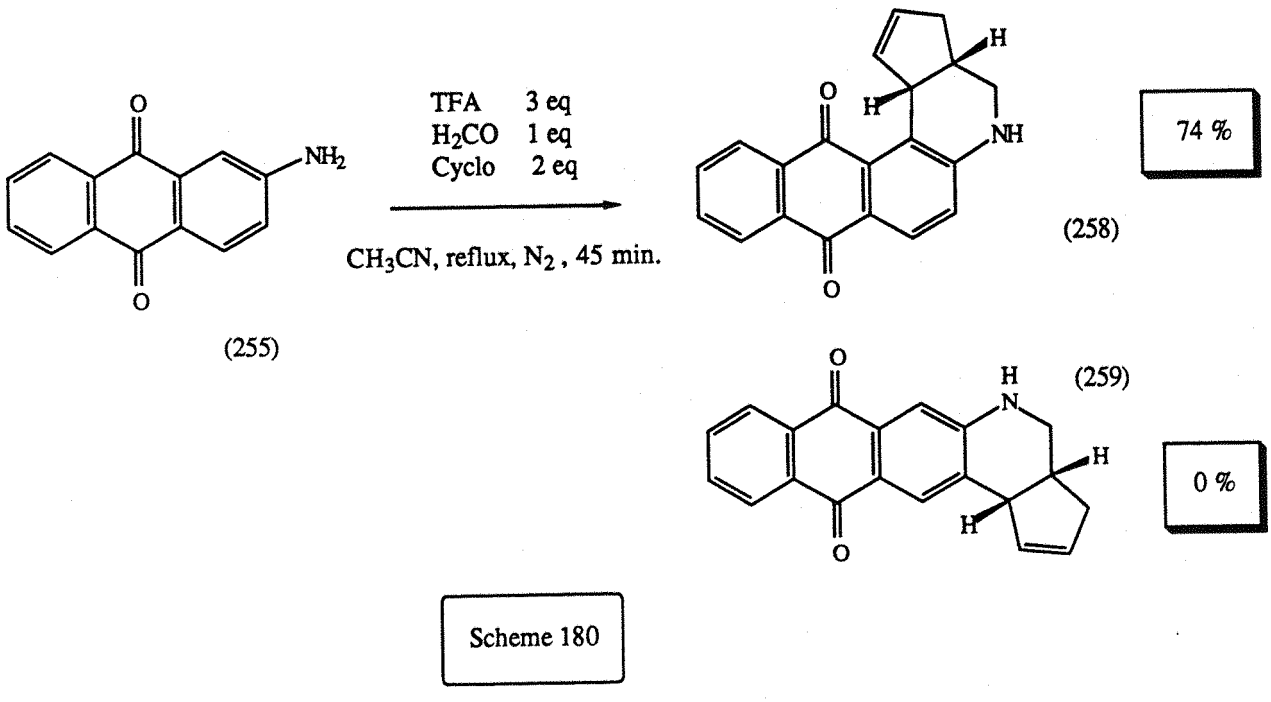
In view of the previously reported results of double cyclisation, the absence of clear separation of the d,l and meso isomers on t.l.c. and by flash chromatography was quite surprising. On the other hand and as expected, a very high overall yield was observed.

b/ Monocyclisation.

In a first approach, the monocyclisation was carried out using purified 2-amino-anthraquinone with TFA, formaldehyde and cyclopentadiene in stoichiometric ratios at room temperature. It led after separation to a major fraction (50 %) corresponding to the mixture of dicyclisation adducts (256) and (257) along with recovered starting amine (31 %). Such a failure could be only explained in terms of relative solubility in acetonitrile of the different species present in the reaction mixture. Indeed, since the salt of the starting material was just partially dissolved before adding formaldehyde and cyclopentadiene, the afforded monocyclisation adduct, which was more soluble than 2-amino-anthraquinone, tended to further react with reagents at the expense of starting amine and to be converted to the dicyclisation products. In line with this statement, the reaction was repeated from a very dilute and almost homogenous mixture of 2-amino-anthraquinone with TFA, formaldehyde and cyclopentadiene in respective ratios 1/3/1/2 at room temperature for 45 minutes. It thus provided along with dicyclocondensation compounds (~25 %) a new more polar and red purple component isolated in 55 % yield. Its mass (M^+(100%)= 301) and IR (N-H vibration band) spectra were in accord with the desired structure (258) (scheme 180). While the 270 MHz ^1H NMR spectrum showed no aromatic singlets but two doublets at 8.10 and 6.80 ppm, extra peaks

which might have been assigned to the second monocyclisation regioisomer (259) could be noticed in the ^{13}C spectrum, but the absence of different tertiary aromatic carbons confirmed the structure (258).

Finally, in order to get a liquid reaction mixture, a further experiment was carried out under the same conditions but at reflux. Thereby, this monocyclisation was optimized to 74 % yield, again in a regioselective fashion. Dicyclisation adducts were afforded in about 14 % yield.



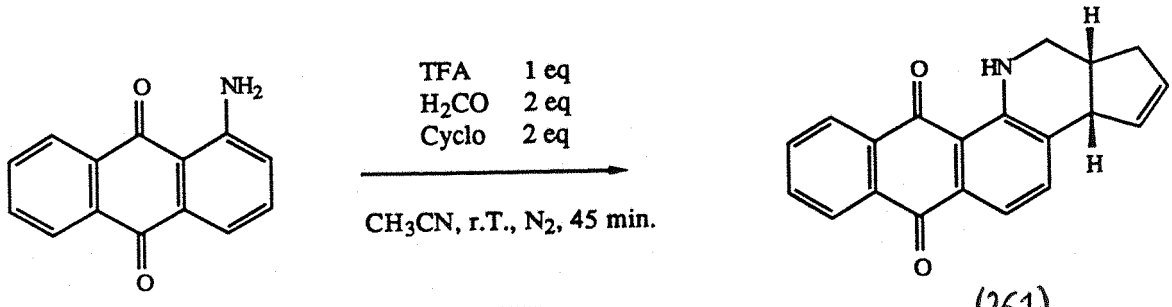
Scheme 180

On the whole, 2-amino-anthraquinone was demonstrated to behave like the bicyclic 7-amino-α-tetralone in the monocyclisation (regioselectively, good yield) and dicyclisation (two disatereoisomers but not easily separable, high yield) processes. Moreover, the additional carbonyl in the quinonoid system permitted a noticable increase of yields in both modes.

2] Monocyclisations of 1-amino- and related 1,4- and 1,5-diamino-anthraquinones: obtention of 11-azasteroids.

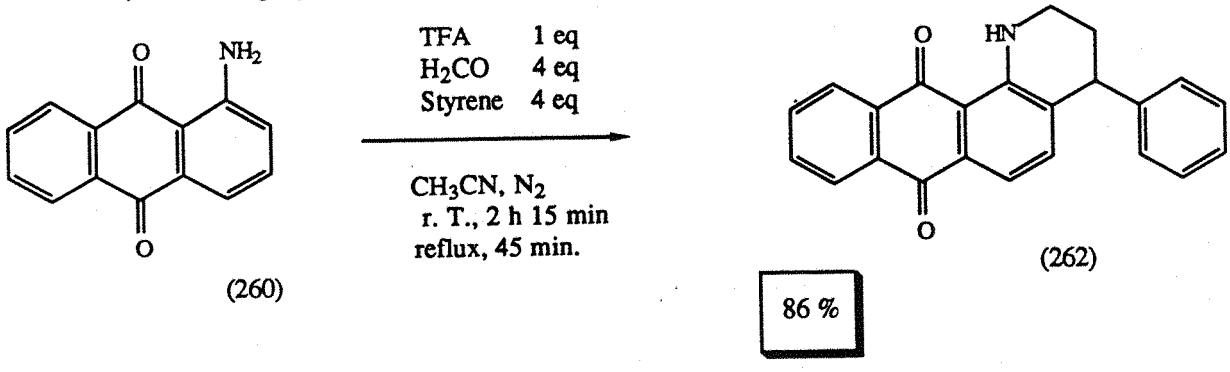
The monocyclisation of 1-amino-anthraquinone (260) (scheme 181) was first examined at room temperature in stoichiometric ratios of reagents for 35 minutes. It led after partial separation to the isolation in 33 % yield of a non polar red purple solid as major reaction product while some starting amine was recovered. It was fully characterized and assigned to the structure (261) by means of its mass (M^+(100%)= 301), ^1H (two aromatic doublets at 7.58 and 7.43 ppm, the aromatic proton at 9.64 ppm because of the hydrogen bond with the oxygen) and ^{13}C NMR spectra.

No further substitution was expected to take place on both aromatic rings while utilizing an excess of reagents. Therefore, the reaction was repeated by observing 1/1/2/2 as respective ratios for starting amine/TFA/formaldehyde/cyclopentadiene, at room temperature for 45 minutes. Under these conditions, compound (261) was afforded and fully separated in 95 % yield.



Scheme 181

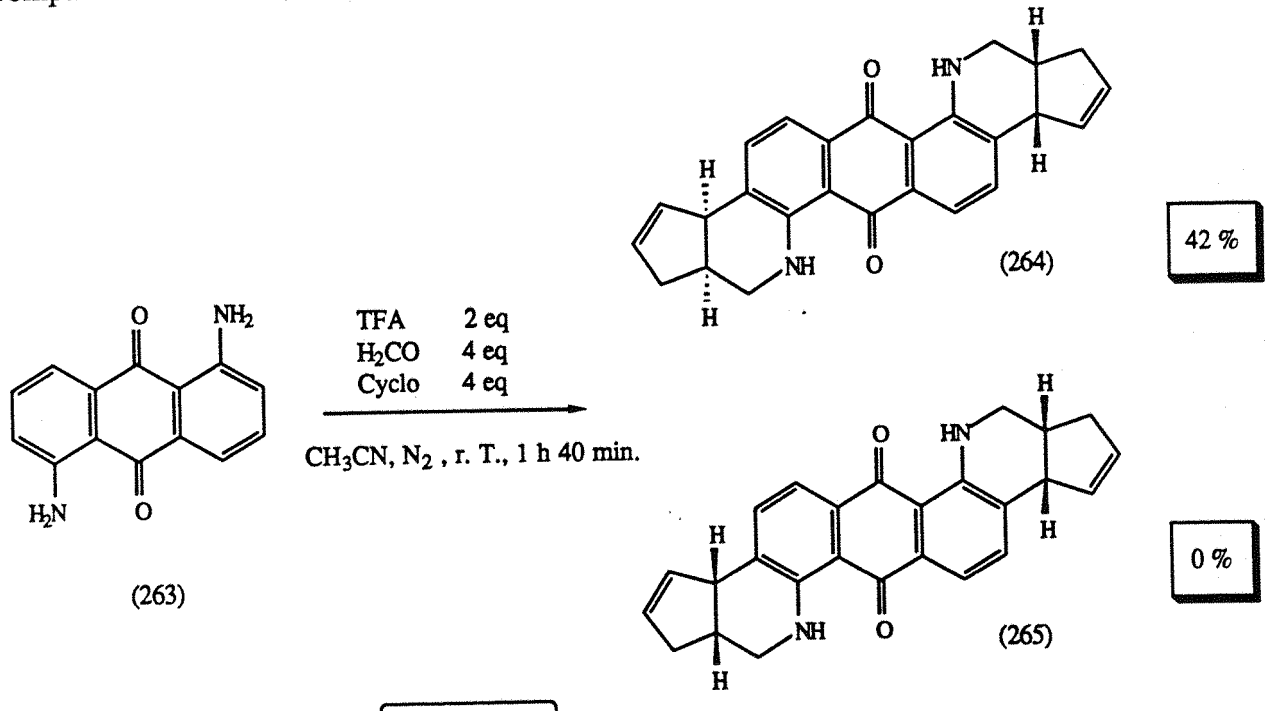
Since this monocyclisation was very successful, it was decided to attempt it with styrene as dienophile. The reaction was carried out with 1/1/4/4 as respective ratios of 1-amino-anthraquinone, TFA, formaldehyde and cyclopentadiene for 3 hours (2 hours 15 minutes at room temperature, 45 minutes at reflux). A major red purple solid was provided and isolated in 86 % yield. It was unambiguously assigned by means of spectroscopic analyses (M^+(100%)= 379, clear ^1H spectrum with distinct aromatic protons) to the structure (262) (scheme 182). Hence, like cyclopentadiene, styrene underwent regioselective cycloaddition (as earlier pointed out by Merriman) and in high yield.



Scheme 182

In view of these results, the carbonyl group close to the amine seemed to possess a strongly activating role in the cycloaddition process by comparison with the 5-amino-α-tetralone case (65 %). The investigation of the diamine directly derived from 1-amino-anthraquinone, 1,5-diamino-anthraquinone (263) (scheme 183), then suggested itself. One could expect the two possible diastereoisomers d,l and meso to be afforded in an overall high yield.

The double monocyclisation of 1,5-diamino-anthraquinone (263) (scheme 183)was carried out with TFA/ formaldehyde/cyclopentadiene in respective ratios 1/2/4/4 at room temperature for 1 hour 40 minutes. A major and less polar component was partially isolated in 36 % yield as a red purple solid. The second fraction separated was a mixture of this former compound and a very minor one showing the same colour on t.l.c.. Neither remaining starting amine nor significant other product was noticed. The mass spectra (M^+(100%)= 394) of both fractions were quite similar and hence seemed to justify the assignment of these two adducts to the wanted double monocyclisation diastereoisomers (264) and (265). The IR (N-H) spectrum, the ^1H (two aromatic doublets at 7.53 and 7.40 ppm, the two amino protons at 9.57 ppm) and above all ^{13}C (only 13 peaks because of the symmetry, none double peak) NMR spectra of the pure fraction unambiguously confirmed it as one pure isomer likely to be the d,l isomer on steric grounds. Further flash chromatographies were run so as to separate the two compounds of the second fraction. The isolation of the minor one appeared very difficult and was not achieved. A supplementary quantity of d,l isomer was obtained (6%) while the remaining fraction was still a mixture in about 2% yield (considering M= 394 g/mol). Consequently, the meso diastereoisomer, if so, was provided in a very minor yield in comparison with the d,l isomer (42 %).



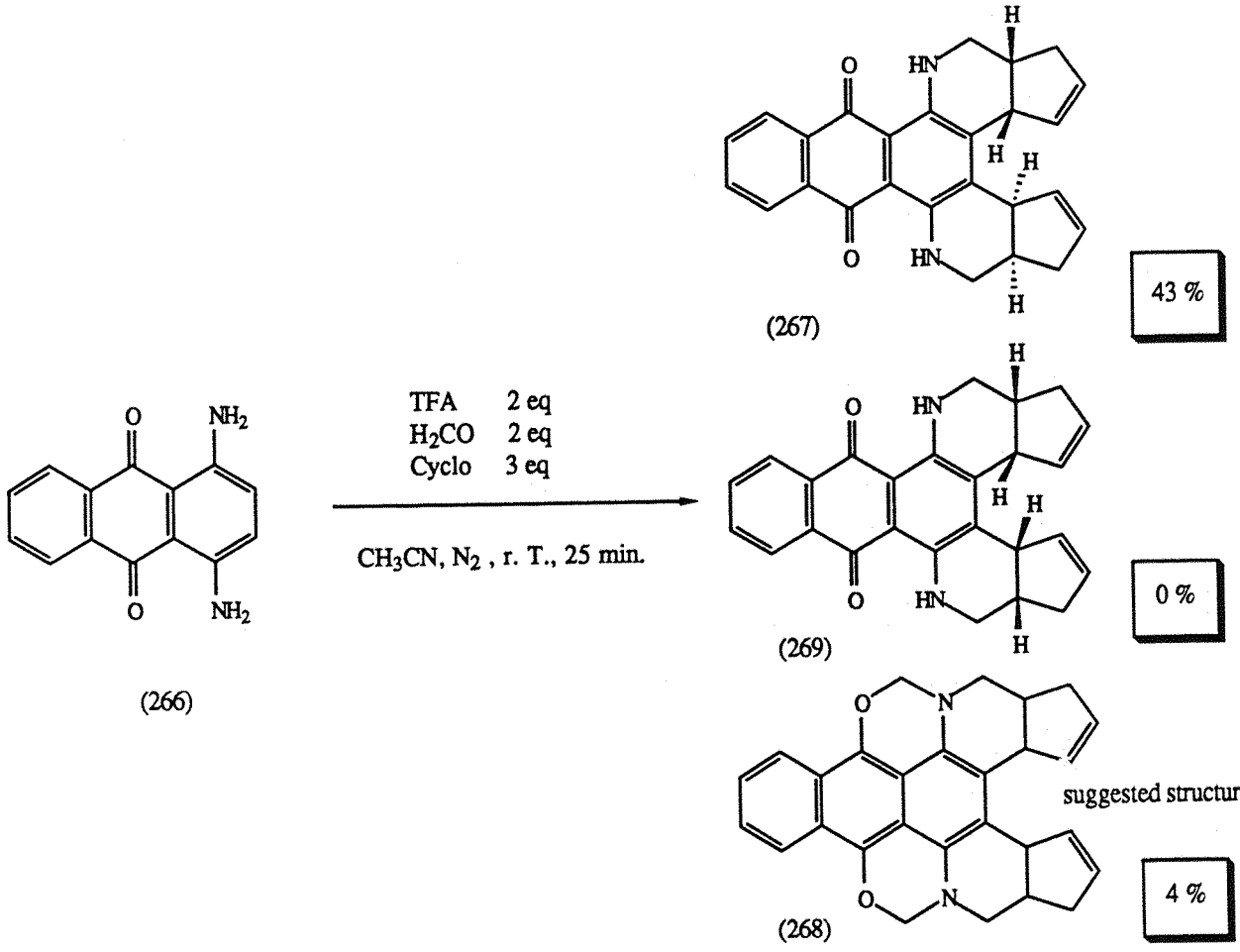
Scheme 183

A further experiment using starting amine, TFA, formaldehyde and cyclopentadiene in ratios 1/2/2/3 respectively was carried out at 0 °C for 10 minutes but no improvement was noticed. Indeed, several columns were again necessary to separate the same major compound (264) in 18 % yield and a minor fraction containing (264), the same more polar red component and some starting material. The low solubility of the reaction product involved tricky extractions (emulsion), long filtrations after drying whereby a very insoluble dark precipitate was removed, and difficult chromatographies. The poor yield (42 %) reflected some of these isolation problems.

The investigation of 1,4-diamino-anthraquinone (266) (scheme 184) was also characterized by the similar problems of solubility, loss of product and difficulty in separation. Moreover the second monocyclisation could be disadvantaged considering the steric hindrance likely in the final cyclisation. In line with this hypothesis, a highly diastereoselective outcome in favour of the d,l isomer was probable.

In a first experiment carried out at room temperature for 1 hour 30 minutes, ratios 1/2/4/4 were used for 1,4-diamino-anthraquinone, TFA, formaldehyde and cyclopentadiene respectively. A brown orange minor solid and two slightly more polar blue solids were separated. One was a pure compound fully characterized as a single diastereoisomer likely to be the d,l isomer (267) (scheme 184) through its mass spectrum (M^+(100%)= 394) and clean ^1H and ^{13}C NMR spectra. Hence (267) was isolated in 13 % yield. The top brownish solid appeared as a pure compound in view of its clear mass spectrum (M^+(100%)= 420). The NMR spectra did not permit a structural assignment. However, its IR spectrum showed none band corresponding to C=O and N-H stretching. Consequently, the structure (268) was suggested. Finally, the second blue fraction contained (267) along with the same dark orange compound. Since no starting amine was recovered, we suspected that the black precipitate removed in filtration after drying constituted the main explanation for the poor result observed. However, the formation and the structure of these by-products were not resolved.

The cyclisation was repeated at room temperature with a shorter reaction time (25 minutes) and with starting amine, TFA, formaldehyde and cyclopentadiene in ratios 1/2/2/3 respectively. The d,l isomer was provided in 43 % yield. Although the reaction products were significantly more soluble than in the 1,5-diamine case, several chromatographies were required to fully isolate a second blue compound. Its mass spectrum also showed 394 (25%). But neither the ^1H nor ^{13}C NMR spectra were clear enough to confirm the meso isomer (269). Since it would have been afforded in only 0.6 % yield (considering M= 394 g/mol), the double monocyclisation was considered highly diastereoselective.



Scheme 184

As expected, the monocyclisation of 1-amino-anthraquinone was highly successful with both cyclopentadiene and styrene as dienophiles. In the former case, the 11-azasteroid (261) was thus afforded in 95 % yield. On the other hand, the related diamines provided only a single distereoisomer which is likely to be the d,l isomer and in a medium yield (~40-45 %). This diastereoselectivity was surprising in the 1,5-diamine case since the Diels-Alder adduct showed no steric hindrance in comparison with the 1,4-diamino derivative. Since no significant by-product was noticed within this series of amino-anthraquinones, the main reason for these lower results was an important loss of material while working up and columning (several times) the reaction mixtures due to their weak solubility.

III] Conclusion to the anthraquinone series.

The investigation of various amino-anthraquinones extended the chemistry of the bicyclic

amino-ketone series to tricyclic systems. While one carbonyl exhibited the same positive effects than previously, the additional carbonyl in the quinonoid nucleus involved a strong deactivation of the nearest aromatic positions which further reacted in the cases of 7-amino-α-tetralone and 6-amino-α-indanone. Consequently, an improvement of yields in both mono- and dicyclisation modes from 2-amino-anthraquinone was observed (74 % and 96 % respectively). The study of 1-amino-anthraquinone (95 % with cyclopentadiene and 86 % with styrene) demonstrated the strong activating effect of a carbonyl group ortho with respect to the amine, by comparison with the case of 5-amino-α-tetralone (65 %). The medium results obtained with the two diamino-anthraquinones did not rule out this statement since they were due to solubility problems while working up and purifying.

[E] COMMENTS

I] General remarks concerning the species.

-> The obtained species were mostly solids, stable and coloured. A change of colour between a starting amine and the corresponding Diels-Alder was usually observed. A monocyclisation product and the dicyclisation derivatives usually showed the same shade, the latter ones being darker. The anthraquinoid adducts exhibited strong and various colours (red, purple, blue) according to the starting amine, which is in accord with their known dyeing features (see previous section [D] II] 1] about their use as dyestuffs).

-> For a "meta" amine undergoing mono- and dicyclisation, the melting points of the different adducts observed the rule:

monocyclisation < dicyclisation diastereoisomer d,l < dicyclisation diastereoisomer meso

-> The following rank of relative polarity for species derived from a same starting amine was always noticed (">" = more polar than):

starting amine > monocyclisation adduct > dicyclisation diastereoisomer meso > dicyclisation distereoisomer d,l

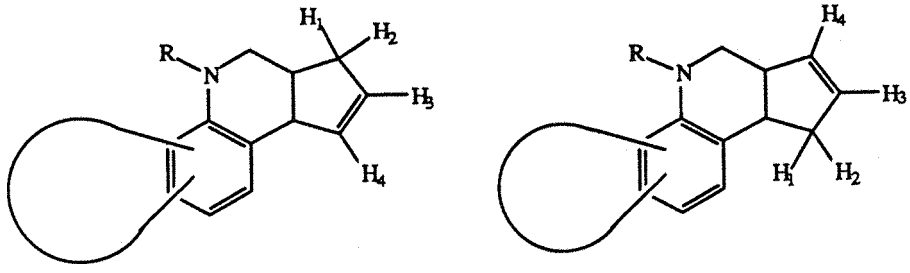
The by-products of the type discussed earlier (in section [C] III] 2] b/) are suspected to be always more polar than the corresponding starting amine.

-> The solubility of cyclisation adducts as well as the starting amines varied from one compound to another. Consequently, reaction and purification conditions changed according to the case. The anthraquinone series constituted the less soluble investigated species.

II] Mechanism and related features.

1] Regioselectivity

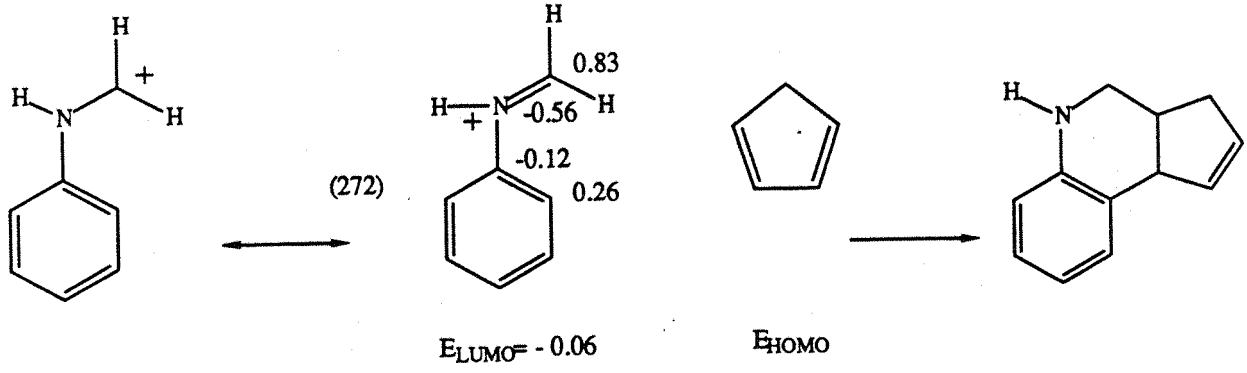
The Diels-Alder cycloadditions reported in this thesis probably take place through a mechanism with inverse electron demand; in other words, the relevant FMO interaction is between the LUMO of the dienic imine and the HOMO of cyclopentadiene. The obtained results showed that cycloaddition took place in a regioselective fashion as regards cyclopentadiene as only one product was observed (t.l.c.: one major spot). Indeed, if the two regioisomers (270) and (271) (scheme 185) showed the same Rf values, the presence of (271) would have been observed in the proton and especially carbon spectra with additional peaks.



(270) (271)

Scheme 185

The regioselective outcome can be confirmed by considering the atomic orbital coefficients of the positions involved in the cycloaddition. Since those of each investigated enamine unit are not available without calculations, one can consider those of the simple N-protonated dienic imine (272) (scheme 186) derived from aniline; these eigenvectors were calcaluted by the ab initio method,[121] while those of cyclopentadiene are well-known[199]. The large/large small/small selection rule directs the cycloaddition outcome, as shown in scheme 186.



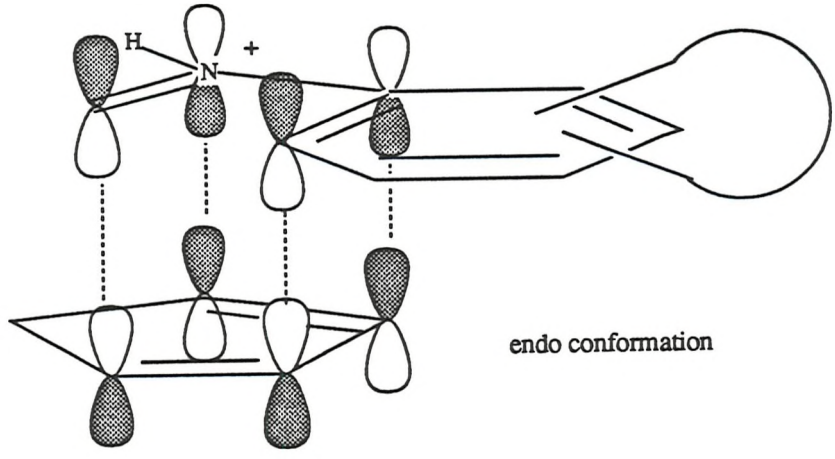
E_{LUMO} = - 0.06 E_{HOMO}

Scheme 186

However, this deduction is an approximation since the nature of the side ring does interfere in these values.

2] Endo/exo selectivity.

As regards the endo/exo alternative, our cycloadditions are likely to occur via an endo transition state in view of the stabilization undergone by the interacting secondary orbitals of the carbon atoms involved in the remaining double bond of cyclopentadiene on the one hand, and of the nitrogen atom and the quaternary aromatic carbon atom on the other hand (scheme 187).



endo conformation

Scheme 187

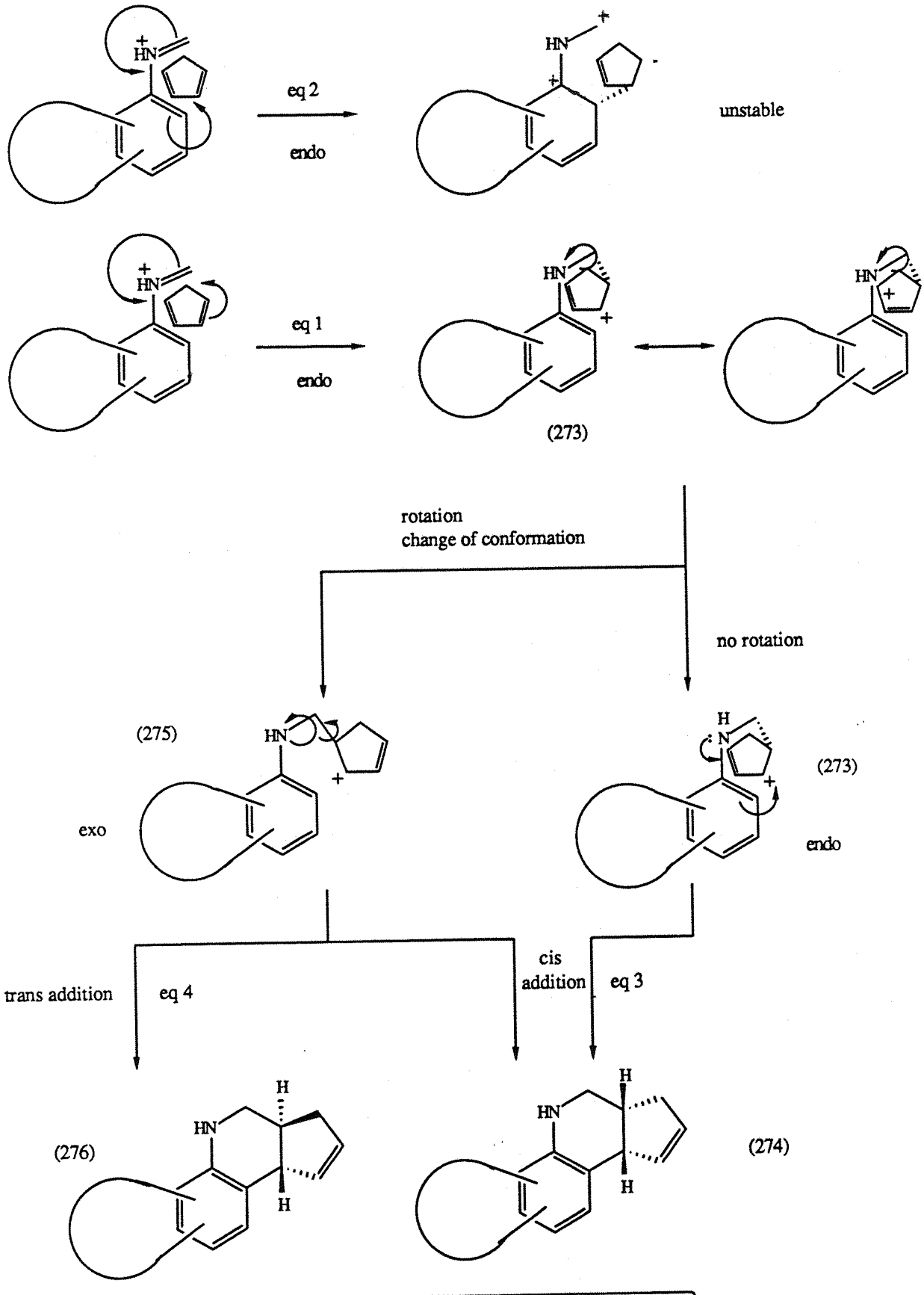
This endo rule is clearly observed when Schiff bases or acyl imines are used as dienes since they lead to cis-orientation for cyclopentadiene and the phenyl or acyl substituent. It is likely that the use of a chiral auxiliary with any of our investigated imines thus forming a chiral substituted enimine would undergo under Lewis acid catalysis a stereofacial selectivity in the addition process. A single endo transition state would consequently be favoured, which would lead to a major enantiomer, as reported by Lucchini (see previous section [D] III] in part 1).

3] Concerted/non concerted mechanism.

As mentioned in the introduction of this thesis, Diels-Alder cycloadditions can occur through a concerted mechanism or a non concerted process via an ionic intermediate (the possibility of a biradical intermediate in a stepwise mechanism is usually neglected). Both alternatives are to afford a single regioisomer. Therefore, the observed regioselectivity does not constitute an argument to

rule out the eventuality of a non concerted mechanism.

The alternative to a concerted process is stepwise formation of the two carbon-carbon bonds. Such a process might involve a stable ionic intermediate (273) (scheme 188, equation 1), in which the stereochemistry of the newly formed bond is determined by the face selectivity. In the case of cyclopentadiene this corresponds to enantioselectivity and hence under these experimental conditions a racemate is to be expected. The second bond forming step would take place from the same face constituting an overall cis-addition (equation 3, (274)), or, if rotation occurs bond formation on the opposite face (equation 4) would constitute trans-addition (product (276)). The occurrence of the flipping of the ionic intermediate (273) depends on its thermodynamic stability and kinetic features. Not only the ionic intermediate is likely to be stabilized in the endo conformation by means of the secondary orbital interactions still interfering at this stage of the cyclisation, but one can also suspect that the formation of the second bond takes place faster than the flipping to the exo conformation. A coupling constant around 8.5-9.5 Hz between the two methine protons would have confirmed the cis relative orientation of our compounds but it could not be discerned in any spectrum. Our observation of a single product assigned the cis stereochemistry in accord with the X-ray structure determination reported by Grieco. However, it does not preclude the stepwise mechanism.



Scheme 188: alternative of a stepwise mechanism

4] Diastereoselectivity.

In the case of the formation of the adducts by dicyclisation, either d,l or meso diastereoisomers can be formed. Grieco had established earlier the preference for formation of the d,l diastereoisomers. In the different cases examined, there is high diastereoselectivity and the major products were assigned the d,l configuration.

III] Spectroscopic data.

1] NMR data.

It was possible to make most assignments in the ^{1}H and ^{13}C NMR spectra without difficulty. Exceptionally in the anthraquinone series some aromatic resonances were difficult to assign. Data are presented in the table below (scheme 189). The data related to the adduct (262) obtained with styrene as dienophile (scheme 183) and the non separated mixture of regioisomers (162) and (163) (scheme 133) are not mentioned (see experimental part). In the table, it is interesting to note the following points :

-> the amino proton(s) in the mono- and double monocyclisation adducts were observed in the range 3.6-11.8 ppm. The "ortho" amino-quinones (entries 16-18) permitted hydrogen bonding to the amino proton and hence resonances were observed in the range 9.6-11.8 ppm. In contrast, in all the other adducts where intramolecular hydrogen bonding was not possible, the N-H resonance was observed in the region 3.6-4.7 ppm. The proton spectra showed no evidence of splitting to the two vicinal protons. The spectrum of the double monocyclisation compound from 1,4-diamino-anthraquinone (entry 18) showed an interesting characteristic. Despite the symmetry of the molecule, two peaks of equal intensity appeared for the two amino protons at 11.35 and 11.79 ppm. It constitutes the only case in which two N-H resonances are observed. As molecular models indicate that the skeleton will suffer considerable steric hindrance, it is likely that the two tetrahydro-pyridine rings are held in different conformations in spite of the apparent molecular symmetry. Such a conformational assignment is likely to lead to two N-H resonances. Addition of D_2O led to slow (over 30 minutes) exchange of both amino protons. The two signals diminished at a comparable rate.

-> the two non equivalent protons H_1 and H_2 (scheme 190) α to the nitrogen atom mostly appeared distinctly in the range 2.9-3.2 ppm. In several spectra (entries 3,4,7,8 and 11), a double doublet (J~ 11-12 and 2-4 Hz) for H_1 and a triplet-like signal (J~ 9-11 Hz) at slightly higher field for H_2 could be observed. The building of a molecular model showing the two limit conformations allowed by flipping of the structure permitted a better understanding of the spectral

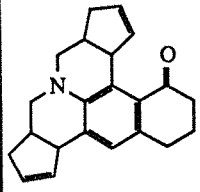
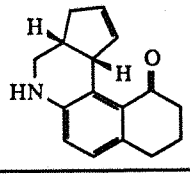
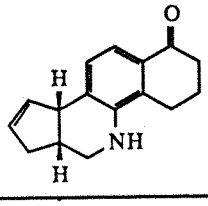
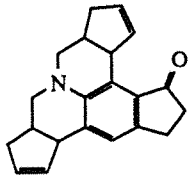
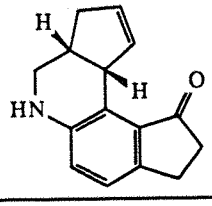
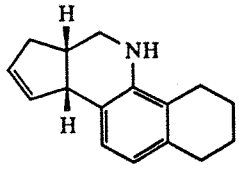
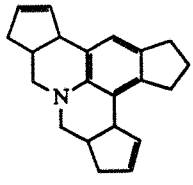
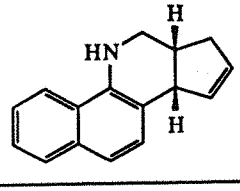
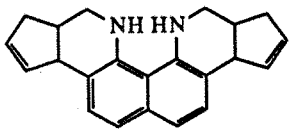
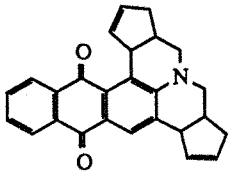
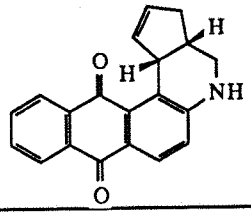
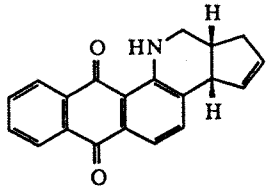
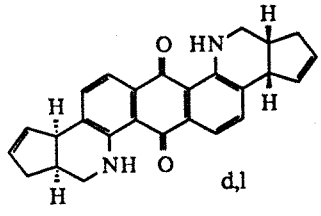
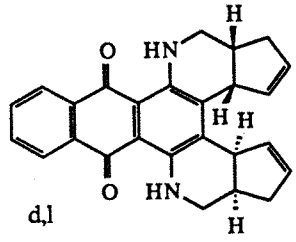
Entry	Diels-Alder adduct[1]	N – H ppm	H ppm H	– C – H ppm	N – CH_2 ppm	– CH ppm	C = C H H ppm
1	 d,l	-----	5.72 (2) 5.62 (2)	5.02 3.89	54.60 53.30	47.65 45.22	137.21 134.94 130.11 128.98
2	meso	-----	5.81 (1) 5.71 (1) 5.63 (2)	4.89 3.88	54.03 52.29	47.68 45.34	138.45 135.25 129.09 128.04
3		3.67	5.67 (2)	4.86	43.74	44.76	137.60 127.5
4		3.83	5.80 5.70	3.92	44.69	46.96	135.33 129.13
5	 d,l	-----	5.80 (1) 5.74 (2) 5.65 (1)	4.66 3.96	54.28 53.76	47.83 43.80	136.22 134.94 130.34 128.99
6	meso	-----	5.84 5.81 5.71 5.64	4.54 3.94	53.64 52.87	47.92 43.99	137.16 135.35 129.06 127.04
7		3.89	5.85 5.66	4.55	44.34	43.31	136.51 128.03
8		3.71	5.81 5.64	3.86	44.83	46.32	136.48 128.34
9	 d,l	-----	5.81 5.77 5.72 5.68	3.88 (2)	54.39 54.03	46.95 45.60	134.06 (2) 129.98 129.52
10	meso	-----	5.86 5.81 5.69 5.64	3.85 (2)	53.95 53.23	47.28 45.90	136.78 134.66 128.52 127.98
11		4.17	5.93 5.69	3.97	44.88	46.95	136.05 128.5

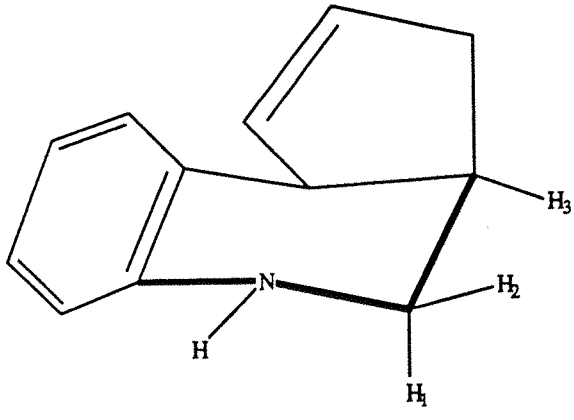
table ..../....

Entry	Diels-Alder adduct[1]	N – H ppm	H ppm H	– C – H ppm	N – CH$_2$ ppm	– CH ppm	C=C H H ppm
12	 d,l + meso	not discerned	5.92 (2) 5.69 (2)	3.97 (2)	45.01	46.76	136.12 128.6
13	 d,l	-----	5.84 (1) 5.77 (3)	5.15 4.04	55.66 52.13	47.44 45.44	136.65 135.23 129.93 128.85
14	meso d,l + meso				53.01 51.28	47.73 45.44	137.66 135.73 129.29 128.04
15		4.71	5.84 5.77	4.97	42.40	45.01	137.15 127.23
16		9.64	5.78 (2)	3.97	42.27	46.85	135.34 127.23
17	 d,l	9.57 (2)	5.79 (2) 5.76 (2)	3.95 (2)	42.33 (2)	46.73 (2)	135.57 (2) 129.48 (2)
18	 d,l	11.35 11.79	5.87 (2) 5.77 (2)	4.15 (2)	41.53 (2)	44.04 (2)	133.08 (2) 131.8 (2)

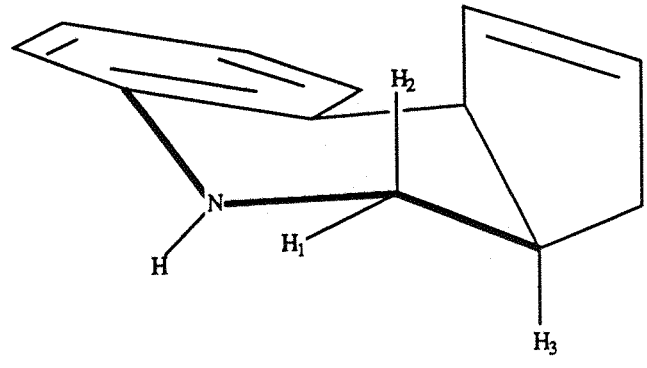
1] Obtained with cyclopentadiene as dienophile. The numbers between brackets indicate, when it is not obvious the number of proton(s) or carbon(s) corresponding to the signal.

Scheme 189: main NMR features of the cycloadducts

observations and suggested an interesting conformational feature. The double doublet is due to the splitting of H_1 by the geminal H_2 (J_{gem}~ 10-11 Hz) and the vicinal methine proton H_3 (H_1H_3 angle ~ 40-50 ^{o} in both conformations, J_{vic}~ 2-4 Hz) and is in accord with each of the two possible conformations. The triplet is due to the similar values of the same geminal coupling constant (H_2 splitting with H_1, J_{gem}~ 10-11 Hz) on the one hand and of the vicinal coupling constant exhibited by H_2 and H_3 when they are anti-periplanar to each other on the other hand. This implies an axial-axial (H_2H_3 angle~ 160 ^{o} from the model, J_{vic}~ 8-9 Hz). This is in accord with the conformation 2 only. In the conformation 1, the H_1H_3 (axial-equatorial) and H_2H_3 (equatorial-equatorial) angles are about 45 ^{o} and 60 ^{o} respectively (values deduced from our model); and the corresponding coupling constants would be about 4 and 2 Hz respectively, which, by comparison with the geminal coupling constant (J_{gem}~ 10-11 Hz) would lead to two distinct double doublets (or a double doublet and a doublet with a bad resolution). Hence, from the spectral analysis, it seems that some of our compounds show only one conformation. This feature may be explained on steric grounds but the unstability of the conformation 1 was not really established. Consequently, the generalization of this characteristic to all our species cannot be stated.



Conformation 1



Conformation 2

Scheme 190

-> the corresponding carbon α to the nitrogen atom was observed in the range 40-45 ppm for the monocyclisation adducts and in the range 50-56 ppm for the dicyclisation products.

-> the two methine protons cis to each other were always observed distinctly. Indeed, the benzylic one was situated within the aromatic cone and consequently had a higher chemical shift (3.0-5.2 ppm) than the other one whose signal was always masked by additional peaks. The position of the downfield signal depended above all on the nature of the side ring with respect to this methine

proton. In line with this point, the slight difference of conformation which exists between the skeletons of tetralone and indanone is likely to be responsible for the variation of chemical shifts observed for this particular methine proton. Indeed, it appeared at about 4.95 ppm for the tetralone-based species (entries 1,2,4,5) and around 4.60 ppm for the indanone-based compounds (entries 3,5-7).

-> The tertiary carbon bearing this downfield methine proton was always clearly observed in the range 43-48 ppm while the second bridged carbon was at higher field around 35 ppm (it is not indicated in the above table).

-> In most cases, the two olefinic protons were observed in the range 5.6-6.0 ppm as two distinct multiplets separated from each other by 0.1-0.2 ppm.

-> the corresponding olefinic carbons were usually observed as two peaks in the ranges 127-130 ppm for one and 135-138 ppm for the other one. The carbon α to the tertiary carbon was more affected by the aromatic ring and consequently was observed at a more downfield position (135-138 ppm) than the other one (127-130 ppm). On the other hand, the chemical shifts of these olefinic carbons did not seem to be noticeably dependent upon either the cyclisation type, the position of the amine ("ortho" or "meta" with respect to the side ring) or the nature of the side ring (with or without a carbonyl group). Lastly, the adduct from 1,4-diamino-anthraquinone (entry 18) was likely to exhibit additional steric and electronic effects which might explain the sensitive different chemical shift values (about 133.1 and 131.8 ppm).

-> the two allylic protons (not reported in the table) also appeared distinctly in the range 2-3 ppm. The probable explanation for this non-equivalence is that they do not similarly suffer the aromatic cone effect. Both couple with each other (J_{gem}~ 15 Hz), with the two olefinic protons (J ~ 2 Hz) and with the vicinal methine proton (J ~ 9 Hz). Practically, only the geminal coupling (J ~ 16 Hz) was observed from the higher field proton while the signal corresponding to the other one could never be discerned.

Additional comment:

-> all the resonances in the proton spectra of the meso diastereoisomers were always at more downfield positions than those of the corresponding d,l isomer. However their carbon spectra showed no significant difference.

2] IR data.

The structure of the mono- or dicyclisation products was partially confirmed by observation of a weak broad band around 3200-3500 cm^{-1} for N-H stretching in the former case. In the anthraquinone series, strong carbonyl bands were observed in the region 1580-1670 cm^{-1} while they were observed between 1665 and 1690 cm^{-1} as far as the bicyclic amino ketones are

concerned. The carbonyl absorption of the anthraquinone derivatives is further discussed in a following section. Typical bands were observed around 2800-3100 cm^{-1} corresponding to C-H stretching, 1490-1610 cm^{-1} for mainly C=C stretching (aromatic and olefinic) and 1325-1470 cm^{-1} for CH_2 bending (a medium doublet was often noticed in the range 1325-1385 cm^{-1}). Finally, many bands were noticed in the region 1170-1330 cm^{-1} (some of them are to denote C_{Ar}-N stretching and C_{Aliph}-N stretching) while non-assigned bands were often observed around 650, 800-850 and 1000 cm^{-1}.

III] Additional comments related to the anthraquinonoid species.

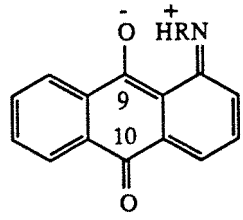
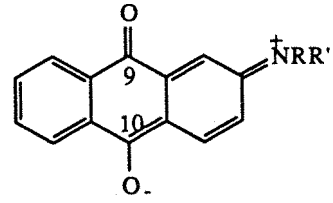
1] C=O absorption.

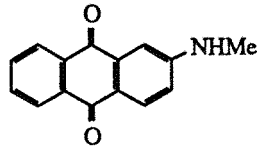
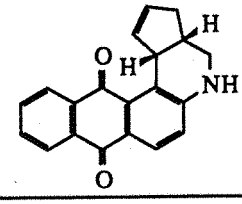
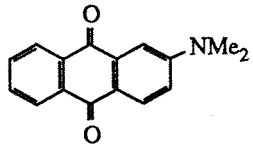
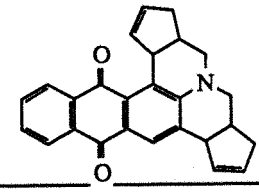
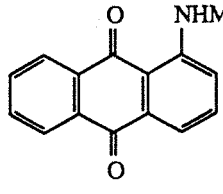
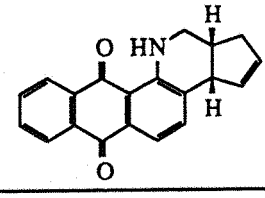
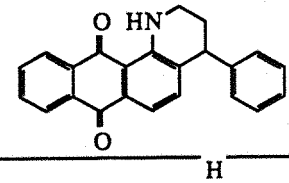
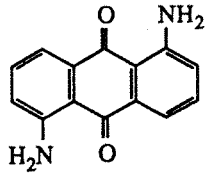
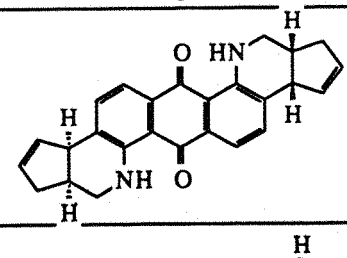
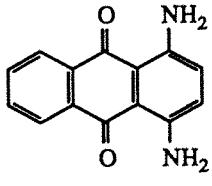
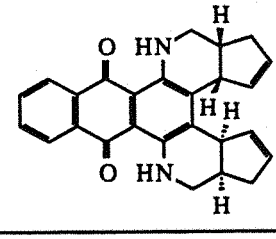
The ν_{max}(C=O) of our anthraquinone derivatives and those of related amines[200-201] are reported in the below table (scheme 191).

The IR spectra of the Diels-Alder adducts obtained from 1- and 2- amino-anthraquinones show two distinct bands for the two different carbonyl groups. The two bands observed at 1680 and 1610 cm^{-1} for the 2-amino derivative (entry 1') are in accord with the values from the literature related to the simple 2-methylamino-anthraquinone (entry 1, 1676 and 1625 cm^{-1}). The second carbonyl at the position C_{10} is shifted lower because of the contribution of the mesomeric structure (277) giving the C=O bond a single bond character. The extent of this resonance is reduced by substitution of alkyl groups on the amine (for 2-dimethylamino- anthraquinone, entry 2: 1667 and 1650 cm^{-1}). Therefore, it is not surprising to notice only one band at 1665 cm-1 for the two carbonyl groups in the case of the dicyclisation adducts (entry 2'). The positions of the carbonyls of the 1-amino-derivatives (entries 3') are similar (1670 and 1630 cm^{-1}) but the assignment of these two values to the carbonyl group is the converse of the previous case. Indeed, the ν_{max}(C=O) of the carbonyl at the position 9 is shifted lower because of a combination of the resonance form (278) and a likely hydrogen bonding. These values are in accord with those from 1-methylamino-anthraquinone (entry 3, 1675 and 1635 cm^{-1}).

Logically, the IR spectra of the cycloadducts from 1,5- and 1,4-diamino-anthraquinones (entries 4' and 5') show only one band for the two equivalent carbonyls, at 1615 cm^{-1} for the former and 1580 cm^{-1} for the latter. The same type of resonance structure as (278) along with some hydrogen bonding occurs with both carbonyl groups in each case. The observed positions are in the same range than those from the corresponding starting 1,5- and 1,4-diamines (entries 4 and 5: 1620 and 1610 cm^{-1} respectively). The very low value for the 1,4-diamino-derivative is unlikely to be due to an overlap with a C=C stretching band.

2] Cyclicvoltammetry.

(278)   (277)

Entry	Starting or related amine[1]	ν_{max} (C_9=O) ν_{max} (C_{10}=O)		Cycloadduct[2]	Entry'
1		1676 1625	1680 1610		1'
2		1667 1650	1665 1665		2'
3		1635 1675	1630 1665		3a'
			1630 1670		3b'
4		1620 1620	1615 1615		4'
5		1610 1610	1580 1580		5'

1] Values from the literature obtained with nujol, except for entry 4 (experimentally with $CHCl_3$).
2] Experimental values obtained with $CHCl_3$.

Scheme 191: comparative table of the carbonyl absorptions of our anthraquinone derivatives with those from related amines

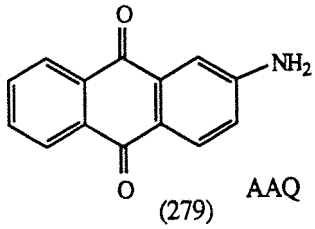
a/ Introduction.[202-204]

Cyclic voltammetry is an oscillographic method of electrochemical analysis. It permits the observation of the response (as a current) at one electrode of an electrochemical system to a time variation of potential. The process can thus be carried out in the anodic or cathodic direction and waves due to the reverse cathodic or anodic reaction respectively are recorded in a i=f(E) curve.

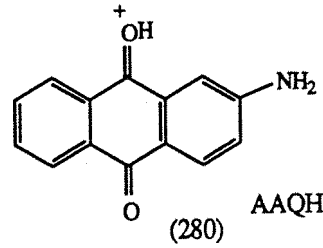
Anthraquinone derivatives have been one of the most studied electronical systems. The cyclovoltammetry of different amino-anthraquinones (AAQ) such as (279) (scheme 192) have shown that these species might have a wide range of applications. When investigated in aprotic solvents, these compounds usually show two one-electron reduction waves which are reversible and which correspond to the successive formation of the semi-quinone radical $AAQ^{\cdot -}$ (281) and a diamagnetic dianion AAQ^{2-} (282) at potentials around -1.0 and -1.6 V respectively. When a proton donor solvent is used (phenol or benzoic acid), it interferes with the two distinct reduction waves. On the other hand, their oxidation leads to a sequence of irreversible waves mostly at potentials beyond 1.2 V, corresponding to the oxidation of amine to imine. The cyclovoltammetric behaviour of 1-amino-, 2-amino-, 1,4- and 1,5-diamino-anthraquinones has been further studied recently mainly in order to develop their ability of affording molecular films. Indeed, such electroactive films might show attractive applications as sensors, electro- and photochromic displays, catalysts, corrosion inhibitors, microelectronic devices and in information storage, ...

b/ Recent related work.[205]

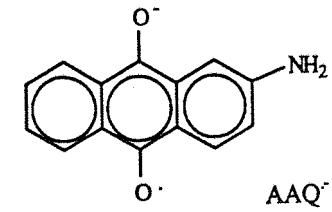
A complete cyclovoltammetric study of 2-amino-anthraquinone AAQ (279) (scheme 192) was reported in 1989, the main results of which are indicated in the following table (scheme 192). It was investigated in DMSO as aprotic solvent and with $Bu_4N^+ClO_4^-$ as supporting electrolyte. At medium concentrations (8-9 mM), four reversible waves A, B, C and D were observed. A and B were very close to each other (around -0.69 and -0.75 V respectively) and their relative intensities were dependent upon each other. The wave C appeared very weakly and the potential peak was not detectable, but it was situated around -0.9 V. Finally, the wave D showed the higher current intensity at about -1.19 V. The overall system is summed up in scheme 192 below.



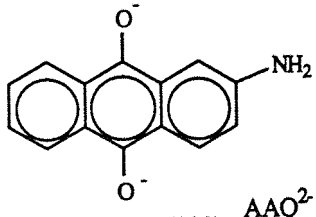
(279) AAQ



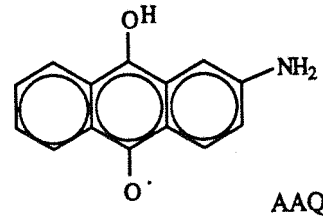
(280) $AAQH^+$



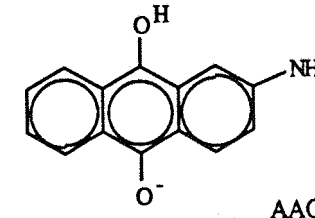
(281) $AAQ^{\cdot-}$



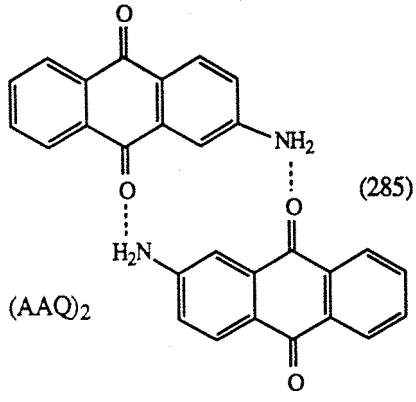
(282) AAQ^{2-}



(283) $AAQH^{\cdot}$

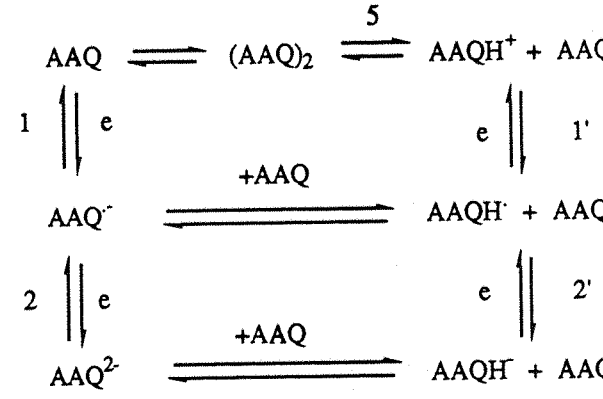


(284) $AAQH^-$



(285)

$(AAQ)_2$



c (mM)	A	B	D
1.79	--	-0.85	-1.192
3.66	-0.68	-0.795	-1.195
5.45	-0.68	-0.780	-1.195
8.96	-0.69	-0.750	-1.195
12.26	-0.71	--	-1.190

Scan rate: 0.036 V/s

Table of the peak potentials (in V) of the discerned reduction waves A, B and D from 2-amino-anthraquinone against the concentration.

Scheme 192

The waves B and D led to the formation of the semi-quinone anion radical $AAQ^{\cdot-}$ (281) and the diamagnetic dianion AAQ^{2-} (282) (equations 1 and 2) respectively. A was assigned to the reduction of species leading to the protonated form AAQH· (283) (equation 1') of $AAQ^{\cdot-}$. Consequently, the wave C denoted the monoelectronic reduction of AAQH· (283) to $AAQH^-$ (284) (equation 2'). It was assessed that the initial protonated species are more likely to be afforded from a hydrogen bonded complex $(AAQ)_2$ (285) according to equation 5 than to be the protonated ketone

$AAQH^+$ (280). It was confirmed by the observed concentration dependance of the waves A and B.

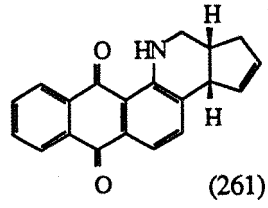
c/ Cyclovoltammetric behaviour of the Diels-Alder cycloadduct (261).

In line with these cyclovoltammetric studies and the ability from certain oxygen-based anthraquinone derivatives of carrying metal cations (earlier section), it was decided to look at the cyclovoltammetric behaviour (only the reduction process) of our cycloadduct derived from 1-amino-anthraquinone (261) (scheme 181).

1) Results.

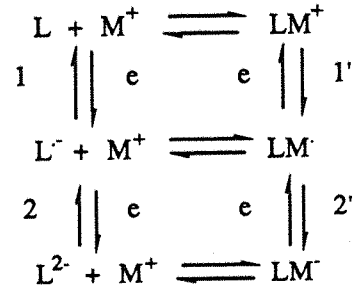
The cyclovoltammogrammes were scanned under the following conditions: ECS as reference electrode, glassy carbon electrode, acetonitrile as solvent, tetratertiobutylammonium perchlorate as supporting agent ($[^tBu_4N^+ClO_4^-]$= 0.1 M), [AAQ]= $2x10^{-4}$ M, when added $[Li^+ClO_4^-]$= $0.5x10^{-4}$ -> $2x10^{-4}$ M. The electrochemical equations are summed up in scheme 193 below.

L=AAQ=



(261)

$M^+ = Li^+$



Scheme 193

The two classical reversible reduction waves leading to the anion radical $AAQ^{\cdot+}$ and the dianion AAQ^{2-} were observed at about -1.06 and -1.55 V (see cyclic voltammogram 1). When $LiClO_4$ was added in suitable concentration, a novel irreversible band could be noticed in the range -0.65/-0.80 V along with the previous first reversible reduction wave at about -1.04 V (see cyclic voltammogram 2). The new wave reflects the reduction process of the complex $(AAQ/Li)^+$ into $(AAQ/Li)^{\cdot}$ (equation 1') and its appearance at a less cathodic potential than the process 1 confirms its easier reducibility.

Moreover, in presence of lithium, the wave corresponding to the monoelectronic process 2 could not been clearly discerned. Only a shoulder was noted in the range -1.40/-1.60. The perturbation of the second reduction process 2 by the occurrence of the competitive reduction process 2' is likely to explain this change in the aspect of the curve.

ECS / Glassy Carbon / Pt

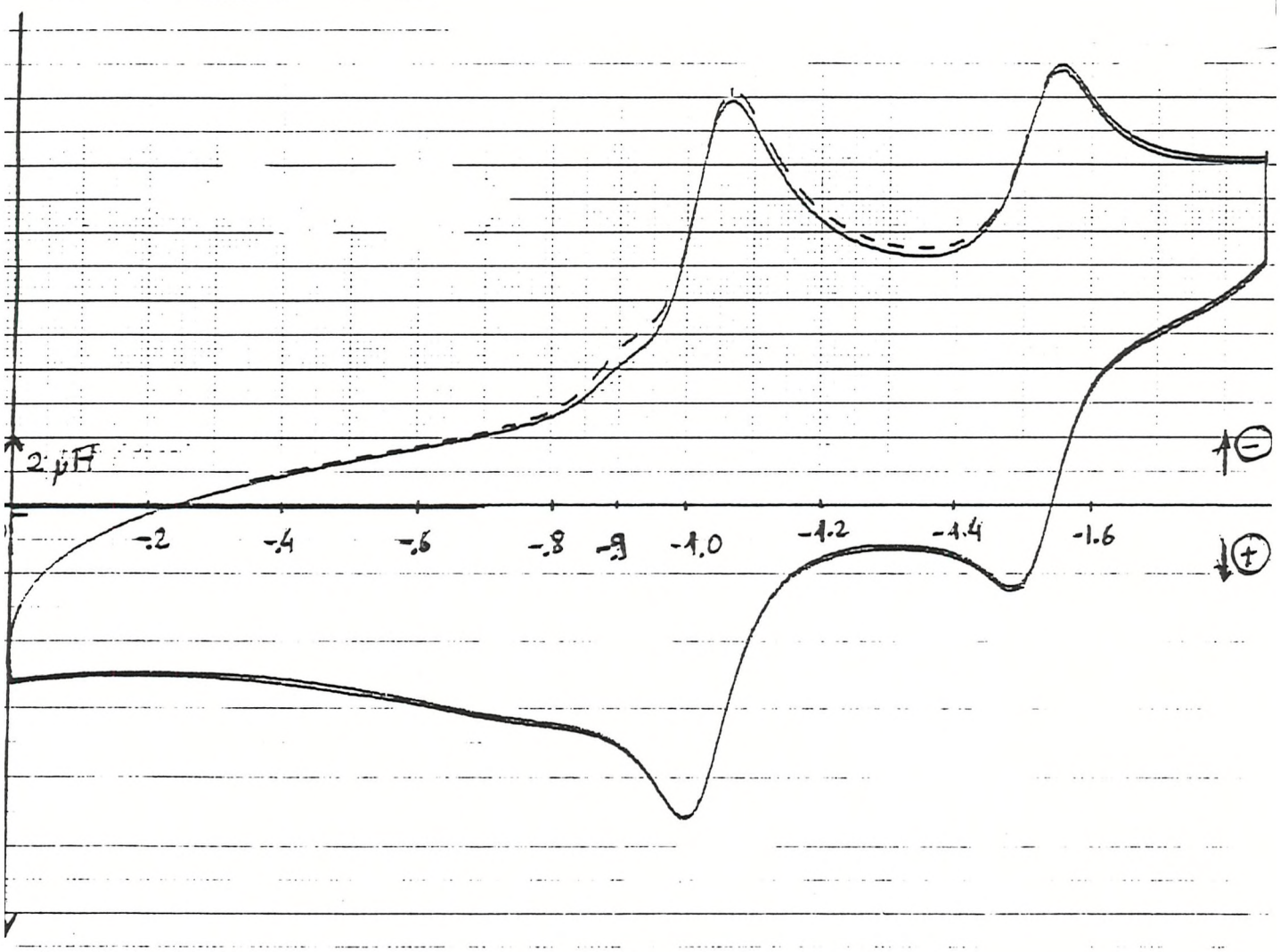
CH_3CN

[TBAP]= 0.1 M

[AAQ]= $2x10^{-4}$ M

X-> 0.1 V/cm

Y-> 2 µA/cm



Cyclic voltammogram 1

ECS / Glassy Carbon / Pt

CH_3CN

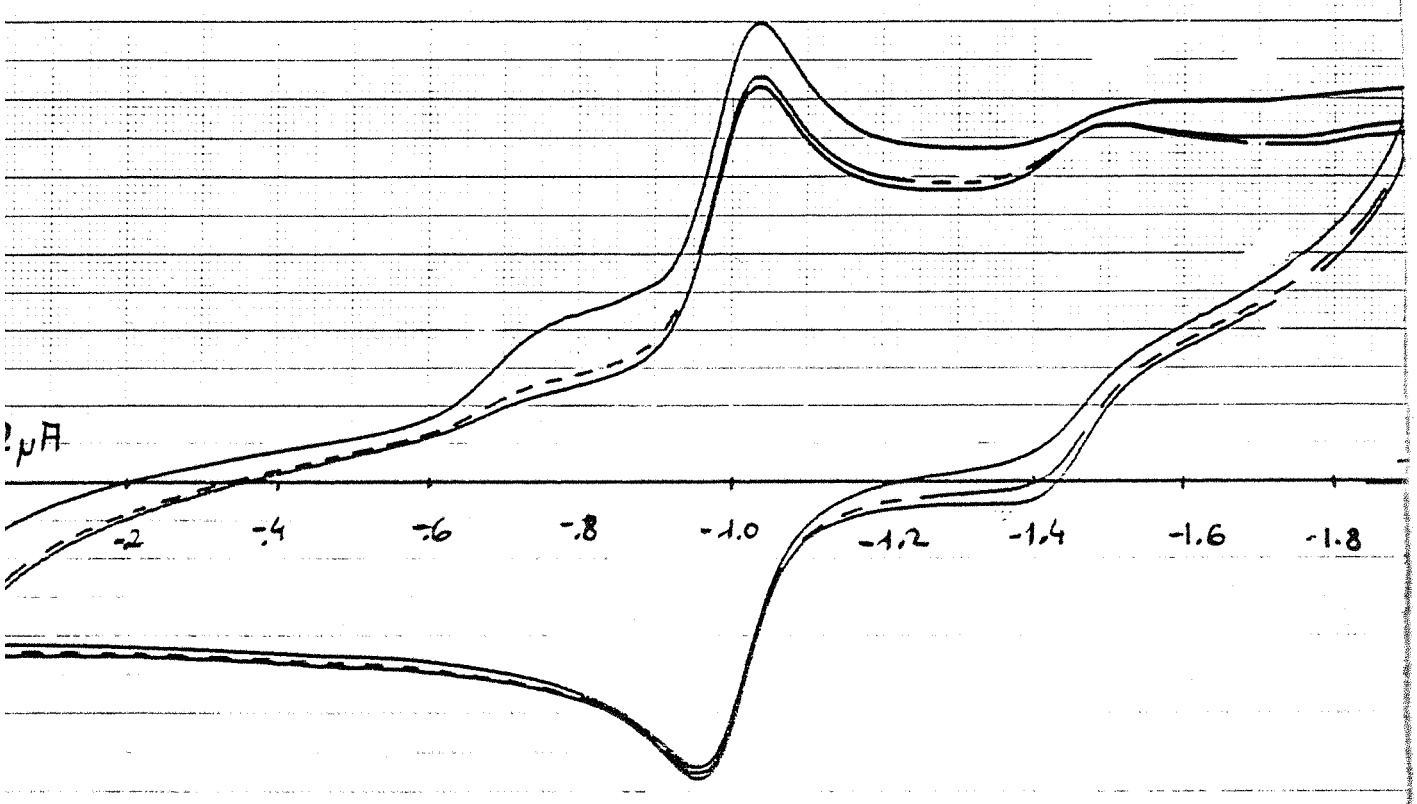
[TBAP]= 0.1 M

[AAQ]= $2x10^{-4}$ M

[$LiClO_4$]= $2x10^{-4}$ M

X-> 0.1 V/cm

Y-> 2 µA/cm



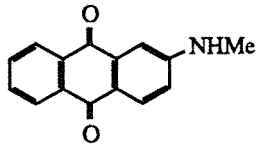
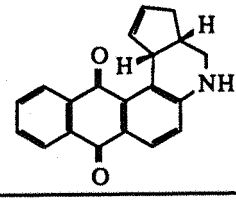
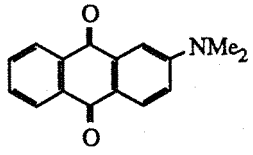
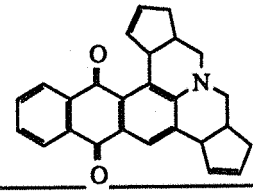
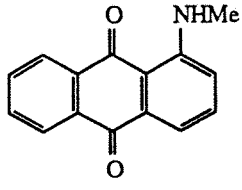
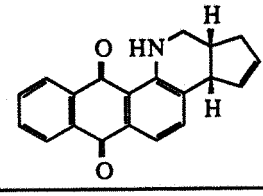
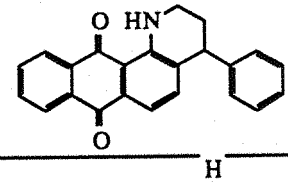
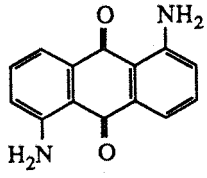
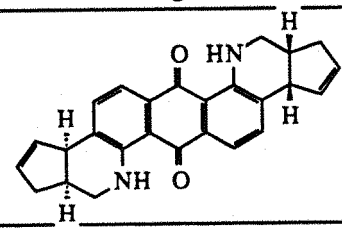
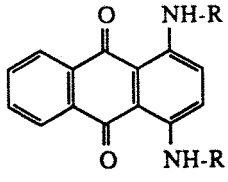
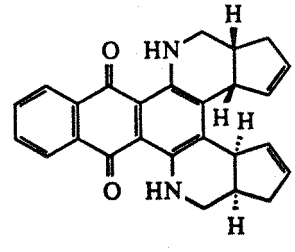
Cyclic voltammogram 2

3) Conclusion.

This cyclovoltammetric study shows that our 1-amino-anthraquinone derivative complexes to Li^+ (1 equivalent). The metal cation is supposed to be trapped between the nitrogen atom and the closer carbonyl oxygen atom. This is the first demonstration that 1-amino-anthraquinones behave in a similar manner to the 1-hydroxyanthraquinones. The peak displacement in the presence of Li^+ shows a potential application for the sensing of lithium ions. A more thorough analysis of the different 1,4- and 1,5-diamino-anthraquinones is needed in order to clarify this potential.

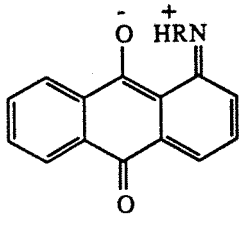
3] UV data.

The spectra were run with absolute ethanol as solvent, with concentrations in the range $0.5x10^{-5}$ to 10^{-3} M and a l=1 cm thick cell. The results are indicated in the table below (scheme 194). The wave lengths and corresponding extinction coefficients in the UV and visible areas of some related amines (from the literature[206,207]) are also mentioned. The absorption bands between 250 and 315 nm are associated with π->π* transitions. The bands in the visible region are associated with n->π* transitions. One can observe a good correlation of the wave lengths in the UV area between our cycloadducts and related amines. The presence of additional substituents either in the ring or on the nitrogen atom is responsible for minor variations. It is more difficult to compare the extinction coefficients. These obtained are mostly lower than those corresponding to related amines, except in the case of the dicycloadducts (2'), the data of which are quite similar to those of N,N-dimethylamino-anthraquinone (2). This might suggest that the skeleton from dicyclisation does not prevent complete resonance as shown by (277), and that the molecule consequently does not adopt a conformation hindering conjugation. It is interesting to compare the data of the adducts (4') and (5') with those of the related diamines (4) and (5). Indeed, the visible absorption bands at 500 nm for 1,5-diamino-anthraquinone and 554 and 596 nm for the 1,4-diamine are observed at 527 nm for (4) and 593 and 638 nm for (5) respectively. Such a variation cannot be explained by the difference of either solvent employed (o-chlorophenol for (4) and (5), ethanol for (4') and (5')) or substitution but rather implies a stronger hydrogen bonding with the nearby carbonyl oxygen in (4') and (5') with respect to the case of the cycloadduct (278). One can also note the double headed peak in the 1,4-diamino derivative (593 and 638 nm) which is not observed in the case of the 1,5-diamino adduct. On the other hand, the extinction coefficients corresponding to these wave lengths do not show the same variation with respect to those of the starting diamines. It is likely to be due to a strain existing only in the case of the 1,4-diamine (5') which tends to stabilize the resonance form (286). This suggestion is in line with the previously mentioned observations concerning its C=O absorption (ν_{max}= 1580 cm^{-1}), the two distinct resonances for the amino protons and the isolation of an orange by-product in the reaction (see scheme 184, proposed structure (268)). Consequently, (5') might show interesting cyclovoltammetric properties.

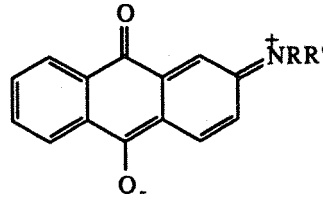
Entry	Starting or related amine[1]	λ_{max} nm	ε	ε	λ_{max} nm	Cycloadduct[2]	Entry'
1		243 287 303 345 462	31200 17000 21400 8000 5700	18400 8900 11000 3600	248 271 312 480		1'
2		244 290 307 352 472	31800 15000 19600 8900 5900	32600 20500 4600	251 319 472		2'
3		243 272 312 503	31400 11000 7000 7100	23800 4900 2900 4100	249 274 316 510		3a'
				9500 3700 5300	274 317 512		3b'
4		500	11900	19800 10800 24000	286 310 527		4'
5	 R=H R=H R=Me	554 596 620	13400 13800 --	~8300 3300 2800 3000 3700 2900 6000 7900	~260 282 344 377 399 556 593 638		5'

1] With methanol except for entry 4 (o-chlorophenol) and entry 5 (o-chlorophenol when R=H, dichloromethane when R=Me).

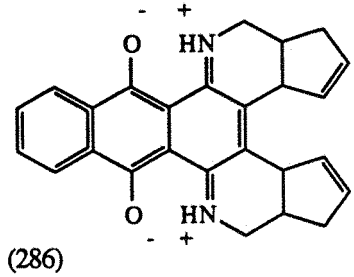
2] With absolute ethanol.



(278)



(277)



(286)

Scheme 194

[F] GENERAL CONCLUSIONS

The acid-catalysed Diels-Alder reactions reported by Grieco in 1988 in which aromatic iminium ions, generated in situ from simple aniline derivatives and formaldehyde cycloadd in an inverse electron demand process to cyclopentadiene as dienophile, was extended to various bicyclic and tricyclic aromaric mono- and diamines. Monocyclisations, double monocyclisations and dicyclisations were investigated. By using a variety of amines, the general features of these cycloadditions were studied.

The reported cyclisations unambiguously occur regioselectively with respect to cyclopentadiene, stereoselectively (cis-addition) and in a high diastereoselectivity in favour of the d,l isomer as far as double monocyclisations and dicyclisations are concerned. These chemical features suggest a concerted Diels-Alder process. Nevertheless, a stepwise mechanism via an ionic intermediate cannot be neglected.

Dicyclisations constituted the most successful type of cycloaddition, the two diastereoisomers being afforded in high overall yields whatever the starting amine. On the other hand, monocyclisations led to various results according to the case.

A leading characteristic of the chemistry dicussed in this thesis is the necessity of suitably activating the reacting aromatic ring so as to observe in a major way the [4+2] Diels-Alder cycloaddition at the expense of any side aromatic substitution whose potential occurrence is clear in view of the reaction conditions. As shown by the cyclisation mechanism, an increase of the desired reactivity lies on the one hand in the electrophilic character of the aromatic position involved in the cyclisation, and on the other hand in the electrophilicity of the remaining aromatic positions not involved in the cyclisation process, which thereby strongly disfavours any side electrophilic substitution. The obvious alternative of blocking these latter positions with a substituent was not investigated. The influence of the nature of the side ring was clearly demonstrated by studying amines with an aliphatic or aromatic side ring. The reactions from some simple amino-naphthalenes appeared far less selective than those with the tetralin- , indane- and anthraquinone- based amines. The results obtained within this second category of starting materials showed the directing role exhibited by one or two carbonyl group(s) α to the aromatic ring in the cyclisation outcome. Indeed, according to its relative position with respect to the amino group, it was observed that the carbonyl:

-> strongly activates the Diels-Alder process when it is "ortho" to the amine (cases of 1-amino-, 1,4- and 1,5-diamino-anthraquinones and 1-amino-5,6,7, 8-tetrahydro-naphthalene).

-> activates selectively one single monocyclisation position when it is "meta" to the amine, which consequently leads to the formation of one single regioisomer (cases of 6-amino-α-indanone,

7-amino-α-tetralone, 2-amino-anthraquinone and 5-amino-indane).
-> strongly disfavours side reactions when it is "opposite" to the amino group (cases of 5-amino-α-tetralone, 1-, 2-amino- and 1,5-diamino-anthraquinones).

In the absence of a carbonyl in the side ring, a low reaction temperature permitted the obtention of the desired cycloadducts in reasonable yields (cases of 1-amino-5,6,7,8-tetrahydro-naphthalene, 5-amino-indane and 1-amino-naphthalene) but its efficiency was limited (no effect in the case of 1,8-diaminonaphthalene).

This chemistry hence provided under mild conditions (room temperature, short reaction time, easy work-up, purification by flash chromatography) a series of new heterocyclic compounds, a number of which have the 11-azasteroidal skeleton and may be of considerable biological interest. Others possess a C_2 symmetry axis and might appear asinteresting chirality carriers in asymmetric synthesis. Finally, certain of the anthraquinonoid series, besides their potential application as dyestuffs, may exhibit outstanding electrochemical properties in line with their ability to trap some metal cations.

The results reported in this thesis confirm that the strong reactivity of aromatic iminium ions as dienes constitute a leading recent extension of the hetero Diels-Alder reactions and a powerful synthetic tool in the synthesis of various complex molecules of high interest at the present time.

CHAPTER 3 : EXPERIMENTAL PART

I] General procedure and analytical instrumentation.

-> Petroleum ether ("petrol") refers to petroleun ether distilling between the range 40-60 ^{o}C; Ether refers to diethyl ether; α-Tetralone is used for 3,4-dihydro-1(2*H*)-naphthalenone; TFA is used for trifluoroacetic acid; Anthraquinone is used for anthracene-9,10-dione.

-> Cyclopentadiene used was freshly distilled.

-> All the compounds were stored under nitrogen.

-> Analytical thin layer chromatography as carried out using precoated silica gel plates (SIL G-25UV$_{254}$; 0.25 mm, Macherey-Nagel) and precoated basic aluminium oxide plates (ALOX-25UV$_{254}$; 0.25 mm; Macherey-Nagel). Compounds were visualised by UV fluorescence.

-> Flash column chromatography was performed on silica gel (C60 Sorbsil; May and Baker), and deactivated (3 % water by weight) basic aluminium oxide (pH 9.3-9.7; type 5016A; Fluka).

-> Melting points were determined using an electrothermal melting point apparatus and are uncorrected.

-> Elemental analyses were carried out at University College, London.

-> Mass spectra (electron impact) were recorded on a VG Analytical 70-250-SE spectrometer.

-> Infrared spectra were recorded on a Perkin-Elmer 298 spectrometer as solutions in chloroforms in 0.1 mm thickness cells. Absorption maxima are quoted in wave numbers (cm-1) relative to a polystyrene standard. The following abbreviations are used to describe the degree of absorption and the aspect of the band: str-strong, m-medium, w-weak, br-broad, sh-sharp, v-very, dbt-doublet.

-> Ultra Violet (and visible) spectra were recorded in absolute ethanol on a SP 800 UV (190-850 nm) spectrometer (UNICAM). Results are reported in chapter 2, section [E] IV] 3].

-> The cyclic voltammograms were recorded with a PPRI wave form generator (High Tech. Instruments), a potentiostat equipped with IR compensation and a PM 8271 Philips X-Y-t recorder. Results are reported in chapter 2, section [E] IV] 2] c/.

-> ^{1}H Nuclear magnetic resonance spectra were recorded at 60 MHz on a Hitachi-Perkin-Elmer R-24B spectrometer, at 270 MHz on a Joel JNM-GX270 spectrometer. Chemical shifts are quoted as δ-values in ppm and coupling constants (J) are given in Hz. In parenthesis are given the operating frequency of the spectrometer, the solvent and the internal standard used. The following abbreviations are used to describe the nature of the proton resonances: s-singlet, d-doublet, dd-double doublet, t-triplet, q-quintet. The following abbreviations are used to describe the nature of the coupling: vic-vicinal, gem-geminal, a-axial, e-equatorial.

-> ^{13}C Nuclear magnetic resonance spectra were recorded at 68 MHz on a Joel JNM-GX270 spectrometer. Chemical shifts are quoted as δ-values in ppm.

I] Preparation of the starting amines.

5-Nitro- and 7-nitro-α-tetralones.

α-Tetralone (1.00 g ; 6.84 mmol) was added dropwise over 0.5 h. with stirring to fuming nitric acid (10 ml) so that the yellow mixture was maintained below -5 °C. The solution was stirred for a further 1 h. at this temperature. The yellow mixture was poured into ice and stirred for 40 min.. Then the heterogenous mixture obtained was filtered and the residue was washed with cold water and dried to give a yellow solid. Recrystallization from ethanol afforded as yellow crystals 7-nitro-α-tetralone (0.30 g; 23 %; Rf= 0.38 in petrol/ether/ethanol 82/9/9). The mother liquors from recrystallization were concentrated to give a light brown solid (0.90 g).

Flash chromatography on silica gel (80 g) of this latter solid (eluant petrol/ether/ethanol 82/9/9) gave two main fractions:

-> 7-nitro-α-tetralone: very light yellow crystals, 0.31 g, 24 %, Rf=0.38, mp=104-105 °C (lit[152]: 105 °C).

-> 5-nitro-α-tetralone: light yellow crystals, 0.31 g, 24 %, Rf=0.45, mp=102 °C (lit[208]: 102.5 °C).

(Rf values in petrol/ether/ethanol 82/9/9).

7-Nitro-α-tetralone and 5-nitro-α-tetralone were thus obtained in 47 % and 24 % yields respectively (overall yield 71 %).

5-Nitro-α-tetralone (143):

δ_H(60 MHz, $CDCl_3$, TMS)= 8.28 (1H, dd, ArC_6-H, J=8, 2); 8.02 (1H, dd, ArC_8-H, J=8, 2); 7.42 (1H, t, ArC_7-H, J=8); 3.15 (2H, m, C_2-H_2); 2.68 (2H, m, C_4-H_2); 2.17 (2H, m, C_3-H_2).

7-Nitro-α-tetralone (144):

δ_H (60 MHz, $CDCl_3$, TMS)= 8.70 (1H, d, ArC_8-H, J=2.5); 8.18 (1H, dd, ArC_6-H, J=9, 2.5); 7.40 (1H, d, ArC_5-H, J=9); 3.07 (2H, t, C_2-H_2, J=6); 2.72 (2H, t, C_4-H_2, J=6); 2.23 (2H, m, C_3-H_2).

7-Amino-α-tetralone.

7-Nitro-α-tetralone (1.00 g ; 5.23 mmol) was dissolved in glacial acetic acid (10 ml).While warming the yellow liquid, water (8 ml) was slowly added with stirring to give a homogenous yellow solution at about 60 °C. Iron powder (1.17 g ; 20.9 mmol ; 4 eq) was added under stirring in 15 min. so that the temperature was maintained between 70 and 90 °C. The dark grey

heterogenous mixture was stirred under these conditions for 2 h.. The solution was cooled to room temperature, diluted with water (300 ml), and neutralised to pH=8.5 by slowly adding solid sodium bicarbonate.The mixture was extracted with dichloromethane (5x100 ml), the organic layers were combined and the solvent was only partially removed under reduced pressure.The yellow liquid (about 100 ml) was acidified to pH=1 with hydrochloric acid (1N) and the mixture was washed with water (4x50 ml).The combined aqueous layers were basified to pH=10 with sodium hydroxide (1N) and extracted with dichloromethane (3x100 ml).The combined yellow organic layers were dried over anhydrous magnesium sulphate and, after filtration, the solvent was removed under reduced pressure to give as a light orange solid the title compound (0.73 g; 87 % ; m.p.:138-140 °C (lit[152]: 136 °C); Rf=0.13 (petrol/ether/ethanol 82/9/9)).

7-Amino-α-tetralone (139):
δ_H(270 MHz,TMS, $CDCl_3$)= 7.32 (1H, d, ArC_8-H, J=2.7); 7.05 (1H, d, ArC_5-H, J=8.1); 6.83 (1H, dd, ArC_6-H, J=8.1, 2.6); 3.74 (2H, m, NH_2); 2.84 (2H, t, C_2H_2, J=6.0); 2.60 (2H, t, C_4H_2, J=6.5); 2.08 (2H, q, C_3H_2, J=6.3).

δ_C(270 MHz, $CDCl_3$, TMS)= 198.98 (C_1=O); 145.15 (ArC_7-NH_2); 134.95 (ArC_{8a}); 133.28 (ArC_{4a}); 129.80 (ArC_5); 121.06 (ArC_6); 112.20 (ArC_8); 39.33 (OC-C_2); 28.97 (Ar-C_4); 23.73 (CH_2-C_3).

5-Amino-α-tetralone .

5-Nitro-α-tetralone (0.28 g ; 1.46 mmol) was dissolved in glacial acetic acid (5 ml) to give a yellow liquid. While warming, water (3 ml) was slowly added under stirring to give a homogenous yellow solution at about 60 °C. Iron powder (0.33 g ; 5.91 mmol ; 4 eq) was added under stirring in 10 min. so that the temperature was kept between 70 and 90 °C. The dark grey heterogenous mixture was stirred under these conditions for 40 min.. The solution was cooled to room temperature, diluted with water (150 ml) and neutralized to pH=8.5 by slowly adding solid sodium bicarbonate.The mixture was extracted with dichloromethane (3x100 ml), the organic layers were combined, dried over anhydrous magnesium sulphate and, after filtration, the solvent was removed under reduced pressure to give as a light yellow brown solid the title compound (0.20 g ; 85 % ; m.p.=115-118 °C (lit[209]:119-120 °C); Rf=0.15 (petrol/ether/ethanol 82/9/9)).

5-Amino-α-tetralone (138):
δ_H(60 MHz, $CDCl_3$, TMS)= 7.3 (1H, m, ArC_8-H); 6.93 (1H, t, ArC_7-H, J=8); 6.65 (1H, dd, Ar_6-H, J=8, 2); 3.55 (2H, s, NH_2); 2.50 (4H, m, C_2-H_2, C_4-H_2); 2.00 (2H, m, C_3-H_2).

6-nitro-α-indanone.

Potassium nitrate (6.86 g ; 67.85 mmol) dissolved in concentrated sulphuric acid (21 ml) was added dropwise over 40 min. to a solution of α-indanone (8.23 g ; 62 .37 mmol) in concentrated sulphuric acid (69 ml) previously cooled to 0 °C, which made the temperature increase to 7 °C. After adding, the orange mixture was stirred for 3 h 50 min from 0 to 10 °C. The reddish reaction mixture was poured into ice and left overnight. Filtration of the greenish heterogenous mixture led to a solid which was next dissolved in dichloromethane and dried over anhydrous magnesium sulphate. After filtration, the yelllow liquid was concentrated under vacuum to give a green solid (11.14 g).

Flash chromatography on silica gel with petrol/ether/ dichloromethane 2/8/0 to 0/5/5 as eluent gave two main fractions:

-> A: white solid, starting α-indanone, Rf=0.54 (ether).

-> B: 6-nitro-α-indanone (146), green solid, 7.89 g, 71 %, Rf=0.38 (ether), recrystallisation from ethanol led to pale greenish crystals, m.p.=72-73.5 °C (lit[153]:74 °C).

6-Nitro-α-indanone (146):

δ_H(60 MHz, TMS, $CDCl_3$)= 8.40 (1H, d, ArC_7-H, J=2.5); 8.33 (1H, dd, ArC_5-H, J=7.5, 2.5); 7.58 (1H, ArC_4-H, J=7.5); 3.30 (2H, m, C_2H_2); 2.83 (2H, m, C_3H_2).

6-Amino-α-indanone.

6-Nitro-α-indanone (3.70 g ; 20.88 mmol) was dissolved in glacial acetic acid (37 ml).While warming the yellow liquid, water (29 ml) was slowly added with stirring to give a homogenous solution at about 60 °C. Iron powder (4.66 g ; 83.44 mmol ; 4 eq) was added under stirring in 20 min. so that the temperature was closely maintained between 70 and 90 °C.The dark heterogenous mixture was stirred under these conditions for 2h.. The solution was cooled to room temperature, diluted with water (500 ml), and neutralised to pH=8.5 by slowly adding solid sodium bicarbonate. The mixture was extracted with dichloromethane (1 l), the combined yellow organic layers were dried over anhydrous magnesium sulphate and, after filtration, the solvent was removed under reduced pressure to give a yellowish solid (2.78 g).

Flash chromatography on silica gel run with eluant ether led to two main fractions:

-> A: 6-amino-α-indanone, pale yellow solid, 2.33 g, 76 %, Rf= 0.35 (ether). Recrystallisation in ethanol gave pale yellow needles, m.p.=170-175 °C (lit[153]:171 °C).

-> B: yellowish solid, 0.22 g, m.p.=174-176 °C, structure not elucidated.

6-Amino-α-indanone (140):

δ_H(270 MHz, TMS, $CDCl_3$)= 7.26 (1H, s, ArC_7-H); 6.97 (2H, m, ArC_4-H, ArC_5-H); 3.81 (2H, m, NH_2); 3.02 (2H, t, C_2H_2, J=5.6); 2.66 (2H, t, C_3H_2, J=5.7).

δ_C(270 MHz, $CDCl_3$, TMS)= 207.58 (C_1=O) 146.08, 145.82 (ArC_{7a}, ArC_6-NH_2); 138.42 (ArC_{3a}); 127.32 (ArC_4); 123.07 (ArC_5); 107.97 (ArC_7); 37.04 (Ar-C_3); 24.52 (OC-C_2).

II] Cyclisations of the bicyclic amines.

Dicyclocondensation of 7-amino-α-tetralone with formaldehyde and cyclopentadiene leading to 4-oxo-1,2,3,4,4c,7a,8,9,10,10a,13a-undecahydro-benzo [f]-7*H*-cyclopenta[1,2-c]-11*H*-cyclopenta[1',2':3,4]pyrido[3,2,1-ij]quinoline (151) and (152).

Trifluoroacetic acid (0.71 g ; 6.23 mmol) was added to 7-amino-α-tetralone (0.50 g : 3.10 mmol) partially dissolved in acetonitrile (8 ml) to give a light greenish solution of the amine (0.39 M). After 10 min. of stirring under nitrogen, a mixture at 0 °C of cyclopentadiene (0.41 g; 6.20 mmol) and formalin solution 37 % (0.50 g ; 6.16 mmol) in acetonitrile (1ml) was added in 1 min. to the mixture. The dark reaction mixture was stirred under nitrogen at room temperature for a further 1 h. . The mixture was added to a saturated sodium bicarbonate solution (100 ml) and was extracted with dichloromethane (3x100 ml). The combined organic layers were dried over anhydrous magnesium sulphate and, after filtration, were concentrated under reduced pressure to give a brown red oil (0.96 g).

Flash chromatography on silica gel (70 g) run with eluant petrol/ether 9/1 led to two main fractions:

-> A: d,l diastereoisomer (151), yellow solid, 0.64 g, 65 %, Rf=0.67. Recrystallisation fron ethanol/petrol led to yellow-brown crystals, m.p.=131-133 °C.

-> B: meso diastereoisomer (152), yellow solid, 0.18 g, 18 %, Rf=0.57. Recrystallisation from ethanol/petrol led to yellow-brown crystals, m.p.=143-144.5 °C.

(Rf values in petrol/ether 3/7).

The two diastereoisomers d,l and meso were thus afforded in 83 % overall yield (relative ratios 78:22 respectively).

Diastereoisomer d,l (151):

δ_H(270 MHz, TMS, $CDCl_3$)= 6.89 (1H, s, ArC_{14}-H); 5.72 (2H, m, C=C_5-H, C=C_{13}-H); 5.62 (2H, m, CH_2-C_6H=C, CH_2-C_{12}H=C); 5.02 (1H, m, =C-C_{4c}H); 3.89 (1H, m, =C-C_{13a}H); 2.82 (7H, m, C_8H_2-N, $C_{10}H_2$-N, C_3H_2-CO, CH_2-C_{7a}-H); 2.61 (5H, m, Ar-C_1H_2, C_7H_2-C=, $C_{11}H_2$-C=, CH_2-C_{10a}H); 2.31 (2H, m, C_7H_2-C=, $C_{11}H_2$-C=); 2.02 (

2H, q, CH_2-$C_2\underline{H_2}$-CH_2, J=6.3).

δ_C(68 MHz, $CDCl_3$, TMS)= 200.67 (O=$\underline{C}_3$); 145.33 (Ar$\underline{C}_{14b}$-N); 137.21 (HC=$\underline{C}_5$H); 135.97 (Ar$\underline{C}_{4a}$); 134.94 (HC=$\underline{C}_{13}$H); 132.27 (Ar$\underline{C}_{13b}$); 130.11 (CH_2-$\underline{C}_6$H=CH); 128.98 (CH_2-$\underline{C}_{12}$H=CH); 128.88,128.65 (Ar$\underline{C}_{14a}$, Ar$\underline{C}_{4b}$); 127.48 (Ar$\underline{C}_{14}$-H); 54.60 (N-$\underline{C}_8H_2$); 53.30 (N-$\underline{C}_{10}H_2$); 47.65 (=C-$\underline{C}_{4c}$H); 45.22 (=C-$\underline{C}_{13a}$H); 41.92 (=C-$\underline{C}_7H_2$); 37.55, 37.40 (=C-$\underline{C}_{11}H_2$, OC-$\underline{C}_3H_2$); 30.92 (Ar-$\underline{C}_1H_2$); 23.38 (CH_2-$\underline{C}_2H_2$-CH_2).

ν_{max}($CHCl_3$)= 3060 (w), 3000 (w, sh), 2930 (m, br) 2850 (w) (C-H stretching); 1725 (w, br); 1665 (m, br, C=O); 1595 (w, sh), 1480 (w, sh) (C=C stretching); 1440 (w, v br), 1350 (w, sh) (CH_2 bending); 1295 (m, br, C_{Ar}-N stretching); 1220 (m, v br).

m/z(e.i.): Found= 317.1757 (M^+100%) ; 302 (9) ; 288 (20) ; 276 (39) ; 261(12). $C_{22}H_{23}NO$ requires 317.17796.

Elemental analysis: calculated: C=83.24 H=7.30 N=4.41
Found: C=82.81 H=7.08 N=4.35

Diastereoisomer meso (152):
δ_H(270 MHz, TMS, $CDCl_3$)= 7.00 (1H, s, ArC_{14}-$\underline{H}$); 5.81 (1H, m, C=C_5-$\underline{H}$); 5.71 (1H, m, C=C_{13}-$\underline{H}$); 5.63 (2H, m, CH_2-$C_6\underline{H}$=, CH_2-$C_{12}\underline{H}$=); 4.89 (=C-$C_{4c}\underline{H}$); 3.88 (=C-$C_{13a}\underline{H}$); 2.46-2.89 (12H, m, N-$C_8\underline{H_2}$, N-$C_{10}\underline{H_2}$, $C_3\underline{H_2}$-CO, Ar-$C_1\underline{H_2}$, =C-$C_7\underline{H_2}$, =C-$C_{11}\underline{H_2}$, CH_2-$C_{7a}\underline{H}$, CH_2-$C_{10a}\underline{H}$); 2.06 (4H, m, CH_2-$C_2\underline{H_2}$-CH_2, =C-$C_7\underline{H_2}$, =C-$C_{11}\underline{H_2}$).

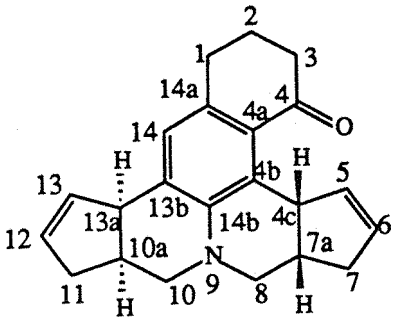
δ_C(68 MHz, $CDCl_3$, TMS)= 200.65 (O=$\underline{C}_4$); 144.41 (Ar$\underline{C}_{14b}$-N); 138.45 (HC=$\underline{C}_5$H); 135.76 (Ar$\underline{C}_{4a}$); 135.25 (HC=$\underline{C}_{13}$H); 131.74 (Ar$\underline{C}_{13b}$); 129.09 (HC=$\underline{C}_5$H-CH_2); 128.88 (Ar$\underline{C}_{14a}$); 128.04 (HC=$\underline{C}_{12}$H-CH_2); 127.57 (Ar$\underline{C}_{4b}$); 127.26 (Ar$\underline{C}_{14}$-H); 54.03 (N-$\underline{C}_8H_2$); 52.29 (N-$\underline{C}_{10}H_2$); 47.68 (=C-C_{4c}H); 45.34 (=C-$\underline{C}_{13a}$H); 42.05 (=C-$\underline{C}_7H_2$); 37.71, 37.22 (=C-$\underline{C}_{11}H_2$, OC-$\underline{C}_3$); 34.80 (CH_2-$\underline{C}_{7a}$H); 34.75 (CH_2-$\underline{C}_{10a}$H); 30.95 (Ar-$\underline{C}_1$); 23.38 (CH_2-$\underline{C}_2H_2$-CH_2).

ν_{max}($CHCl_3$)= 3070 (w), 3015 (w, sh), 2910 (m, br), 2860 (m, sh) (C-H stretching); 1665 (str, br, C=O); 1595 (m, sh), 1550 (w, sh), 1480 (m, sh) (C=C stretching); 1440 (m, br), 1350 (m, sh) (CH_2 bending); 1300 (str, br, C_{Ar}-N stretching); 1220 (w, br); 1150 (w, sh); 910 (w, sh); 650 (w, sh).

m/z(e.i.): Found= 317.1773 (M^+100%) ; 302 (8) ; 288 (18) ; 276 (36) ; 261(11). $C_{22}H_{23}NO$

requires 317.17796.

Elemental analysis: calculated: C=83.24 H=7.30 N=4.41
Found: C=82.13 H=6.97 N=4.20



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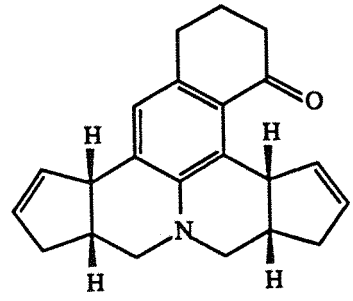


(152)

Dicyclocondensation of 6-amino-α-indanone with formaldehyde and cyclopentadiene leading to 3-oxo-2,3,3c,6a,7,8,9,9a,12a-nonahydro-1*H*,6*H*-dicyclopenta [2,1-f:1,2-c]-10*H*-cyclopenta[1',2':3,4]pyrido[3,2,1-ij]quinoline (153) and (154)

Trifluoroacetic acid (0.93 g ; 8.16 mmol) was added to 6-amino-α-indanone (0.60 g ; 4.08 mmol) partially dissolved in acetonitrile (12 ml) to give a yellow heterogenous mixture. After 10 min. of stirring under nitrogen, a mixture at 0 °C of cyclopentadiene (0.54 g ; 8.17 mmol) and formalin solution 37 % (0.66 g : 8.13 mmol) in acetonitrile (2 ml) was added to the previous mixture. The dark red reaction mixture was stirred under nitrogen at room temperature for a further 1.5 h. The brown green reaction mixture was added to a saturated sodium bicarbonate solution (100 ml) and was extracted with dichloromethane (2x100 ml). The organic layers were combined, dried over anhydrous magnesium sulphate and, after filtration, were concentrated under reduced pressure to give a brown oil (1.24 g).

Flash chromatography on silica gel (50 g) with petrol/ether 1/9 to ether as eluent gave two main fractions:

-> A: d,l diastereoisomer (153), yellow solid 0.91 g, 74 %, Rf=0.68. Recrystallization from ethanol/petrol led to yellow brown crystals, m.p.=151-153 °C.

-> B: meso diastereoisomer (154), yellow solid, 0.17 g, 14 %, Rf=0.64. Recrystallisation from ethanol/petrol led to brown crystals, m.p.=194-196 °C.

(Rf values in ether/petrol 7/3).

The two diastereoisomers d,l and meso were thus obtained in an 88 % overall yield (relative ratios 84:16 respectively).

Diastereoisomer d,l (153):
m/z(e.i.)= Found: 303.1612 (M^+100%); 288 (8.9); 276 (19.2); 262 (31.1); 246 (6.1); 236 (5.1); 221 (5.1); 204 (5.8); 152 (8.3). $C_{21}H_{21}NO$ requires 303.16231.

δ_H(270 MHz, TMS, $CDCl_3$)= 7.07 (1H, s, ArC_{13}-H); 5.80 (1H, m, $HC=C_4H$); 5.74 (2H, m, $HC=C_5H$, $HC=C_{12}H$); 5.65 (1H, m, $HC=C_{11}H$); 4.66 (1H, m, $=C-C_{3c}H$); 3.96 (1H, m, $=C-C_{12a}H$); 2.96 (2H, m, $N-C_7H_2$, $N-C_9H_2$); 2.76-2.90 (5H, m, $N-C_7H_2$, $N-C_9H_2$, C_2H_2-CO, $CH_2-C_{6a}H$); 2.59-2.71 (5H, m, $Ar-C_1H_2$, $CH_2-C_{9a}H$, $C_6H_2-CH=$, $C_{10}H_2-CH=$); 2.36 (2H, m, $C_6H_2-C=$, $C_{10}H_2-C=$).

δ_C(68 MHz, TMS, $CDCl_3$)= 207.71 ($O=C_3$); 146.50 ($ArC_{13b}-N$); 145 10 (ArC_{3a}); 136.22 ($HC=C_4H$); 134.94 ($HC=C_{12}H$); 134.62 (ArC_{12b}); 131.99 (ArC_{13a}); 130.34 ($CH_2-C_5H=CH$); 128.99 ($CH_2-C_{11}H=CH$); 125.88 (ArC_{3b}); 124.50 ($ArC_{13}-H$); 54.28 ($N-C_7H_2$); 53.76 ($N-C_9H_2$); 47.83 ($=C-C_{3c}H$); 43.80 ($=C-C_{12a}H$); 37.56, 37.49, 37.30 ($=C-C_6H_2$, $=C-C_{10}H_2$, $OC-C_2$); 35.69 ($CH_2-C_{6a}H$); 35.34 ($CH_2-C_{9a}H$); 24.69 ($Ar-C_1$).

ν_{max}($CHCl_3$)= 3000 (m, sh), 2930 (str, br), 2850 (m), 2820 (m) (C-H stretching); 1690 (v str, v br, C=O stretching);1600 (m, sh), 1485 (m, sh) (C=C stretching); 1440 (str, sh), 1330 (m, br) (CH_2 bending); 1290 (str, br, C_{Ar}-N stretching); 1140 (w, br); 1070 (w, sh).

Elemental analysis: Calculated: C=83.13 H=6.98 N=4.62
Found: C=82.84 H=6.72 N=4.60

Diastereoisomer meso (154):
m/z(e.i.)= Found: 303.1637 (M^+100%); 288 (8.7); 275 (18.6); 262 (31.3); 246 (6.1); 204 (5.5). $C_{21}H_{21}NO$ requires 303.16231.

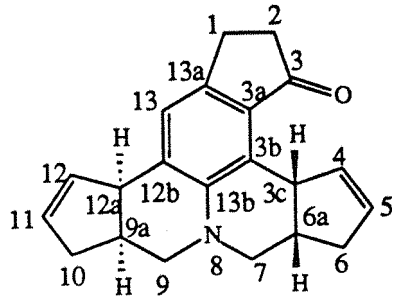
δ_H(270MHz, TMS, $CDCl_3$)= 7.16 (1H, s, ArC_{13}-H); 5.84 (1H, m, $HC=C_4H$); 5.81 (1H, m, $HC=C_{12}H$); 5.71 (1H, m, $CH_2-C_5H=CH$); 5.64 (1H, m, $CH_2-C_{11}H=CH$); 4.54 (1H, m, $=C-C_{3c}H$); 3.94 (1H, m, $=C-C_{12a}H$); 2.98 (2H, m, $N-C_7H_2$, $N-C_9H_2$); 2.50-2.86 ($N-C_7H_2$, $N-C_9H_2$, C_2H_2-CO, $Ar-C_1H_2$, $CH_2-C_{6a}H$, $CH_2-C_{9a}H$, $=C-C_6H_2$, $=C-C_{10}H_2$); 2.03 (2H, m, $=C-C_6H_2$, $=C-C_{10}H_2$).

δ_C(68 MHz, TMS, $CDCl_3$)= 207.57 ($O=C_3$); 146.19 ($ArC_{13b}-N$); 144.35 (ArC_{3a}); 137.16 ($HC=C_4H$); 135.35 ($HC=C_{12}H$); 133.85 (ArC_{12b}); 132.28 (ArC_{13a}); 129.06 ($CH_2-C_5H=CH$); 127.04 ($CH_2-C_{11}H=CH$); 125.01 ($ArC_{13}-H$); 124.52 (ArC_{3b}); 53.64 ($N-C_7H_2$); 52.87 ($N-C_9H_2$); 47.92 ($=C-C_{3c}H$); 43.99 ($=C-C_{12a}H$); 37.64, 37.51, 37.31,

37.22 (=C-$\underline{C}_6H_2$, =C-$\underline{C}_{10}H_2$, OC-$\underline{C}_2H_2$); 34.69 (CH_2-$\underline{C}_{6a}H$); 34.16 (CH_2-$\underline{C}_{9a}H$); 24.61 (Ar-$\underline{C}_1H_2$).

$\nu_{max}(CHCl_3)$= 3070 (w), 3020 (w, sh), 2950 (m, br), 2860 (w, sh), 2830 (w) (C-H stretching); 1690 (str, br, C=O); 1600 (m, sh), 1485 (m, sh), 1440 (m, sh) (C=C stretching); 1340 (m), 1330 (m, sh), 1315 (m) (CH_2 bending); 1295 (m, sh), 1280 (m, sh) (C_{Ar}-N); 1145 (w, sh); 1060 (w, sh); 650 (m, sh).

Elemental analysis: Calculated: C=83.13 H=6.98 N=4.62
Found: C=82.30 H=6.88 N=4.48



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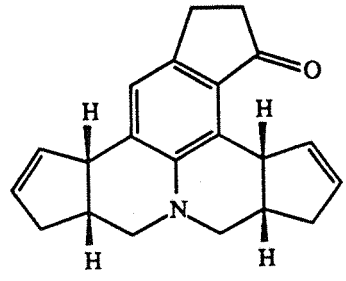


(154)

Dicyclisation of 5-amino-indane leading to 2,3,3c,6a,7,8,9,9a,12a-nonahydro-1*H*,6*H*-dicyclopenta[2,1-f:1,2-c]-10*H*-cyclopenta[1',2':3,4]pyrido[3,2,1-ij]quinoline (156) and (157).

Trifluoroacetic acid (3.00 g; 2 eq) was added to 5-amino-indane 97 % (1.81 g; 13.18 mmol) dissolved in acetonitrile (30 ml) to give a brown homogenous mixture. After 15 min. of stirring at 0 °C under nitrogen, a mixture at 0 °C of cyclopentadiene (2.61 g; 3 eq) and formalin solution 37% (2.14 g; 2 eq) in acetonitrile (2 ml) was added to the former mixture which was stirred under nitrogen between 0 and 5 °C for 2 h 30 min. The brown orange mixture was added to saturated sodium bicarbonate (150 ml) and was extracted with dichloromethane . The combined organic layers were dried over anhydrous magnesium sulphate and, after filtration, were concentrated under reduced pressure to give a brown oil (4.0 g) which turned dark green in a few days.

Flash chromatography on silica gel with petrol/ether 9/1 to 7/3 as eluent gave two main fractions:
-> A: yellow solid, 2.22 g, 58 %, Rf=0.72, diastereoisomer d,l (156). All attemps to get satisfactory crystals failed.
-> B: yellow solid, 0.49 g, 13 %, Rf=0.64, diastereoisomers meso (157). Recrystallisation from ethanol led to pale yellow crystals, mp=124-125 °C.
(Rf values with petrol/ether 7/3 as eluant).

The two diastereoisomers d,l and meso were thus obtained in an 71 % overall yield (relative ratios 82:18 respectively).

Diastereoisomer d,l (156):

δ_H(270 MHz,TMS,$CDCl_3$)= 6.88 (1H, s, ArC_{13}-H); 5.81 (1H, m, $C=C_4$-H); 5.77 (1H, m, $C=C_{12}$-H); 5.72 (1H, m, $C=C_5$-H); 5.68 (1H, m, $C=C_{11}$-H); 3.88 (2H, m, $=C-C_{3c}$-H, $=C-C_{12a}$-H); 2.55-2.81 (12 H, m, N-C_7H_2, N-C_9H_2, CH_2-C_{6a}-H, CH_2-C_{9a}-H, $=C-C_6H_2$, $=C-C_{10}H_2$, Ar-C_1H_2, Ar-C_3H_2); 2.33 (2H, m, $=C-C_6H_2$, $=C-C_{10}H_2$, J_{gem}=16.2); 2.03 (2H, m, $CH_2-C_2H_2-CH_2$).

δ_C(68 MHz,TMS,$CDCl_3$)= 143.81 (ArC_{13b}-N); 140.87 (ArC_{3a}); 136.19, 134.06 ($C=C_4$-H, $C=C_{12}$-H); 133.96 (ArC_{13a}); 129.98, 129.52 ($C=C_5$-H, $C=C_{11}$-H); 124.97 (ArC_{12b}); 122.64 (ArC_{13}-H); 122.50 (ArC_{3b}); 54.39, 54.03 (N-C_7H_2, N-C_9H_2); 46.95, 45.60 ($=C-C_{3c}H$, $=C-C_{12a}H$); 37.33, 37.20 ($=C-C_6H_2$, $=C-C_{10}H_2$); 36.17, 36.02 ($CH_2-C_{6a}H$, $CH_2-C_{9a}H$); 32.46, 32.06 (Ar-C_1H_2, Ar-C_3H_2); 25.75 ($CH_2-C_2H_2-CH_2$).

ν_{max}($CHCl_3$)= 3070 (w, sh), 3020 (m, sh), 2940 (v str, br), 2860 (str, br), 2730 (m) (C-H stretching); 1620 (v str, br), 1490 (m, sh) (C=C stretching); 1445 (m, sh), 1350 (m, br) (CH_2 bending); 1285-1300 (m, br, C_{Ar}-N stretching); 1100-1180 (w, br).

m/z(e.i.)= Found: 289.1833 (M^+100%); 261 (10.5); 248 (25.3); 222 (12.2); 112 (5.1). $C_{21}H_{23}N$ requires 289.18305.

Diastereoisomer meso (157):

δ_H(270 MHz,TMS,$CDCl_3$)= 6.99 (1H, s, ArC_{13}-H); 5.86 (1H, m, $C=C_4$-H); 5.81 (1H, m, $C=C_{12}$-H); 5.69 (1H, m, $C=C_5$-H); 5.64 (1H, m, $C=C_{11}$-H); 3.85 (2H, m, C_{3c}-H, C_{12a}-H); 2.46-2.87 (12H, m, N-C_7H_2, N-C_9H_2, Ar-C_1H_2, Ar-C_3H_2, CH_2-C_{6a}-H, CH_2-C_{9a}-H, $=C-C_6$-H, $=C-C_{10}$-H); 1.97-2.11 (4H, m, $=C-C_6$-H, $=C-C_{10}$-H, $CH_2-C_2H_2-CH_2$).

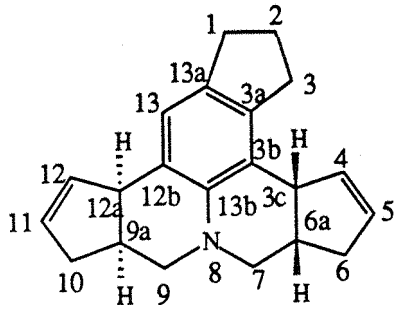
δ_C(68 MHz,TMS,$CDCl_3$)= 143.52 (ArC_{13b}-N); 141.37 (ArC_{3a}); 136.78, 134.66 ($C=C_4$-H, $C=C_{12}$-H); 133.93 (ArC_{13a}); 128.52, 127.98 ($C=C_5$-H, $C=C_{11}$-H); 124.12 (ArC_{12b}); 123.10 (ArC_{13}-H); 121.46 (ArC_{3b}); 53.95, 53.23 (N-C_7H_2, N-C_9H_2); 47.28, 45.90 ($=C-C_{3c}H$, $=C-C_{12a}H$); 37.75, 37.30 ($=C-C_6H_2$, $=C-C_{10}H_2$); 35.24, 35.08 ($CH_2-C_{6a}H$, $CH_2-C_{9a}H$); 32.51, 32.12 (Ar-C_1H_2, Ar-C_3H_2); 25.90 ($CH_2-C_2H_2-CH_2$).

ν_{max}($CHCl_3$)= 3080 (w), 3020 (w, sh), 2950 (str, br), 2860 (m, sh), 2730 (w) (C-H stretching); 1620 (v w), 1490 (m, sh) (C=C stretching); 1445 (m, sh), 1370 (w, sh), 1350 (

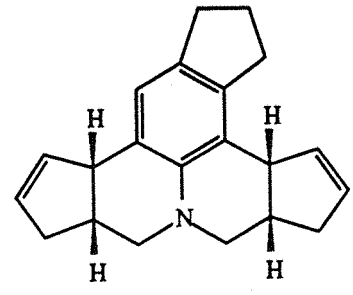
w, sh), 1335 (w, sh) (CH_2 bending); 1290 (str, sh, C_{Ar}-N stretching); 1120-1180 (w, br); 660 (w, sh).

m/z(e.i.)= Found: 289.1815 (M^+100%); 261 (9.5); 248 (25.2); 222 (11.2); 206 (5.8). $C_{21}H_{23}N$ requires 289.18305.

Elemental analysis: Calculated: C=87.15 H=8.01 N=4.84
Found: C=87.34 H=8.01 N=4.88



(156)



(157)

Monocyclocondensation of 7-amino-α-tetralone leading to 11-oxo-3a,4,5,8,9,10,11,11c-octahydro-benzo[f]-3*H*-cyclopenta[1,2-c]quinoline (159).

Trifluoroacetic acid (0.49 g ; 4.30 mmol) in acetonitrile (1ml) was added to 7-amino-α-tetralone (0.70 g ; 4.34 ml) dissolved in acetonitrile (26 ml) to give an orange solution of the amine (0.17 M). After 15 min. of stirring under nitrogen, a mixture at 0 °C of cyclopentadiene (0.29 g ; 4.39 mmol) and formalin solution 37 % (0.35 g ; 4.31 mmol) in acetonitrile (2 ml) was added to the former solution to give a dark mixture which was stirred under nitrogen at room temperature for a further 35 min. . The reaction mixture was added to a saturated sodium bicarbonate solution (150 ml) and was extracted with dichloromethane (2x200 ml). The combined organic layers were dried over anhydrous magnesium sulphate and, after filtration, were concentrated under reduced pressure to give a dark oil (1.00 g).

Flash chromatography on silica gel (100 g) run with eluant petrol/ether/ethanol 86/9/5 led to one main fraction:

-> yellow solid, title product (159), 0.67 g, 64 %, Rf=0.39 (petrol/ ether/ethanol 9/1/1). Recrystallisation in methanol/water led to yellow needles, mp= 83-85 °C.

δ_H(270 MHz, TMS, $CDCl_3$)= 6.90 (1H, d, ArC_7-H, J=8.1); 6.69 (1H, d, ArC_6-H, J=8.1); 5.67 (2H, m, HC=C_1-H); 4.86 (1H, m, =C-C_{11c}H); 3.67 (1H, m, NH); 3.03 (1H, dd, C_4H_2-N, J=10.6,4.3); 2.89 (1H, m, C_4H_2-N); 2.84 (2H, t, $C_{10}H_2$-CO, J=6.0); 2.62 (4H,

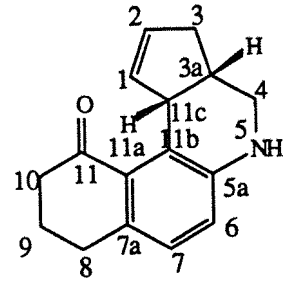
m, Ar-$C_8\underline{H}_2$, $C_3\underline{H}_2$-C=, CH_2-$C_{3a}\underline{H}$); 2.14 (1H, m, $C_3\underline{H}_2$-C=C, J=14.1); 2.02 (2H, q, CH_2-$C_9\underline{H}_2$-CH_2, J=6.3).

δ_C(68 MHz, TMS, $CDCl_3$)= 200.90 (O=$\underline{C}_{11}$); 145.00 (Ar$\underline{C}_{5a}$-NH); 137.60 (C=$\underline{C}_1$-H); 136.42 (Ar$\underline{C}_{11a}$); 131.09 (Ar$\underline{C}_{7a}$); 127.80, 127.23 (C=$\underline{C}_2$-H, Ar$\underline{C}_7$-H); 125.82 (Ar$\underline{C}_{11b}$); 120.71 (Ar$\underline{C}_6$-H); 44.76 (=C-$\underline{C}_{11c}$H); 43.74 (N-$\underline{C}_4H_2$); 41.78 (=C-$\underline{C}_3H_2$); 37.16 (OC-$\underline{C}_{10}$); 35.86 (CH_2-$\underline{C}_{3a}$H); 30.87 (Ar-C_8); 23.35 (CH_2-$\underline{C}_9H_2$-CH_2).

Elemental analysis: Calculated: C=80.30 H=7.16 N=5.85
Found: C=79.90 H=7.14 N=5.89

m/z(e.i.)= Found: 229.1305 (M^+100%); 224 (19.5); 210 (54.1); 198 (38.6); 183 (25.6); 168 (15.1). $C_{16}H_{17}NO$ requires 239.1310 .

ν_{max}($CHCl_3$)= 3340 (w, v br, N-H stretching); 3020 (w, sh), 2950 (m, br), 2860 (w, sh) (C-H stretching); 1680 (str, br, C=O); 1610, 1590 (dbt, m, sh), 1490 (m, sh) (C=C stretching); 1465 (w, sh), 1450 (w, sh), 1410 (w, sh), 1365 (m, sh) (CH_2 bending); 1330 (m, sh), 1310 (str, sh), 1275 (w, sh) (C_{Ar}-N and C_{aliph}-N stretching); 1170 (w); 820 (w, sh); 660 (w, sh).



(159)

Monocyclisation of 6-amino-α-indanone leading to 10-oxo-3a,4,5,9,10,10c-hexa-hydro-3*H*,8*H*-dicyclopenta[1,2-c:2,1-f]quinoline (161).

Trifluoroacetic acid (0.77 g ; 6.76 mmol) was added to 6-amino-α-indanone (1.00 g ; 6.79 mmol) partially dissolved in acetonitrile (28 ml) to give a yellow heterogenous mixture. After 10 min. of stirring under nitrogen, a mixture at 0 °C of cyclopentadiene (0.45 g ; 6.80 mol) and formalin solution 37 % (0.55 g ; 6.78 mmol) in acetonitrile (2 ml) to the former mixture which was stirred under nitrogen at room temperature for 2 h.. The dark green reaction mixture was added to saturated sodium bicarbonate solution (200 ml) and was extracted with dichloromethane (3x100 ml). The combined organic layers were dried over anhydrous magnesium sulphate and, after

filtration, were concentrated under reduced pressure to give a dark green solid (1.50 g).

Flash chromatography on silica gel (100 g) carried out with eluant petrol/ether 6/4 to 0/10 gave four main fractions:

-> A: brown solid, 0.39 g, 19 %, Rf=0.67, dicyclisation diastereoisomer d,l (153).

-> B: brown solid, 0.07 g, 3 %, Rf=0.64, dicyclisation diastereoisomer meso (154).

-> C: yellow solid, tittle product (161), 0.70 g, 46 %, Rf=0.57. Recrystallisation in methanol/petrol led to yellow crystals, m.p.= 165-166 °C.

-> D: yellowish solid, starting amine, 0.19 g, 19 %, Rf=0.31 (ether).

(Rf values with ether/petrol 7/3).

Title compound (161):

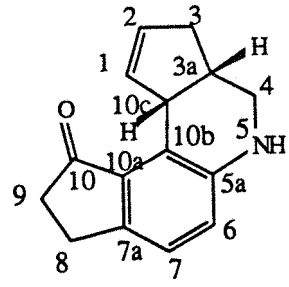
m/z(e.i.)= Found: 225.1153 (M^+100%); 210 (15.9); 197 (21.5); 184 (32.9); 171 (19.6); 154 (5.9). $C_{15}H_{15}NO$ requires 225.11536

δ_H(270 MHz, TMS, $CDCl_3$)= 7.07 (1H, d, ArC_7-H, J=7.9); 6.80 (1H, d, ArC_6-H, J=8.1); 5.85 (1H, m, $C=C_1$-H); 5.66 (1H, m, $C=C_2$-H); 4.55 (1H, m, $=CH-C_{10c}H$); 3.89 (1H, m, NH); 3.09 (1H, dd, $N-C_4H_2$, J=11.0, 4.2); 2.98 (2H, t, $OC-C_9H_2$, J=5.8); 2.92 (1H, t, $N-C_4H_2$, J=10.7); 2.67 (2H, m, $CH_2-C_{3a}H$, $C_3H_2-C=$); 2.65 (2H, t, $Ar-C_8H_2$, J=5.6); 2.16 (1H, m, $C_3H_2-C=$, J=13.7).

δ_C(68 MHz, TMS, $CDCl_3$)= 208.07 ($O=C_{10}$); 147.02 ($ArC_{5a}-N$); 145.09 (ArC_{10a}); 136.51 ($HC=C_1H$); 134.82 (ArC_{7a}); 128.03 ($HC=C_2H$); 124.41 (ArC_7-H); 123.09 (ArC_{10b}); 122.56 (ArC_6); 44.34 ($N-C_4H_2$); 43.31 ($=C-C_{10c}H$); 37.62, 37.19 ($=C-C_3H_2$, $OC-C_9$); 35.31 ($CH_2-C_{3a}H$); 24.91 ($Ar-C_3$).

ν_{max}($CHCl_3$)= 3470 (w, v br, N-H stretching); 3060 (w), 3010 (w, sh), 2940 (m, sh), 2860 (m, sh) (C-H stretching); 1690 (v str, br, C=O); 1610 (w, sh), 1595 (w, sh), 1495 (m, sh) (C=C stretching); 1450 (m, sh), 1360, 1340 (dbt, m, sh) (CH_2 bending); 1300 (str, sh), 1270 (m, sh), 1175 (str, sh) (C_{Ar}-N and C_{aliph}-N stretching); 830 (m, sh); 650 (m, sh).

Elemental analysis:	Calculated:	C=79.97	H=6.71	N=6.22
	Found:	C=79.63	H=6.53	N=6.09



(161)

Monocyclisation of 5-amino-indane leading to 3a,4,5,9,10,10c-hexahydro-3*H*, 8*H*-dicyclopenta[1,2-c:2,1-f]quinoline (162) and 3a,4,5,8,9,10b-hexahydro-3*H*, 7*H*-dicyclopenta[1,2-c:2,1-g]quinoline (163).

Trifluoroacetic acid (1.43 g; 1 eq) was added to 5-amino-indane 97 % (1.71 g; 12.47 mmol) dissolved in acetonitrile (50 ml) to give a brown homogenous mixture. A mixture at 0 °C of cyclopentadiene (0.83 g; 1eq) and formalin solution 37 % (1.01 g; 1 eq) in acetonitrile (2 ml) was added to the former mixture cooled down to -10 °C which was stirred under nitrogen between -10 and 0 °C for 3 h. Finally, the reaction mixture was left under stirring for a further 1 h to room temperature. The brown orange mixture was added to saturated sodium bicarbonate (200 ml) and was extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulphate and, after filtration, were concentrated under reduced pressure to give a brown oil (2.94 g).

Flash chromatography on silica gel run with eluant petrol/ether 9/1 to 7/3 with 3 % triethylamine gave one main fraction:

-> pale yellow solid, 1.80 g, 68 %, Rf=0.36 (petrol/ethanol 9/1), mixture of both regioisomers (162) and (163), in relative ratios 55:45 respectively. All attempts to separate the two compounds by flash chromatography or recrystallisation failed.

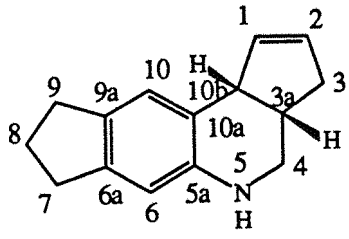
Title compounds (162) ("A") and (163) ("B"):

m/z(e.i.)= Found: 211 (M^+100%); 196 (13.6); 183 (40.5); 170 (31.5); 154 (6.1); 115 (8.0). $C_{15}H_{17}N$ requires 211.

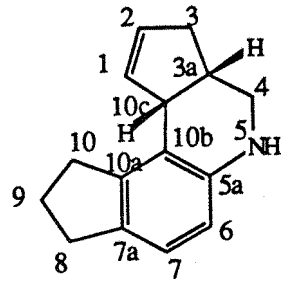
δ_H(270 MHz, TMS, $CDCl_3$)= 7.03 (1H, s, Ar^BC_{10}-H); 6.88 (1H, d, Ar^AC_6-H , J=7.7); 6.49 (1H, s, Ar^BC_6-H); 6.42 (1H, d, Ar^AC_7-H, 7.7); 5.85, 5.81 (1H, m, m, $=^AC_1$-H, $=^BC_1$-H); 5.71, 5.67 (1H, m, m, $=^AC_2$-H, $=^BC_2$-H); 3.85 (1H, m, $^AC_{10c}$-H, $^BC_{10b}$-H); 3.2-3.4 (1H, m, N-H); 3.07 (1H, dd, N^BC_4-H_2, N^AC_4-H_2, J=10.5, 4.3); 2.62-2.91 (7H, m, N^AC_4-H_2, N^BC_4-H_2, Ar-$^AC_{10}H_2$, Ar-$^BC_9H_2$, Ar-$^AC_8H_2$, Ar-$^BC_7H_2$, CH_2-$^AC_{3a}$-H, CH_2-$^BC_{3a}$-H, =C-$^AC_3$-H_2, =C-$^BC_3$-H_2); 2.15 (1H, m, =C-$^AC_3$-H_2, =C-$^BC_3$-H_2); 2.03 (2H, m, $^AC_9H_2$, $^BC_8H_2$).

$\nu_{max}(CHCl_3)$= 3400 (w, br, N-H stretching); 3070 (w), 3020 (m, sh), 2960 (str, br), 2860 (str, sh) (C-H stretching); 1630 (w, br), 1495 (str, br) (C=C stretching); 1460 (m), 1360 (m, sh), 1345 (m, sh) (CH_2 bending); 1315 (m, sh), 1285 (m, sh) (C_{Ar}-N stretching); 1100-1200 (m, w, br); 660 (w, sh).

It was impossible to analyse the carbon spectrum.



(163)



(162)

Monocyclisation of 5-amino-α-tetralone leading to 1-oxo-1,2,3,4,5,6,6a,9a-octa-hydro-benzo[h]-7*H*-cyclopenta[1,2-c]quinoline (164).

Trifluoroacetic acid (0.14 g ; 1.23 mmol) in acetonitrile (1 ml) was added to 5-amino-α-tetralone (0.20 g : 1.24 mmol) dissolved in acetonitrile (5 ml) to give a solution of the amine 0.21 M. After 10 min. of stirring under nitrogen, a mixture at 0 °C of cyclopentadiene (0.08 g ; 1.21 mmol) and formalin solution 37 % (0.10 g ; 1.23 mmol) in acetonitrile (2 ml) was added to the former solution which turned dark. The reaction mixture was stirred under nitrogen at room temperature for a further 35 min. . The reaction mixture was added to a saturated sodium bicarbonate solution (100 ml) and was extracted with dichloromethane (2x100 ml). The combined organic layers were dried over anhydrous magnesium sulphate and, after filtration, were concentrated under reduced pressure to lead to a brown oil (0.26 g).

Flash chromatography on silica gel (60 g) with eluant petrol/ether/ ethanol 9/1/1 gave one main fraction:

-> yellow solid, title compound (164), 0.19 g, 65 %, Rf=0.32 (petrol/ether/ ethanol 9/1/1). All attempts to recrystallize the tittle product (very unstable to warming) failed.

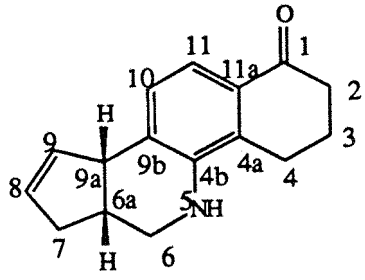
Title compound (164):

δ_H(270 MHz, TMS, $CDCl_3$)= 7.48 (1H, d, ArC_{11}-H, J=7.9); 7.15 (1H, d, ArC_{10}-H, J=7.9); 5.80 (1H, m, $HC=C_9$-H); 5.70 (1H, m, $HC=C_8$-H); 3.92 (1H, m, $=CH-C_{9a}H$); 3.83 (1H, m, NH); 3.20 (1H, dd, N-C_6H_2, J=11.0,4.1); 2.87 (1H, m, N-C_6H_2); 2.70 (2H, m, C_7H_2-C=, CH_2-$C_{6a}H$); 2.60 (4H, m, OC-C_2H_2, Ar-C_4H_2); 2.16 (3H, m, CH_2-C_3H_2-CH_2, =C-C_7H_2).

δ_C(68 MHz, TMS, $CDCl_3$)= 198.71 (O=$\underline{C}_1$); 143.29 (Ar$\underline{C}_{4b}$-N); 135.33 (HC=$\underline{C}_9$H); 130.85 (Ar$\underline{C}_{9b}$); 129.78 (Ar$\underline{C}_{11a}$); 129.13 (CH=$\underline{C}_8$H); 128.72 (Ar$\underline{C}_{4a}$); 127.68 (Ar$\underline{C}_{10}$); 116.42 (Ar$\underline{C}_{11}$); 46.96 (=C-$\underline{C}_{9a}$H); 44.69 (N-$\underline{C}_6H_2$); 38.45, 37.30 (OC-$\underline{C}_2$, $\underline{C}_7H_2$-C=); 35.67 (CH_2-$\underline{C}_{6a}$H); 23.71 (Ar-$\underline{C}_4$); 22.40 (CH_2-$\underline{C}_3H_2$-CH_2).

m/z(e.i.)= Found: 239.1305 (M^+100%); 224 (22.2); 211 (30.2); 198 (41.2); 183 (37.2); 168 (15.1). $C_{16}H_{17}NO$ requires 239.1310 .

ν_{max}($CHCl_3$)= 3440 (w, v br, N-H stretching); 3010 (w), 2950 (m, br), 2860 (w) (C-H stretching); 1690 (v str, br, C=O); 1600 (m), 1575 (str, sh), 1480 (m, br) (C=C stretching); 1345, 1325 (dbt, str, sh, CH_2 bending); 1285 (str, br, CAr-N stretching); 1185 (m, sh, C_{aliph}-N stretching).



(164)

Monocyclisation of 1-amino-5,6,7,8-tetrahydro-naphthalene leading to 1,2,3,4,5, 6,6a,9a-octahydro-benzo[h]-7*H*-cyclopenta[1,2-c]quinoline (166).

Trifluoroacetic acid (0.40 g; 1 eq) was added to 1-amino- 5,6,7,8-tetrahydro-naphthalene 90 % (0.58 g; 3.55 mmol) dissolved in acetonitrile (20 ml) to give a brown homogenous mixture which was cooled down to 0 °C. After 15 min. of stirring under nitrogen, a mixture at 0 °C of cyclopentadiene (0.24 g; 1 eq) and formalin solution 37 % (0.29 g; 1 eq) in acetonitrile (2 ml) was added to the former mixture which was stirred under nitrogen at 0 °C for a further 20 min.. The brown orange mixture was added to saturated sodium bicarbonate (150 ml) and was extracted with dichloromethane . The combined organic layers were dried over anhydrous magnesium sulphate and, after filtration, were concentrated under reduced pressure to give a brown red liquid (0.77 g) .

Flash chromatography on silica gel with petrol/ether 10/0 to 0/10 as eluent gave two main fractions:

-> A: light red brown oil, title compound (166), 0.30 g, 38 %, Rf=0.81.

-> B: yellow oil, 0.20 g, 25 %, Rf=0.71, starting amine.

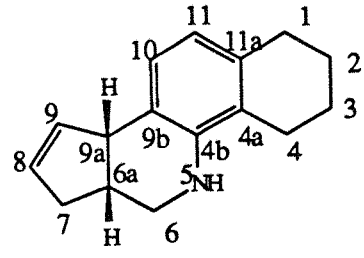
(Rf values with ether as eluant).

Title compound (166):
m/z(e.i.)= Found: 225.1509 (M^+100%); 210 (17.8); 196 (20.7); 184 (24.7); 167 (8.7). $C_{16}H_{19}N$ requires 225.15175

δ_H(270 MHz, TMS, $CDCl_3$)= 6.97 (1H, d, ArC_{10}-H, J=7.7); 6.52 (1H, d, ArC_{11}-H, J=7.7); 5.81 (1H, m, $=C_9$-H); 5.64 (1H, m, $=C_8$-H); 3.86 (1H, m, C_{9a}-H); 3.71 (1H, m, N-H); 3.12 (1H, dd, NC_6-H, J=10.8); 2.85 (1H, m, NC_6-H); 2.70 (4H, m, $=C\text{-}C_7$-H, $CH_2\text{-}C_{6a}$-H, $Ar\text{-}C_4\text{-}H_2$); 2.36 (2H, m, $Ar\text{-}C_1\text{-}H_2$); 2.14 (1H, d, $=C\text{-}C_7$-H, J_{gem}=14.5); 1.83 (2H, m, $C_2\text{-}H_2$); 1.74 (2H, m, $C_3\text{-}H_2$).

δ_C(68 MHz, TMS, $CDCl_3$)= 143.68 (ArC_{4b}-N); 136.48 ($C=C_9$-H); 135.15 (ArC_{11a}); 128.54 (ArC_{4a}); 128.34 ($C=C_8$-H); 126.77 (ArC_{10}-H); 121.40 (ArC_{9b}); 118.93 (ArC_{11}-H); 46.32 ($=C\text{-}C_{9a}$-H); 44.83 ($N\text{-}C_6H_2$); 37.37 ($=C\text{-}C_7H_2$); 36.03 ($CH_2\text{-}C_{6a}$-H); 30.00 ($Ar\text{-}C_1H_2$); 23.91, 23.28, 22.89 (C_2H_2, C_3H_2, $Ar\text{-}C_4H_2$).

ν_{max}($CHCl_3$)= 3400-3470 (mlt, v w, sh, N-H stretching); 3020 (w, sh), 2940 (str), 2860 (m) (C-H stretching); 1610 (w), 1590 (m, sh), 1490 (str, sh) (C=C stretching); 1450 (m, br), 1410 (v, br), 1360 (w, br) (CH_2 bending); 1300 (m, sh, C_{Ar}-N stretching); 1120 (m, br); 660 (w, sh).



(166)

Monocylisation of 1-amino-naphthalene leading to 5,6,6a,9a-tetrahydro-benzo [h]-7*H*-cyclopenta[1,2-c]quinoline (169).

Trifluoroacetic acid (1.14 g ; 10.0 mmol) in acetonitrile (2 ml) was added to 1-amino-naphthalene (1.43 g ; 10.0 mmol) dissolved in acetonitrile (20 ml) at around 15 °C to give a dark purple solution of the amine (0.45 M). After 15 min. of stirring under nitrogen, a mixture at around 0 °C of cyclopentadiene (1.32 g ; 20.0 mmol ; 2 eq) and formalin solution 37 % (0.82 g ; 10.0 mmol) in acetonitrile (3 ml) was added dropwise to the former solution in 30 min. while the reaction mixture temperature was decreased to 1 °C by external cooling, so that the major part of the addition occurred between 5 and 0 °C. After adding, the dark red mixture was stirred at 1 °C under nitrogen for a further 5 min.. A saturated sodium bicarbonate solution (150 ml) was added to the reaction mixture which was extracted with dichloromethane (2x100 ml). The

combined organic layers were dried over anhydrous magnesium sulphate and, after filtration, the solvent was removed under reduced pressure to give a red purple oil (2.02 g). A polar brown by-product precipitated by adding ether and was removed by filtration. The mother liquors were concentrated under reduced pressure to give a dark red oil (0.90 g).

Flash chromatography on silica gel (80 g) with petrol/ether/ethanol 90/5/5 as eluent gave one main fraction:

-> yellow solid, title compound (169), 0.45 g, 20 %, Rf=0.45 (petrol/ether/ethanol 85/10/5). Recrystallisation from dichloromethane/petrol led to yellow crystals, mp=68-70 °C.

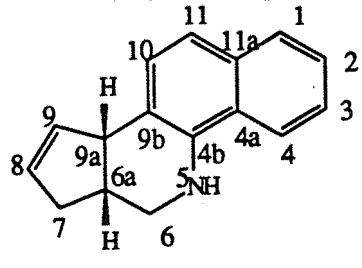
m/z(e.i.)= Found: 221.1200 (M^+100%); 204(16); 192(24); 167(13); 156(14). $C_{16}H_{15}N$ requires 221.12045.

δ_H(270 MHz, TMS, $CDCl_3$)= 7.74 (1H, m, ArC_4-H); 7.68 (1H, m, ArC_1-H); 7.39 (2H, m, ArC_2-H, ArC_3-H); 7.31 (1H, d, ArC_{10}-H, J=8.4); 7.25 (1H, d, ArC_{11}-H, J=8.4); 5.93 (1H, dd, $HC=C_9$-H, J_{cis}=5.5, J=1.8); 5.73 (1H, m, $HC=C_8$-H); 4.17 (1H, m, N-H); 3.99 (1H, m, $=C-C_{9a}$-H); 3.27 (1H, dd, $N-C_6H_2$, $J_{e,a}$=4.3, J_{gem}=10.6); 2.96 (1H, t, $N-C_6H_2$, $J_{a,a}$~J_{gem}=10.3 (9.7 and 10.8)); 2.68-2.74 (2H, m, CH_2-C_{6a}-H, $=C-C_7H_2$); 2.20 (1H, d, $=C-C_7-H_2$, Jgem=15.4).

δ_C(68 MHz, TMS, $CDCl_3$)= 140.44 (ArC_{4b}-N); 136.05 ($HC=C_9$-H); 132.76 (ArC_{11a}); 128.70, 128.67, 128.26 ($HC=C_8$-H, ArC_1-H, ArC_{10}-H); 125.25, 125.05 (ArC_2-H, ArC_3-H); 123.59 (ArC_{4a}); 119.68 (ArC_4-H); 119.11 (ArC_{9b}); 118.03 (ArC_{11}-H); 46.95 ($=C-C_{9a}$-H); 44.88 ($N-C_6H_2$); 37.37 ($=C-C_7H_2$); 35.92 ($CH_2-C_{6a}H_2$).

ν_{max}($CHCl_3$)= 3300-3500 (mlt, v w, sh, N-H stretching); 3060 (w, sh), 3010 (w), 2930 (w), 2850 (w) (C-H stretching); 1575 (m, sh), 1515 (w) (C=C stretching); 1475 (w, br), 1400 (str, bsh) (CH_2 bending); , 1360 (str, sh), 1305 (w, sh) (C_{Ar}-N stretching); 1305 (w, sh); 1280 (w); 1115 (m, br); 650 (w, sh).

Elemental analysis: Calculated : C=86.84 H=6.83 N=6.33
Found : C=86.47 H=7.05 N=6.13



(169)

Double monocyclisation of 1,8-diaminonaphthalene leading to 3a,7b,10a,11,12,

13,14,14a-octahydro-10*H* -cyclopenta[1',2':3,4]quinolino[7,8-h]-1*H* -cyclopenta [1,2-c]quinoline (225) and (226).

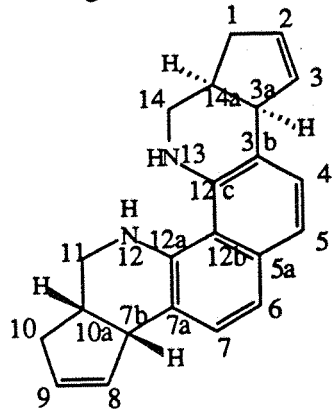
Trifluoroacetic acid (1.44 g ; 12.63 mmol) in acetonitrile (2 ml) was added to non purified technical 1,8-diaminonaphthalene (1.00 g ; 6.32 mmol) partially dissolved in acetonitrile (18 ml). After 10 min. of stirring under nitrogen, a mixture at 0 °C of cyclopentadiene (0.83 g ; 12.56 mmol) and formalin solution 37 % (1.03 g ; 12.69 mmol) in acetonitrile (2 ml) was added to the former dark mixture. The obtained mixture was stirred under nitrogen at room temperature for a further 35 min. . The reaction mixture was added to a saturated sodium bicarbonate solution (250 ml). The very dark emulsion was filtrated, the black solid (1.35 g) hence removed was washed with dichloromethane (200 ml). The aqueous liquor was extracted with dichloromethane (4x200 ml). All the organic layers were combined, dried over anhydrous magnesium sulphate and, after filtration, were concentrated under reduced pressure to give a dark brown solid (1.12 g).

Flash chromatography on silica gel (150 g) with petrol/ether 6/4 to ether as eluent led to one main fraction:

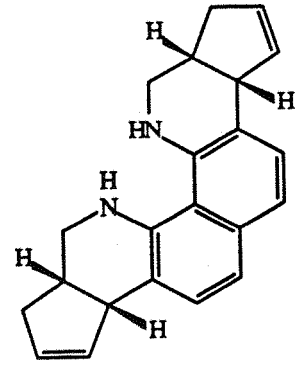
-> dark pink solid, title compounds (225) and/or (226), 0.06 g, 3.0 %, Rf=0.71 (petrol/ether 9/1).

m/z(e.i.)= Found: 314 (M^+100%); 285 (10.0); 247 (20.6); 235 (7.1); 207 (5.9); 183 (5.1); 136 (7.8); 116(6.5). $C_{22}H_{22}N_2$ requires 314 .

δ_H(270 MHz, TMS, $CDCl_3$)= 7.26 (2H, d, ArC_4-H, ArC_7-H, J=8.7); 7.09 (2H, d, ArC_5-H, ArC_6-H, J=8.7); 5.92 (2H, m, $HC=C_3$-H, $HC=C_8$-H); 5.69 (2H, m, CH_2-$C=C_2$-H, CH_2-$C=C_9$-H); 3.97 (2H, m, =C-C_{3a}-H, =C-C_{7b}-H); 3.27 (2H, dd, N-C_{11}-H_2, N-C_{14}-H_2, J_{gem}=11.2, $J_{e,a}$=4.2); 2.95 (2H, m, N-C_{11}-H_2, N-C_{14}-H_2); 2.73 (4H, m, =C-C_1H_2, =C-$C_{10}H_2$, CH_2-C_{10a}H, CH_2-C_{14a}H); 2.20 (2H, m, =C-C_1H_2, =C-$C_{10}H_2$).
The two amino protons are suspected to show the same chemical shift as ArC_4-H and ArC_7-H in view of the integration curve (corresponding to four protons).



(225)



(226)

III] Cyclisations of the amino-anthraquinones.

Dicyclisation of 2-amino-anthraquinone leading to 5,16-dioxo-5,5c,8a,9,10,11, 11a,14c,16-nonahydro-8*H*,12*H*-cyclopenta[1,2-c]-naphtho[2,3-f]-cyclopenta[1', 2':3,4]pyrido[3,2,1-ij]quinoline (256) and (257).

Trifluoroacetic acid (0.61 g; 3 eq) was added to 2-amino-anthraquinone (0.40 g; 1.79 mmol) partially dissolved in acetonitrile (30 ml) to give a brown heterogenous mixture. After 15 min. of stirring under nitrogen, a mixture at 0 °C of cyclopentadiene (0.36 g; 3 eq) and formalin solution 37 % (0.44 g; 3 eq) in acetonitrile (3 ml) was added to the former mixture which turned red very quickly while stirring under nitrogen at room temperature for 45 min.. The dark red mixture was added to saturated sodium bicarbonate (150 ml) and was extracted with dichloromethane (2x150 ml). The combined organic layers were dried over anhydrous magnesium sulphate and, after filtration, were concentrated under reduced pressure to give a dark red oil (0.80 g).

Flash chromatography on alumina (100 g) with ether/ethyl acetate 10/0 to 5/5 as eluent gave two main fractions:

-> A: red solid, 0.65 g, 96 %, Rf=0.74. Mixture of both diastereoisomers d,l (256) ("M") and meso (257) ("m") in relative ratios 80:20 respectively (deduced from the integration curve). Recrystallisation from ethanol led to cottonish red crystals, m.p.=169-171 °C.

-> B: red solid, 0.01 g, Rf=0.70.

(Rf values with ether as eluant).

Title compounds (256) and (257):

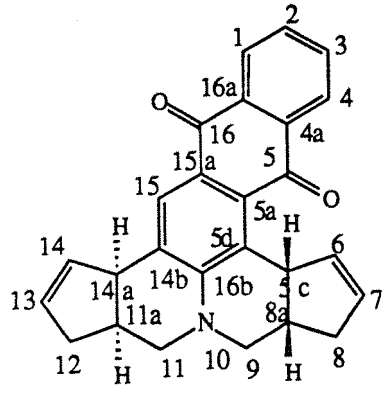
δ_H(270 MHz, TMS, $CDCl_3$)= 8.19 (2H, m, ArC_{11}-H, ArC_{14}-H); 8.06 (1H, s, ArC_9-H); 7.69 (2H, m, ArC_{12}-H, ArC_{13}-H); 5.84 (1H, m, $=C_1$-H); 5.73 (3H, m, $=C_2$-H, $=C_7$-H, $=C_8$-H); 5.15 (1H, m, C_{15c}-H); 4.04 (1H, m, C_{8a}-H); 3.04 (2H, m, NC_4-H, NC_5-H); 2.67-2.89 (6H, m, NC_4-H, NC_5-H, C_{3a}-H, C_{5a}-H, C_3-H, C_6-H); 2.29 (2H, m, C_3-H, C_6-H).

δ_C(68 MHz, TMS, $CDCl_3$)= 186.05, 182.63 (OC_5, OC_{16}); 151.44 (ArC_{16b}-N); 137.66 ($=C_6$-H: m); 136.65 ($=C_6$-H: M);135.73 ($=C_{14}$-H: m); 135.23 ($=C_{14}$-H: M);133.34, 133.30 (ArC_2-H, ArC_3-H: M+m); 130.56 (ArC_{5b}: M+m); 129.93, 129.29, 128.85, 128.50 ($=C_7$-H, $=C_{13}$-H: M+m) 129.74, 128.10, 128.04 (ArC_{5a}, ArC_{5b}, ArC_{14b}: M+m); 127.88, 127.22 (ArC_1-H, ArC_4-H: M+m); 126.25 (ArC_{15}-H: M+m); 124.82 (ArC_{15a}: M+m); 55.66 (NC_9H_2: M); 53.01 (NC_9H_2: m); 52.13 ($NC_{11}H_2$: M); 51.28 ($NC_{11}H_2$: m); 47.73 ($=C$-C_{5c}-H: m); 47.44 ($=C$-C_{5c}-H: M); 45.44 ($=C$-C_{14a}-H: M+m); 37.56, 37.01 ($=C$-C_8H_2, $=C$-$C_{12}H_2$: m); 37.37, 37.24 ($=C$-C_8H_2, $=C$-$C_{12}H_2$: M); 35.39, 35.29 (CH_2-C_{8a}-H, CH_2-C_{11a}-H: M);

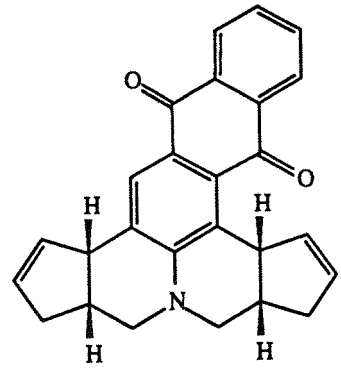
34.24, 34.13 (CH_2-$\underline{C}_{8a}$-H, CH_2-$\underline{C}_{11a}$-H: m).

$\nu_{max}(CHCl_3)$= 3005 (w, br), 2940 (w, br), 2850 (w, sh) (C-H stretching); 1710 (w, br); 1665 (str, sh, C=O); 1570 (str, sh), 1495 (w) (C=C stretching); 1445 (w, sh), 1410 (w, sh), 1340, 1330 (dbt, str, sh) (CH_2 bending); 1295 (str, br), 1280 (str, br), 1250 (m) (C_{Ar}-N and C_{aliph}-N stretching).

m/z(e.i.)= Found: 379.1561 (M^+100%); 364 (6.1); 35 (10.5); 338 (14.2); 325 (5.3). $C_{26}H_{21}NO_2$ requires 379.15723.



(256)



(257)

Monocyclisation of 2-amino-anthraquinone 8,13-dioxo-3a,4,5,8,13,13c-hexa-hydro-3*H*-cyclopenta[1,2-c]-naphtho[2,3-f] quinoline (258).

Trifluoroacetic acid (0.37 g; 3 eq) was added to 2-amino-anthraquinone (0.25 g; 1.12 mmol) partially dissolved in acetonitrile (110 ml) to give a brown heterogenous mixture which was warmed at reflux (~ 80 °C) under stirring and nitrogen. A mixture at 0 °C of cyclopentadiene (0.15 g; 2 eq) and formalin solution 37 % (0.09 g; 1 eq) in acetonitrile (4 ml) was added in 20 min. to the former mixture. The homogenous reaction mixture was stirred under nitrogen at reflux for a further 25 min.. After cooling to room temperature, the dark red mixture was added to saturated sodium bicarbonate (200 ml) and was extracted with dichloromethane (2x150 ml). The combined organic layers were dried over anhydrous magnesium sulphate and, after filtration, were concentrated under reduced pressure to give a red solid (0.37 g).

Flash chromatography on alumina (100 g) with ether/dichloromethane/ethyl acetate 10/0/0 to 0/8/2 as eluent gave two main fractions:

-> A: red solid, 0.06 g, 14 %, Rf=0.74, dicyclisation products.

-> B: purple solid, 0.25 g, 74 %, Rf=0.65, title compound (258). Recrystallisation from methanol led to cottonish purple crystals, mp=169-171 °C

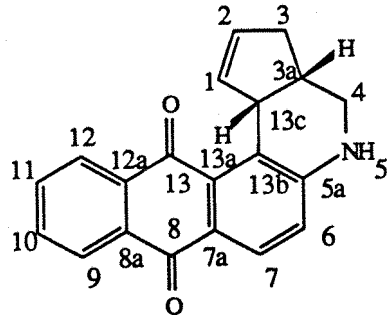
(Rf values with ether as eluant).

Title compound (258):
m/z(e.i.)= Found: 301.1107 (M^+100%); 286 (12.2); 272 (25.4); 260 (22.9); 247 (9.9); 167 (17.5); 149 (42.2). $C_{20}H_{15}NO_2$ requires 301.11028.

δ_H(270 MHz,TMS,$CDCl_3$)= 8.20 (2H, m, ArC_9-H, ArC_{12}-H); 8.10 (1H, d, ArC_7-H, J=8.7); 7.71 (2H, m, ArC_{10}-H, ArC_{11}-H); 6.80 (1H, d, ArC_6-H, J=8.7); 5.84 (1H, m, $C=C_1$-H); 5.77 (1H, m, $C=C_2$-H); 4.97 (1H, m, C_{13c}-H); 4.71 (1H, m, N-H); 3.14 (1H, m, $N\text{-}C_4\text{-}H_2$); 3.04 (1H, m, $N\text{-}C_4\text{-}H_2$); 2.61-2.78 (2H, m, $CH_2\text{-}C_{3a}$-H, $=C\text{-}C_3$-H); 2.12 (1H, m, $=C\text{-}C_3$-H, J_{gem}=15.8).

δ_C(68 MHz,TMS,$CDCl_3$)= 186.34 (OC_{13}); 182.42 (OC_8); 151.47 (ArC_{5a}-N); 137.15 ($C=C_1$-H); 135.34, 135.17 (ArC_{8a}, ArC_{12a}); 134.04 (ArC_{13a}); 133.37, 133.51 (ArC_{10}-H, ArC_{11}-H); 129.41 (ArC_{13b});128.39 ($C=C_2$-H), 128.08, 127.23 (ArC_9-H, ArC_{12}-H); 126.39 (ArC_7-H); 124.53 (ArC_{7a}); 119.13 (ArC_6-H); 45.01 ($=C\text{-}C_{13c}$-H); 42.40 (NC_4H_2); 36.99 ($=C\text{-}C_3H_2$); 34.85 ($CH_2\text{-}C_{3a}$-H).

ν_{max}($CHCl_3$)= 3460 (w, sh, N-H stretching); 3100-3000 (v w, br), 2960 (v w, br), 2870 (v w, sh) (C-H stretching); 1680 (m, br), 1600 (str, sh) (C=O); 1590 (str, sh), 1580 (m, sh), 1510 (w) (C=C stretching); 1340 (str, sh), 1310 (v str, sh) (CH_2 bending); 1300 (m, sh), 1290 (m, sh), 1100-1200 (m, w, br) (C_{Ar}-N and C_{aliph}-N stretching).



(258)

Monocyclisation of 1-amino-anthraquinone leading to 6,11-dioxo-3a,6,11,12,13, 13a-hexahydro-1*H*-cyclopenta[1,2-c]-naphtho[2,3-h]quinoline (261).

Trifluoroacetic acid (0.50 g; 1 eq) was added to 1-amino-anthraquinone 97 % (1.00 g; 4.34 mmol) partially dissolved in acetonitrile (40 ml) to give a red brown heterogenous mixture. After 10 min. of stirring under nitrogen, a mixture at 0 °C of cyclopentadiene (0.59 g; 2 eq) and formalin solution 37 % (0.70 g; 2 eq) in acetonitrile (2 ml) was added to the former mixture

which turned red purple while stirring under nitrogen at room temperature for 45 min.. The dark mixture was added to saturated sodium bicarbonate (100 ml) and was extracted with dichloromethane (5x100 ml). The combined organic layers were dried over anhydrous magnesium sulphate and, after filtration, were concentrated under reduced pressure to give a dark purple solid (1.40 g).
Flash chromatography on alumina (250 g) with ether/dichloromethane 10/0 to 0/10 as eluent gave one main fraction:
-> dark purple solid, title product (261), 1.24 g, 95 %, Rf=0.65 (ether/petrol 5/5). Recrystallisation from methanol led to purple woolish crystals, m.p.=165-167 °C.

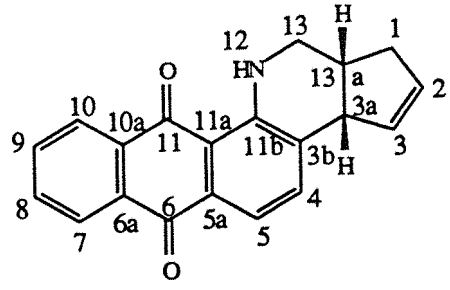
m/z(e.i.)= Found: 301.1086 (M^+100%); 286 (18.2); 273 (21.6); 260 (31.7); 247 (6.0); 149 (7.1). $C_{20}H_{15}NO_2$ requires 301.11028.

δ_H(270 MHz,TMS,$CDCl_3$)= 9.64 (1H, s, N-H); 8.25 (2H, d, ArC_{10}-H, J=6.8); 8.22 (1H, d, ArC_7-H, J=6.8); 7.71 (2H, m, ArC_8-H, ArC_9-H); 7.58 (1H, d, ArC_5-H, J=7.6); 7.43 (1H, d, ArC_4-H, J=7.6); 5.78 (2H, m, H-C_2=C_3-H); 3.97 (1H, m, C_{3a}-H); 3.31 (1H, m, NC_{13}-H_2); 2.99 (1H, m, NC_{13}-H_2); 2.70 (2H, m, =C-C_{13a}-H, =C-C_1-H_2); 2.18 (1H, m, =C-C_1-H, Jgem=14.7).

δ_C(68 MHz,TMS,$CDCl_3$)= 184.91 (OC_{11}); 183.73 (OC_6); 150.29 (ArC_{11b}-N); 135.34, 135.02 (C=C_3-H, ArC_4-H); 135.17 (ArC_{5a}); 133.91, 132.99 (ArC_8-H, ArC_9-H); 133.47, 133.28 (ArC_{6a}, ArC_{10a}); 132.39 (ArC_{3b}); 129.68 (C=C_2-H), 126.82 (ArC_7-H, ArC_{10}-H); 116.23 (ArC_5-H); 113.20 (ArC_{11a}); 46.85 (=C-C_{3a}-H); 42.27 (N$C_{13}H_2$); 37.27 (=C-C_1H_2); 34.16 (CH_2-C_{13a}-H).

ν_{max}($CHCl_3$)= 3530 (v w, br), 3210 (w, br) (N-H stretching); 3020 (w, br), 2950 (w, br), 2850 (w, sh) (C-H stretching); 1665 (str, sh), 1630 (str, sh) (C=O); 1600, 1580 (dbt, str, sh), 1510 (str, sh) (C=C stretching); 1460 (w, sh), 1380, 1365 (dbt, m) (CH_2 bending); 1330, 1315 (dbt, m); 1270 (v str, br), 1245 (m, br), 1185 (w, sh), (C_{Ar}-N and C_{aliph}-N stretching); 990 (str, sh).

Elemental analysis:	Calculated:	C=79.72	H=5.02	N=4.65
	Found:	C=78.68	H=4.95	N=4.54



(261)

Monocyclisation of 1-amino-anthraquinone (with styrene) leading to 7,12-dioxo-4-phenyl-1,2,3,4,7,12-hexahydro-naphtho[2,3-h]quinoline (262).

Trifluoroacetic acid (0.99 g; 1 eq) was added to 1-amino-anthraquinone 97 % (2.00 g; 8.68 mmol) partially dissolved in acetonitrile (45 ml) to give a red brown heterogenous mixture. After 10 min. of stirring under nitrogen, a mixture of styrene(1.81 g; 2 eq) and formalin solution 37 % (1.41 g; 2 eq) in acetonitrile (2 ml) was added to the former mixture which was stirred under nitrogen at room temperature for 40 min. The same quantities of styrene and formaldehyde were then added to the dark red reaction mixture which was stirred at room temperature for a further 1 h 35 min. It was finally warmed at smooth reflux (75-80 °C) for 45 min. After cooling to room temperature, the dark mixture was added to saturated sodium bicarbonate (100 ml) and was extracted with dichloromethane (5x100 ml). The combined organic layers were dried over anhydrous magnesium sulphate and, after filtration, were concentrated under reduced pressure to give a dark red solid (3.0 g).

Flash chromatography on alumina (250 g) with ether/dichloromethane 10/0 to 0/10 as eluent gave one main fraction:

-> red purple solid, title compound (262), 2.52 g, 86 %, Rf=0.64 (ether/petrol 5/5). Recrystallisation from ethanol led to purple woolish crystals, mp= 178.5-180 °C.

m/z(e.i.)= Found: 339.1239 (M^+100%); 324 (13.1); 260 (49); 248 (5.4); 91 (10.4). $C_{23}H_{17}NO_2$ requires 339.12593.

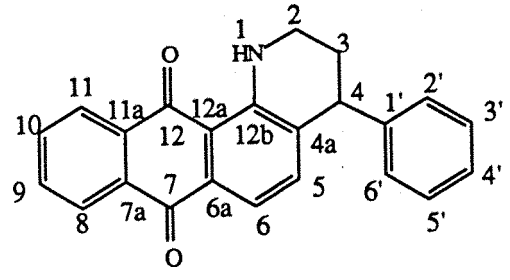
δ_H(270 MHz, TMS, $CDCl_3$)= 10.11 (1H, m, N-H); 8.29 (1H, d, ArC_{11}-H, J=7.4); 8.23 (1H, d, ArC_8-H, J=7.3); 7.66-6.78 (2H, m, ArC_9-H, ArC_{10}-H); 7.45 (1H, d, ArC_6-H, J=7.5); 7.33 (1H, t, J~7.0), 7.30 (1H, t, J~7.0), 7.25 (1H, t, J=6.8) ($ArC_{3'}$-H, $ArC_{4'}$-H, $ArC_{5'}$-H); 7.12 (2H, d, $ArC_{2'}$-H, $ArC_{6'}$-H, J=7.0); 7.06 (1H, d, ArC_5-H, J=7.5); 4.20 (1H, t, CH_2-C_4-H, J~5.7); 3.52 (1H, m, NC_2-H_2); 3.42 (1H, m, NC_2-H_2); 2.09-2.25 (2H, m, CH_2-C_3H_2).

δ_C(68 MHz, TMS, $CDCl_3$)= 184.93 (O=C_{12}); 183.76 (O=C_7); 149.51 (ArC_{12b}-N); 144.28 ($ArC_{1'}$); 135.33, 135.28 (ArC_5-H, ArC_{6a}); 133.94, 132.92 (ArC_9-H, ArC_{10}-H); 133.30 (

$Ar\underline{C}_{7a}$, $Ar\underline{C}_{11a}$); 132.30 ($Ar\underline{C}_{4a}$); 128.83, 128.50 ($Ar\underline{C}_{2'}$-H, $Ar\underline{C}_{3'}$-H, $Ar\underline{C}_{5'}$-H, $Ar\underline{C}_{6'}$-H); 126.95 ($Ar\underline{C}_{4'}$); 126.79 ($Ar\underline{C}_{8}$-H, $Ar\underline{C}_{11}$-H); 115.64 ($Ar\underline{C}_{6}$-H); 111.94 ($Ar\underline{C}_{12a}$); 43.67 (CH_2-$\underline{C}_4$H); 38.34 ($N\underline{C}_2$-H_2); 28.48 (CH_2-$\underline{C}_3H_2$).

$\nu_{max}(CHCl_3)$= 3510 (v w, br), 3290 (w, br) (N-H stretching); 3080 (w, br), 3020 (w, br), 2970 (w, br), 2870 (w, br) (C-H stretching); 1670 (str, sh, C=O); 1630 (str, sh, C=O); 1600 (str, sh), 1580 (str, sh), 1520 (str, sh) (C=C stretching); 1470 (w, br), 1385, 1365 (dbt, m, sh) (CH_2 bending); 1300-1275 (str, br, C_{Ar}-N stretching); 1230 (m, br), 1185 (m, sh) (C_{Alip}-N stretching); 1015 (m, sh); 650 (m, sh).

Elemental analysis: Calculated: C=81.40 H=5.05 N=4.13
Found: C=80.32 H=4.79 N=4.05



(262)

Double monocyclisation of 1,5-diamino-anthraquinone leading to 6,14-dioxo-3a, 6,7,8,8a,11a,14,15,16,16a-decahydro-benzo[1,2-h:4,5-h']bis-(cyclopenta[1,2-c] quinoline) (264).

Trifluoroacetic acid (0.93 g; 2 eq) was added to 1,5-diamino-anthraquinone 97 % (1.00 g; 4.07 mmol) partially dissolved in acetonitrile (25 ml) to give a purple heterogenous mixture. After 15 min. of stirring under nitrogen, a mixture at 0°C of cyclopentadiene (1.08 g; 4 eq) and formalin solution 37% (1.32 g; 4 eq) in acetonitrile (4 ml) was added to the former mixture which was next stirred under nitrogen at room temperature for 1 h 40 min.. The dark purple mixture was added to saturated sodium bicarbonate (200 ml) and was extracted with dichloromethane (long, emulsion). The combined organic layers were dried over anhydrous magnesium sulphate and, after filtration, were concentrated under reduced pressure to give a dark purple solid (1.3 g).

Several flash chromatographies on alumina with ether/ethyl acetate 10/0 to 0/10 as eluent gave two main fractions:

-> A: purple solid, 0.67 g, 42 %, Rf=0.74. Title compound, diastereoisomer d,l (264). Recrystallization in ethanol led to a purple powder, mp>240 °C

-> B: purple solid, 0.02 g, Rf=0.74, 0.65.

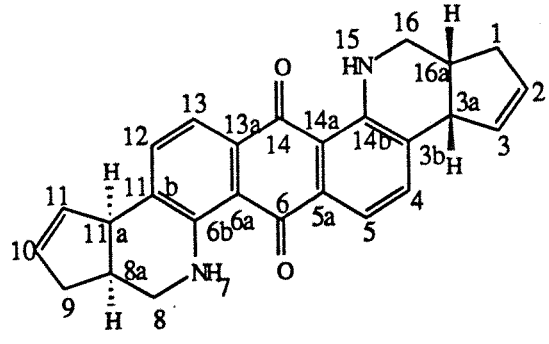
(Rf values with ether as eluant).

Title compound, diastereoisomer d,l (264):
m/z(e.i.)= Found: 394.1653 (M^+100%); 379 (5.6); 366 (13.2); 353 (14.7); 328 (7.4). $C_{26}H_{22}N_2O_2$ requires 394.16813.

δ_C(68 MHz, TMS, $CDCl_3$)= 185.39 (O$\underline{C}_6$, O$\underline{C}_{14}$); 149.88 (Ar$\underline{C}_{6b}$-N, Ar$\underline{C}_{14b}$-N); 135.57, 134.87 (C=$\underline{C}_3$-H, Ar$\underline{C}_4$-H, C=$\underline{C}_{11}$-H, Ar$\underline{C}_{12}$-H); 134.26, 130.73 (Ar$\underline{C}_{3b}$, Ar$\underline{C}_{11b}$, Ar$\underline{C}_{5a}$, Ar$\underline{C}_{13a}$); 129.48 (C=$\underline{C}_2$-H, C=$\underline{C}_{10}$-H); 115.36 (Ar$\underline{C}_5$-H, Ar$\underline{C}_{13}$-H); 113.40 (Ar$\underline{C}_{14a}$, Ar$\underline{C}_{6a}$); 46.73 (=C-$\underline{C}_{3a}$-H, =C-$\underline{C}_{11a}$-H); 42.33 (N$\underline{C}_8H_2$, N$\underline{C}_{16}H_2$); 37.30 (=C-$\underline{C}_1H_2$, =C-$\underline{C}_9H_2$); 34.28 (CH_2- $\underline{C}_{8a}$-H, CH_2-$\underline{C}_{16a}$-H).

δ_H(270 MHz, TMS, $CDCl_3$)= 9.57 (2H, m, N-$\underline{H}$, N-$\underline{H}$); 7.53 (2H, d, ArC_5-$\underline{H}$, ArC_{13}-$\underline{H}$, J=7.6); 7.40 (2H, d, ArC_4-$\underline{H}$, ArC_{12}-$\underline{H}$, J=7.6); 5.79 (2H, m, C=C_3-$\underline{H}$, C=C_{11}-$\underline{H}$); 5.76 (2H, m, C=C_2-$\underline{H}$, C=C_{10}-$\underline{H}$); 3.95 (2H, m, =C-C_{3a}-$\underline{H}$, =C-C_{11a}-$\underline{H}$); 3.26-3.35 (2H, m, NC_8-$\underline{H}$, NC_{16}-$\underline{H}$); 2.97 (2H, m, NC_8-$\underline{H}$, NC_{16}-$\underline{H}$); 2.65-2.75 (4H, m, =C-C_1-$\underline{H}$, =C-C_9-$\underline{H}$, CH_2-C_{8a}-$\underline{H}$, CH_2-C_{16a}-$\underline{H}$); 2.16 (2H, m, =C-C_1-$\underline{H}$, =C-C_9-$\underline{H}$).

ν_{max}($CHCl_3$)= 3510 (v w, br), 3300 (w, br) (C-H stretching); 3010 (w, sh), 2940 (w, br), 2850 (w, sh) (N-H stretching); 1615 (str, sh, C=O); 1590 (str, sh), 1570 (str, sh), 1505 (m, sh) (C=C stretching); 1455 (w, sh), 1370 (m, sh), 1350 (m, sh) (CH_2 bending); 1325 (w, sh), 1260 (v str, v br) (C_{Ar}-N and C_{aliph}-N stretching); 1065 (m, sh).



(264)

Double monocyclisation of 1,4-diamino-anthraquinone leading to 9,14-dioxo-3a, 3d,6a,7,8,9,14,15,16,16a-decahydro-1H,6H-dicyclopenta[2,1-a:1,2-k]-naphtho [2,3-f]-4,7-phenanthroline (267).

Trifluoroacetic acid (0.93 g; 2 eq) was added to 1,4-diamino-anthraquinone 97 % (1.00 g; 4.07 mmol) partially dissolved in acetonitrile (40 ml) to give a purple heterogenous mixture. After 15

min. of stirring under nitrogen, a mixture at 0 °C of cyclopentadiene (0.81 g; 3 eq) and formalin solution 37 % (0.66 g; 2 eq) in acetonitrile (3 ml) was added to the former mixture which turned blue very quickly while stirring under nitrogen at room temperature for 25 min..

The dark blue mixture was added to saturated sodium bicarbonate (200 ml) and was extracted with dichloromethane (long, emulsion). The combined organic layers were dried over anhydrous magnesium sulphate and, after filtration, were concentrated under reduced pressure to give a dark blue solid.

Two flash chromatographies run on alumina with eluant petrol/ether/ dichloromethane 2/8/0 to 0/0/10 gave three main fractions:

-> A: orange brown solid, 0.06 g, 4 %, Rf=0.72. Proposed structure (268) (scheme 184).

-> B: blue solid, 0.69 g, 43 %, Rf=0.65, title compound, diastereoisomer d,l (267). Recrystallization from methanol led to blue dark crystals, mp= 223-224 °C.

-> C: blue solid, 0.01 g, 0.6 %, Rf=0.53. Structure not elucidated

(Rf values with ether as eluant).

A:

m/z(e.i.)= Found: 420 (M^+100%); 379 (15.6); 210 (6.9); 189 (10.7).

$\nu_{max}(CHCl_3)$= no bands for N-H and C=O stretchin g.

B: Title compound, diastereoisomer d,l (267):

m/z(e.i.)= Found: 394.1652 (M^+100%); 379 (4.5); 365 (4.0); 353 (16.3); 337 (5.0); 327 (3); 312 (3). $C_{26}H_{22}N_2O_2$ requires 394.16813.

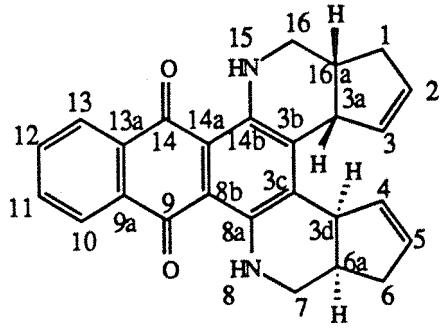
δ_H(270 MHz, TMS, $CDCl_3$)= 8.32 (2H, m, ArC_{10}-H, ArC_{13}-H); 7.67 (2H, m, ArC_{11}-H, ArC_{12}-H); 5.87 (2H, m, $=C_4$-H, $=C_5$-H); 5.77 (2H, m, $=C_3$-H, $=C_6$-H); 4.15 (2H, m, C_{4a}-H, C_{4d}-H); 3.27-3.33 (2H, m, NC_1-H, NC_8-H); 3.13 (2H, m, NC_1-H, NC_8-H); 2.67-2.82 (4H, m, C_{1a}-H, C_{7a}-H, C_2-H, C_7-H); 2.21 (2H, m, C_2-H, C_7-H, J_{gem}=16.0).

δ_C(68 MHz, TMS, $CDCl_3$)= 180.90 (OC_9, OC_{14}); 146.34 (ArC_{14b}-N, ArC_{8a}-N); 134.76, 133.66 (ArC_{9a}, ArC_{13a}, ArC_{3b}, ArC_{3c}); 133.08, 131.91, 131.76 ($C=C_3$-H, $C=C_4$-H, $C=C_2$-H, $C=C_5$-H, ArC_{11}-H, ArC_{12}-H); 126.04 (ArC_{10}-H, ArC_{13}-H); 108.30 (ArC_{14a}, ArC_{8b}); 44.04 ($=C$-C_{3a}-H, $=C$-C_{3d}-H); 41.53 (N-C_7H_2, N-$C_{16}H_2$); 37.45 ($=C$-C_1H_2, $=C$-C_6H_2); 34.45 (CH_2-C_{6a}-H, CH_2-C_{16a}-H).

$\nu_{max}(CHCl_3)$= 3460 (v w, v br, N-H stretching); 3070 (v w), 3010 (w, sh), 2940 (w, br), 2850 (w, sh) (C-H stretching); 1580 (str, br, C=O(and C=C stretching)); 1560 (str), 1505 (w, sh) (C=C stretching); 1455 (m, sh), 1380 (m, sh), 1360 (w, sh) (CH_2 bending); 1320 (m,

sh), 1270 (str, sh), 1210 (w, br) (C_{Ar}-N and C_{aliph}-N stretching); 1020 (m, sh).

Elemental analysis: Calculated: C=79.17 H=5.62 N=7.10
Found: C=78.34 H=5.55 N=7.02



(267)

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